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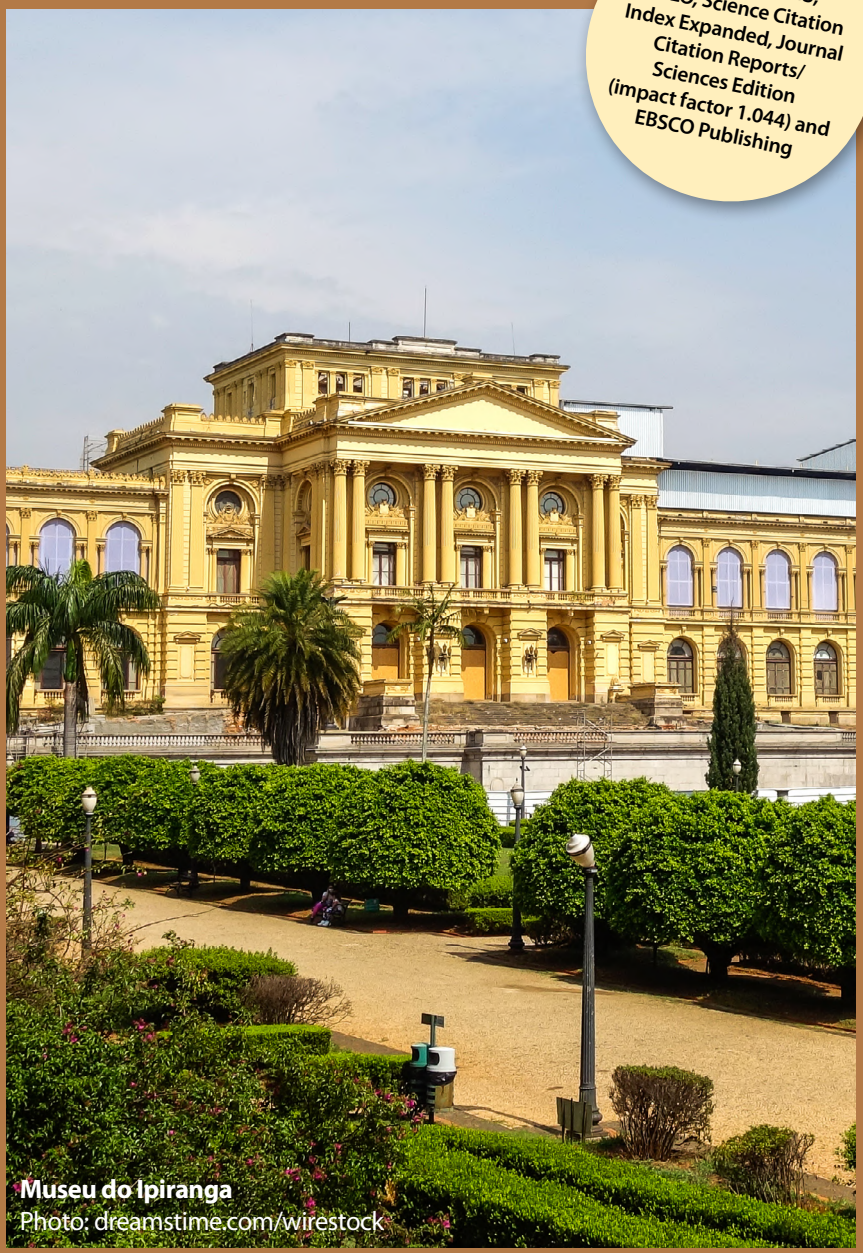

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Post-COVID-19 cardiological alterations

Alexandre de Matos Soeiro[I], Paulo Manuel Pêgo-Fernandes[II]

Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR

[I]MD, PhD. Attending Physician, Division of Cardiology, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.
https://orcid.org/0000-0002-3777-1947

[II]MD, PhD. Full Professor, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR; Director, Scientific Department, Associação Paulista de Medicina, São Paulo (SP), Brazil.
https://orcid.org/0000-0001-7243-5343

Since the end of the year 2019, the world has experienced a rapid and progressive public health emergency. The disease caused by the virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), named COVID-19 (coronavirus-19), has been shown to be a broad-spectrum and unpredictable condition in which while some patients remain practically asymptomatic, others may present a disease course involving severely compromised lungs. This is the greatest cause of the morbidity and mortality attributed to this disease.[1,2]

However, early in the course of COVID-19, the disease has been shown to have a wide-ranging and potentially alarming interface with the cardiovascular system. Angiotensin-converting enzyme 2 (ACE2) receptors have been shown to have a direct connection with viral pathogenesis, and these may form the cellular gateway in type 2 pneumocytes, macrophages and cardiomyocytes.[1] Thus, patients with cardiovascular diseases have been found to be more susceptible to severe forms of COVID-19. Hypertension, arrythmias, myocardiopathies and coronary artery disease are among the main comorbidities present in patients who are critically ill with COVID-19. Likewise, myocardial injury has been shown to be a potential marker for mortality in COVID-19. The mechanisms for cardiovascular lesions that have been proposed remain incompletely established but it has been suggested that these may involve direct damage to cardiomyocytes, systemic inflammation, interstitial fibrosis of the myocardium, immune-mediated response to interferon, excessive cytokine response by T cells, endothelial dysfunction, destabilization of coronary platelets and hypoxia.[1,2]

Patients with cardiovascular diseases, and particularly hypertensive patients, present morbidity rates of up to 10.5% after becoming infected with COVID-19. A recent analysis on 5,700 patients hospitalized in New York showed that the most prevalent comorbidities were hypertension (57%), obesity (42%) and diabetes (34%).[2] Another study conducted in China among 1,527 patients hospitalized with COVID-19 showed that the prevalences of hypertension, cardiovascular disease and diabetes were, respectively, 17.1%, 16.4% and 9.7%. These prevalences were two to four times higher in patients with severe COVID-19 than in mild cases of the disease.[3]

As mentioned earlier, another finding relating to COVID-19 mortality has been the presence of myocardial injury. Elevation of troponin levels has been shown to be significantly related to higher mortality and to cardiac arrhythmias. Increased levels of this marker occur more frequently in individuals with chronic cardiovascular diseases than in previously healthy individuals. Higher prothrombotic and inflammatory activity and hypoxia contribute to occurrences of myocardial injury. However, presence of myocarditis, stress-induced cardiomyopathy, acute heart failure and direct lesions of cardiomyocytes also contribute to these occurrences. Even conditions that are not directly related to the heart but common in COVID-19 can lead to increased troponin levels. These may include pulmonary embolism, sepsis and critical states among patients. Shi et al.[4] showed that the rate of occurrence of myocardial injury among patients hospitalized with COVID-19 was 19.7%, and that this had a direct positive correlation with disease presentations of greater severity. Another similar study showed that myocardial injury occurred in up to 41% of the patients with moderate-to-severe conditions. Furthermore, the mean troponin level among patients who died was 40.8 ng/dl, versus 3.3 ng/dl among those who survived.[4]

Among the cardiovascular manifestations relating to COVID-19, cardiac arrhythmias were observed in 16.7% of the hospitalized patients: 7% of those who did not require intensive care observation and 44% of those who were admitted to an intensive care unit. The manifestations ranged from benign arrythmias such as atrial fibrillation to atrioventricular blockage and ventricular

tachycardia/fibrillation. Metabolic dysfunctions, inflammation and activation of the sympathetic nervous system are thought to be the main predisposing factors for heart rhythm alterations.

Heart failure has been reported in up to 23% to 33% of patients hospitalized with COVID-19 in China. It was observed in 52% of the patients who died, versus in 12% of those who survived. Myocardial injury can be caused both by myocarditis and by imbalance of demand/consumption.[2,5] Specifically, acute myocarditis has been presented in some samples as the cause of death in up to 7% of patients with COVID-19, and it can be presented in a fulminating manner. However, such diagnoses are not necessarily confirmed, and this percentage may have been overestimated. Two particular features are now being evaluated within this context. Firstly, some cases of myocarditis among patients with COVID-19 may be caused by infections due to other concomitant viruses. Secondly, while acute myocarditis may be present at the most critical moment within the course of COVID-19, some patients have an autoimmune reaction and present subacute myocarditis several weeks after the initial infectious event. All of these suppositions are being studied.[6]

Myocardial ischemia has become another concern in relation to presentations of COVID-19. The various mechanisms for endothelial dysfunction, the prothrombotic state, the inflammation and the destabilization of atherosclerotic plaques consequently lead to potential for these patients to remain more exposed to acute coronary events. The real incidence of these phenomena continues to be uncertain. However, it is known that most infarcts are of type 2, due to imbalance between demand and consumption. Greater difficulty in found in treating patients with type 1 infarct, for whom the time to implement catheterization, the antithrombotic therapy and the safety of the team involved need to be assessed in combination, in order to achieve the best management for the patient.[2]

Lastly, in addition to the acute cardiovascular diseases that are present during the course of COVID-19, we are now starting to deal with the sequelae: these are sometimes irreversible or have a slow and difficult recovery process. Many survivors of severe COVID-19 continue to complain of symptoms for long periods, even after their discharge from hospital. It remains unknown whether this might represent a new post-COVID syndrome. Approximately 21.4% to 43.4% of the patients continue to report having dyspnea two to six months after becoming infected with COVID-19. Palpitations and chest pain are reported by, respectively, 9% to 32% and 5% to 44% of the patients. Around 58% of the patients who present cardiovascular manifestations during the acute phase of COVID-19 continue to show cardiological sequelae on cardiac magnetic resonance imaging 50 days later, with reduction of the ejection fraction and presence of edema and myocardial fibrosis.[7]

In this light, instituting cardiovascular rehabilitation programs now takes on fundamental importance. In addition to the patients with COVID-19 who have presented severe cardiological sequelae, it needs to be borne in mind that all other patients with cardiopathies but without COVID-19 infection have also reduced their physical activity levels consequent to social isolation. It has been estimated that individuals have reduced their physical activity by up to 25% during the pandemic, in relation to their previous levels. Some centers in the United States have implemented in-person and telemedicine rehabilitation systems for these patients, with priority given to those with conditions of greater severity, and have obtained good follow-up results.[8]

Thus, we conclude that there is now better understanding of COVID-19 and its cardiovascular manifestations. We now know the extent to which the presence of cardiovascular comorbidities and the cardiological manifestations of COVID can worsen the prognosis. Nonetheless, many questions regarding their physiopathology and treatment remain open, to be targeted in future clinical studies.

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Deficiency of vitamins C and E in women of childbearing age in Brazil: a systematic review and meta-analysis

Rosa Camila Lucchetta[I], Sophia de Andrade Cavicchioli[II], Ana Luísa Rodriguez Gini[III], Marcela Forgerini[IV], Fabiana Rossi Varallo[V], Mariane Nunes de Nadai[VI], Fernando Fernandez-Llimos[VII], Patricia de Carvalho Mastroianni[VIII]

School of Pharmaceutical Sciences, Universidade Estadual Paulista (UNESP), São Paulo (SP), Brazil

[I]PhD. Pharmacist and Postdoctoral Researcher, Department of Drugs and Medicines, School of Pharmaceutical Sciences, Universidade Estadual Paulista (UNESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-4004-1320

[II]Undergraduate Student, Universidade de Araraquara (UNIARA), Araraquara (SP), Brazil.
https://orcid.org/0000-0002-4922-4131

[III]Undergraduate Student, Department of Drugs and Medicines, School of Pharmaceutical Sciences, Universidade Estadual Paulista (UNESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-2643-810X

[IV]Pharmacist and Doctoral Student, Department of Drugs and Medicines, School of Pharmaceutical Sciences, Universidade Estadual Paulista (UNESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-2905-8519

[V]PhD. Pharmacist and Professor, Department of Pharmaceutical Sciences, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo (FCFRP-USP), Ribeirão Preto (SP), Brazil.
https://orcid.org/0000-0003-4016-1442

[VI]MD, PhD. Professor, Faculdade de Odontologia de Bauru, Universidade de São Paulo (FOB-USP), Bauru (SP), Brazil.
https://orcid.org/0000-0002-6706-7117

[VII]PhD. Pharmacist and Professor, CINTESIS – Center for Health Technology and Services Research, Laboratory of Pharmacology, Department of Drug Sciences, Faculty of Pharmacy, Universidade do Porto, Porto, Portugal.
https://orcid.org/0000-0002-8529-9595

[VIII]PhD. Pharmacist and Professor, Department of Drugs and Medicines, School of Pharmaceutical Sciences, Universidade Estadual Paulista (UNESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-8467-7278

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AUTHORS' KEYWORDS:
Hypovitaminosis.
Lactating.
Nutritional epidemiology.
Maternal nutrition.

ABSTRACT

BACKGROUND: Despite the several options available for supplements containing vitamins C and E, evidence regarding the prevalence of deficiency or insufficiency of these vitamins is weak.

OBJECTIVES: To estimate the prevalence of deficiency or insufficiency of vitamins C and E and associated factors among women of childbearing age, in Brazil.

DESIGN AND SETTING: Systematic review and meta-analysis conducted at a Brazilian public university.

METHODS: A search from index inception until May 2020 was conducted. Meta-analyses were performed using inverse variance for fixed models, with summary proportions calculation using Freeman-Tukey double arcsine (base case). Reporting and methodological quality were assessed using the Joanna Briggs Institute tool for prevalence studies.

RESULTS: Our review identified 12 studies, comprising 1,316 participants, especially breastfeeding women. There was at least one quality weakness in all studies, mainly regarding sampling method (i.e. convenience sampling) and small sample size. The prevalence of vitamin C deficiency ranged from 0% to 40%. Only vitamin E deficiency was synthetized in meta-analyses, with mean prevalences of 6% regardless of the alpha-tocopherol cutoff in plasma, and 5% and 16% for cutoffs of < 1.6-12.0 mmol/l and < 16.2 mmol/l, respectively. The cumulative meta-analysis suggested that a trend to lower prevalence of vitamin E deficiency occurred in recent studies.

CONCLUSIONS: Although the studies identified in this systematic review had poor methodological and reporting quality, mild-moderate vitamin C and E deficiencies were identified, especially in breastfeeding women. Thus, designing and implementing policies does not seem to be a priority, because the need has not been properly dimensioned among women of childbearing age in Brazil.

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INTRODUCTION

Vitamins C and E are antioxidants agents and cofactors of various metabolic and enzymatic reactions. They also participate in several physiological processes, such as in repairing oxidative stress, antitumor processes and hormone production.[1-3] Vitamins C and E also participate in human embryological development and their deficiency is associated with low weight in babies, prematurity, and malformations.[4,5]

Vitamin C and E deficiencies have also been correlated with occurrences of scurvy, anemia, hyperbilirubinemia, tiredness and depressive conditions.[6,7] These deficiencies may occur because vitamins are not synthesized in the body, but are obtained through ingestion of vegetables, legumes, fruits and nuts, among other foods.[8,9]

Despite the recognized importance of these vitamins and the known risk of vitamin deficiencies, evidence among women of childbearing age is limited. The prevalence of vitamin C deficiency in adult women has been estimated to range from 6.9% in the United States to 14% in England,[10] while vitamin E deficiency has been found to range from 20% to 90%, depending on the population subgroup analyzed, the comorbidities presented and age.[2] Some Brazilian primary studies have estimated that the prevalences of ascorbic acid[11,12] and alpha-tocopherol[13,14] deficiencies/insufficiencies are 30.8% and 62%-88.1% respectively, and have hypothesized that a problem of regional relevance may exist.

Studies eliciting the prevalence of a condition reflect the burden of this condition on society, and they assist in defining priorities for healthcare policies and decision-making. Well-designed

cross-sectional studies are the most appropriate study design for estimating prevalence. If conducting these primary studies is not feasible, a systematic review gathering together the existing data may be the most appropriate approach for providing an idea of the magnitude of the problem and for achieving greater national representativeness.[15]

To our knowledge, no systematic review on this topic considering Brazilian data exists.

OBJECTIVE

The aim of this study was to estimate the prevalences of vitamins C and E deficiencies or insufficiencies and their associated factors, among women of childbearing age in Brazil.

METHODS

Study design, protocol and registration

A systematic review was performed in accordance with the recommendations of the Cochrane Collaboration,[16] Meta-analysis of Observational Studies in Epidemiology (MOOSE)[17] and Joanna Briggs Institute (JBI).[18] The results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] The protocol for this review is available at OSF[20] and PROSPERO (CRD42020221605). This study forms part of a larger study that evaluated vitamin A, B, C, D and E, calcium, iodine, iron and zinc deficiencies in women of childbearing age in Brazil.

Information sources, search strategy and eligibility criteria

Electronic searches were conducted through a pre-defined search strategy, which was described in the protocol,[20] in the following databases: PubMed, LILACS, WHO, CAPES dissertations and theses (gray literature) and Scopus.[21] The search encompassed the entire period from database inception to May 2020. The reference lists of reviews and studies that were included were also searched.

Studies that fulfilled the following inclusion criteria, in accordance with the CoCoPop acronym,[22] were included: i) Condition: vitamin C and E deficiency or insufficiency; ii) Context: Brazil without restriction of setting; and iii) Population: women of childbearing age (15 to 49 years old) without any restriction on diseases or physiological status (i.e. non-pregnant, pregnant or breastfeeding). Data from studies that reported the deficiencies of interest using a different population classification (e.g. women aged 15 to 44 or pregnant teenagers) or different laboratory parameters, were separated for appropriate subgroup analyses.

Although cross-sectional studies are the ideal and are the study design most used for reporting prevalence, many studies have the potential to report this parameter, such as national surveys or longitudinal studies. Thus, all types of studies were included, except reviews, letters, comments, reports and case series. No language restriction was applied.

Study selection and data extraction

Two researchers independently screened the titles and abstracts and evaluated the full-text articles. Discrepancies were resolved through consensus meetings, using another researcher as a referee. The eligibility process was conducted using spreadsheets.

The following data were independently extracted by five researchers: (i) study characteristics (type of study, analysis period and state), characteristic of the population (e.g. pregnant women), micronutrient deficiency, sampling method and funding; (ii) participants' characteristics, i.e. ethnicity, comorbidities, drug therapy or supplement in use, body mass index (BMI), age, education and per capita income; and (iii) prevalence estimates (n/N (%)) for the total population and for subgroups when available.

Methodological quality in individual studies

Given that no validated tool for assessing the risk of bias in prevalence studies exists, an assessment of the methodological and reporting quality based on the JBI Critical Appraisal Checklist for studies reporting prevalence data[27] was conducted. The methodological rigor and completeness of the most critical domains were considered.[28] The evaluation was performed independently by two reviewers. In the absence of consensus, points of disagreement were resolved by seeking the opinion of another investigator.

Synthesis of results

Although no predefined cutoffs for assessing deficiencies of vitamins C and E were considered as inclusion criteria in the present review, only studies that considered the same cutoff were grouped.

The data synthesis was primarily done through meta-analysis. Transitivity assessment was performed by comparing CoCoPop acronyms[22] between studies (population inclusion and exclusion criteria and subpopulation definitions). If important discrepancies were identified, sensitivity analyses with the exclusion of the study in question were performed. To conduct direct meta-analyses, the data collected were transferred and analyzed separately in the R software, version 3.6.3 (R studio 1.2.5033),[23] using the READR[24] and META packages.[25]

Direct proportional meta-analyses were conducted using the inverse variance method (base case) and GLMM method (sensitivity analysis).[25] To calculate weighted summary proportions, Freeman-Tukey double arcsine transformation (PFT) (base case) and Logit transformation (PLOGIT) (sensitivity analysis) were considered in fixed-effect models (base case) and random-effect models (sensitivity analysis).[19,25] Although high heterogeneity was expected and, therefore, a random-effect model could be expected, it has been recommended that a fixed-effect model is preferable for assessing prevalence, because otherwise the weighting will

not properly consider the weights of the studies.[26] Thus, analyses were conducted using both models, and potential differences were discussed.

The results from the meta-analysis were given as the proportion combined with its 95% confidence interval (CI), along with a list of the proportions (presented as percentages) with their respective 95% CI that had been found in the individual studies included in the meta-analysis. A Higgins inconsistency test (I^2) with an estimator for tau^2 was used through the DerSimonian-Laird method (base case), with statistical adjustment by means of Hartung and Knapp to a random model (sensitivity analysis).

A cumulative meta-analysis was carried out to assess changes and trends over time and to highlight emerging or decreasing conditions, along with their potential relationship with public policies that had been implemented.

Sensitivity analyses were performed by means of the leave-one-out method. Subgroup and meta-regression analyses, considering the period of analysis, state and region of Brazil, comorbidities, age or status (i.e. non-pregnant, pregnant or breastfeeding) were planned for meta-analyses with at least 10 studies. Alternative statistical methods were also conducted to validate the conclusions. Potential publication bias was assessed using rank tests (base case) and linear regression or the method of moments (sensitivity analysis), with at least 10 studies per meta-analysis.[25]

Data sharing and data accessibility

The data that support the findings of this study are openly available in OSF at http://doi.org/10.17605/OSF.IO/J9QMH.[20]

RESULTS

Selection process

Our systematic review identified 1,977 records in the electronic databases after removal of duplicates (PubMed, LILACS and Scopus) and 91 additional records identified through other sources (manual search, WHO database and CAPES database of dissertations and theses). Through the selection process, 259 published papers were included in the systematic review regardless of the micronutrient assessed. These included 12 studies (14 papers) about vitamins C and E (see supplementary data: Figure S1 and Table S2, available in OSF: https://osf.io/j9qmh/),[20] consisting of eight cross-sectional studies, three prospective cohorts and one randomized clinical trial (**Table 1**).

Characteristics of studies and participants

The studies were conducted between 2002 and 2017, in cities in the northeastern region (n = 8) and southeastern region (n = 4), among women who were selected mainly from maternity clinics (n = 5) and hospitals (n = 4). Only Gurgel et al.[29] reported that they used convenience sampling, while the sampling method was not reported in the remaining 11 studies. This lack of information may point towards use of convenience sampling. All the studies received some funding (**Table 1**).

A total of 1,316 participants were included, and the majority were breastfeeding (n = 1,037), with mean ages in the different studies ranging from 16.9 to 30.0 years. Most of the studies included healthy women or excluded women with chronic or infectious diseases (n = 9), and also excluded participants using supplements containing vitamin C or E (n = 9). No study reported prevalence among non-pregnant and non-breastfeeding women. Gurgel et al.[29] did not report on the use of medicines or supplements and Monteiro et al.[30] only reported on the use of antiretroviral therapy. Furthermore, most of the studies did not report mean BMI, ethnicity, educational level or per capita income. Only five studies[11,31-35] reported on the participants' educational level, and showed that the majority had low levels (data not shown). Six studies[11,12,32-36] reported on per capita income and showed that the majority of the participants had monthly per capita income of less than one minimum wage (data not shown). The main characteristics of the participants are described in **Table 1**.

Quality assessment

In the quality assessments, all studies presented at least one 'No' answer, which suggests that, overall, there was poor reporting or methodological quality. The main questions with 'No' answers were in relation to the following: the sampling method, since most studies used convenience samples; the sample size, due to non-reporting of a target; the description of the subjects and setting, due to absence of information on ethnicity, comorbidities, BMI, educational level or per capita income; and lack of appropriate statistical analysis, e.g. not taking into account the number of participants with events or the total number of participants observed).

The response rate was considered unclear with regard to most studies assessing vitamin E and, consequently, no reliable estimate of vitamin E deficiency could be made. Considering that an adequate sample size depends on an estimate of prevalence, the estimated prevalence will directly influence the adequate response rate. For instance, if a prevalence of vitamin E deficiency of up to 6% is assumed, most of the studies achieved an adequate response rate. However, if a prevalence of at least 17% is assumed, none of the studies included presented an adequate response rate.

The questions for which all the answers were 'Yes' were in relation to the sample frame and validity of methods used for identifying the deficiencies. A detailed assessment of the methodological quality of the studies included is presented in **Table 2**.

Table 1. Description of the characteristics of the studies included and participants

Study	Study type	Vitamins	Inclusion period	State/ region	Setting	Funding	Characteristic (n)	Comorbidities	Mean BMI, kg/m² (± SD)	Mean age, years (± SD)
Madruga de Oliveira A et al.[11,32]	CS	C	2002	SP/ southeast	Maternity	CNPq	Pregnant smokers (40); pregnant nonsmokers (87); and breastfeeding (117)	Healthy	NR	NR/20-34 years (77.0%)
Machado et al.[12]	CS	C and E	2010-2011	SP/ southeast	Outpatient	UNIFESP	Pregnant (49)	HIV+	NR	30.0 (6.5)
de Azeredo and Trugo[14]	CS	E	NR	RJ/ southeast	Hospital	CNPq, FAPERJ, and CAPES	Breastfeeding teenagers (72)	Healthy	23.1 (3.2)	16.9 (1.4)
Clemente et al.[31]	RCT	E	2012-2013	RN/ northeast	Maternity hospital	CNPq	Breastfeeding (109)	Healthy	NR	24.1 (5.6)
de Lira et al.[37,39]	CS	E	2010	RN/ northeast	Hospital	CNPq	Breastfeeding (103)	NR (some chronic and infectious diseases were excluded)	NR	24.0 (7.0)/14 to 41 years
Garcia et al.[38]	CS	E	2008	RN/ northeast	Maternity hospital	CNPq	Breastfeeding (32)	NR (some chronic diseases were excluded)	NR	25.0 (6.3)/14 to 36 years
Gurgel et al.[29]	CS	E	2009-2011	RN/ northeast	Maternity hospital	UFRN	Breastfeeding (209)	Healthy	NR	NR/14 to 45 years
Monteiro et al.[30]	PC	E	NR	SP and RJ/ southeast	NR	NICHD	Breastfeeding (97)	HIV+	NR	NR/20-29 years (51.5%)
da Silva Ribeiro et al.[33]	CS	E	2012-2013	RN/ northeast	Hospital	UFRN	Breastfeeding (58)	NR (some chronic and infectious diseases were excluded)	NR/around 28.0	NR/around 24.0
Ribeiro et al.[34]	CS	E	2013-2014	RN/ northeast	Hospital	UFRN	Pregnant (103)	NR (some chronic and infectious diseases were excluded)	NR	NR/18-24 years (59.0%)
Rodrigues[36]	PC	E	2012-2015	RN/ northeast	Maternity hospital	UFRN	Breastfeeding (mothers of children born preterm and at term) (124)	NR	Mothers of preterm: 28.3 (5.2); and mothers of term: 28.3 (4.3)	Mothers of preterm: 26.0 (6.7); and mothers of term: 24.5 (6.0)
da Silva et al.[35]	PC	E	2016-2017	RN/ northeast	Outpatient	UFRN	Breastfeeding (nonsmokers) (116)	NR (some infectious diseases were excluded)	NR	27.8 (7.4)

BMI = body mass index; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; CS = cross-sectional; FAPERJ = Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro; HIV+ = human immunodeficiency virus-positive; NICHD = National Institute of Child Health and Human Development; NR = not reported; PC = prospective cohort; RCT = randomized clinical trial; RJ = Rio de Janeiro; RN = Rio Grande do Norte; SD = standard deviation; SP = São Paulo; UFRN = Universidade Federal do Rio Grande do Norte; UNIFESP = Universidade Federal de São Paulo.

Prevalence analysis

Only two studies (three papers) were found to report on the prevalence of deficiency or insufficiency of vitamin C.[11,12,32] These studies used different cutoffs for ascorbic acid in plasma and, therefore, it was not possible to include them in any meta-analysis. De Oliveira et al.[11,32] used a cutoff of < 22.7 mmol/l (0.4 mg/dl) and identified prevalences ranging from 27.0% (non-smoker pregnant women) to 40.0% (smoker pregnant women), while Machado et al.[12] found that the prevalence of vitamin C deficiency (< 11 mmol/l) was 0%, but that 12.2% of the pregnant women evaluated had suboptimal plasma levels (11-28 mmol/l).

Eleven studies reported on the prevalence of deficiency or insufficiency of vitamin E.[12,14,29-31,33-39] Different cutoffs for alpha-tocopherol in plasma were used, but a meta-analysis with three subgroups could be conducted. Machado et al.[12] and Monteiro et al.[30] were not included in any vitamin E meta-analysis because their cutoffs of < 9.7 mmol/l, 9.7-16.2 mmol/l and < 7 mmol/l were not used in any other study. These two studies identified prevalences ranging from 0% to 22.4%.

Among the eleven studies, the prevalence of vitamin E deficiency ranged from 0% to 62.5%. Subgroup analyses were conducted on the mother's weight or BMI, age, gestational weight gain, parity, delivery type, public or private maternity hospital, days after delivery, preterm or term infant, educational level, housing type (rural or urban) and per capita income. No statistical differences in prevalence ($P < 0.05$) were identified among these subgroups. No meta-analysis on these subgroup analyses was possible, either because only one study reported the subgroup or because different cutoffs were considered.

In the meta-analysis for the base case, an overall prevalence of 6% (95% CI 5%-8%) was identified, while 5% (95% CI 4%-7%) and 16% (95% CI 11%-23%) were estimated for the cutoffs of 11.6-12.0 mmol/l and 16.2 mmol/l cutoffs, respectively (**Figure 1**). A cumulative meta-analysis was performed considering the year of publication, and this showed a smaller trend of prevalence of vitamin E deficiency or insufficiency, with a slight join point in 2015 (**Figure 2**).

A sensitivity analysis using the leave-one-out method was conducted but was unable to reduce the heterogeneity (89%-96%), and the overall prevalence ranged from 4% to 8% (see supplementary data: Table S3, available in OSF: https://osf.io/j9qmh/).[20] In this analysis, withdrawal of the study by Ribeiro et al.,[34] which was the only study that did not include breastfeeding women, resulted in a prevalence of vitamin E deficiency of 7% (95% CI 5%-8%), with I^2 of 96%. The studies with most influence on the variations were those of de Azeredo et al.,[14] on teenager breastfeeding, and Clemente et al.,[31] on breastfeeding in general. Sensitivity analyses using alternative statistical methods identified prevalences ranging from 8% to 17% (see supplementary data: Table S4, available in OSF: https://osf.io/j9qmh/).[20]

Meta-regression analyses were conducted on publication year ($P < 0.01$) and cutoffs ($P < 0.001$), and both of these variables explained the heterogeneity (**Figure 3**). No meta-regression or subgroup analyses on other variables was possible. It was also not possible to conduct statistical and visual analyses on publication bias for any meta-analysis because the requirements for a minimum number of studies or different results and sample sizes were not met.

Table 2. Methodological and reporting quality assessment, using Joanna Briggs Institute tool for prevalence studies

Studies	Questions								
	1	2	3	4	5	6	7	8	9
Madruga de Oliveira A et al.[11,32]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	No [f]	No [g]
Machado et al.[12]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	Yes	No [g]
de Azeredo and Trugo.[14]	Yes	No [a]	No [c]	Yes	Yes	Yes	NA [e]	No [f]	Unclear [h]
Clemente et al.[31]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	Yes	Unclear [h]
de Lira et al.[37,39]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	No [f]	Unclear [h]
Garcia et al.[38]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	Yes	Unclear [h]
Gurgel et al.[29]	Yes	No [b]	Yes	No [d]	Unclear [d]	Yes	NA [e]	Yes	Unclear [h]
Monteiro et al.[30]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	Yes	Unclear [h]
da Silva Ribeiro et al.[33]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	No [f]	Unclear [h]
Ribeiro et al.[34]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	Yes	Unclear [h]
Rodrigues.[36]	Yes	No [a]	No [c]	Yes	Yes	Yes	NA [e]	No [f]	Unclear [h]
da Silva et al.[35]	Yes	No [a]	No [c]	No [d]	Unclear [d]	Yes	NA [e]	No [f]	Unclear [h]

1. Was the sample frame appropriate to address the target population? 2. Were study participants recruited in an appropriate way? 3. Was the sample size adequate? 4. Were the study subjects and setting described in detail? 5. Was data analysis conducted with sufficient coverage of the identified sample? 6. Were valid methods used for the identification of the condition? 7. Was the condition measured in a standard, reliable way for all participants? 8. Was there appropriate statistical analysis? 9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

NA = not applicable; [a]Not reported, but taken to have been convenience sampling; [b]Reported as convenience sampling; [c]No target sample size was reported; [d]Most of the studies did not report ethnicity, comorbidities, body mass index, age, educational level or per capita income; [e]Not applicable, since the methods were automated and highly replicable; [f]Numerator (n) or denominator (N) of prevalence was not reported; [g]These studies presented a response rate for vitamin C assessment of fewer than 320 participants; [h]No reliable estimate of vitamin E deficiency was possible: if a prevalence of 6% or less is assumed, most of the studies achieved an adequate response rate; however, if a prevalence of 17% or higher is assumed, none of the studies presented an adequate response rate.

DISCUSSION

In this systematic review, twelve studies assessing the prevalence of vitamins C and E deficiency, especially among breastfeeding women, were identified. Two studies reported on vitamin C deficiency (0% to 40%) and eleven reported on vitamin E deficiency (0% to 62.5%), with a mean prevalence of 6% identified through the meta-analysis. The low frequency of assessment of vitamin C and E deficiencies in the past may explain why no systematic review reporting the prevalence of deficiency of these vitamins was found.[6] It is important to note that our findings suggest that

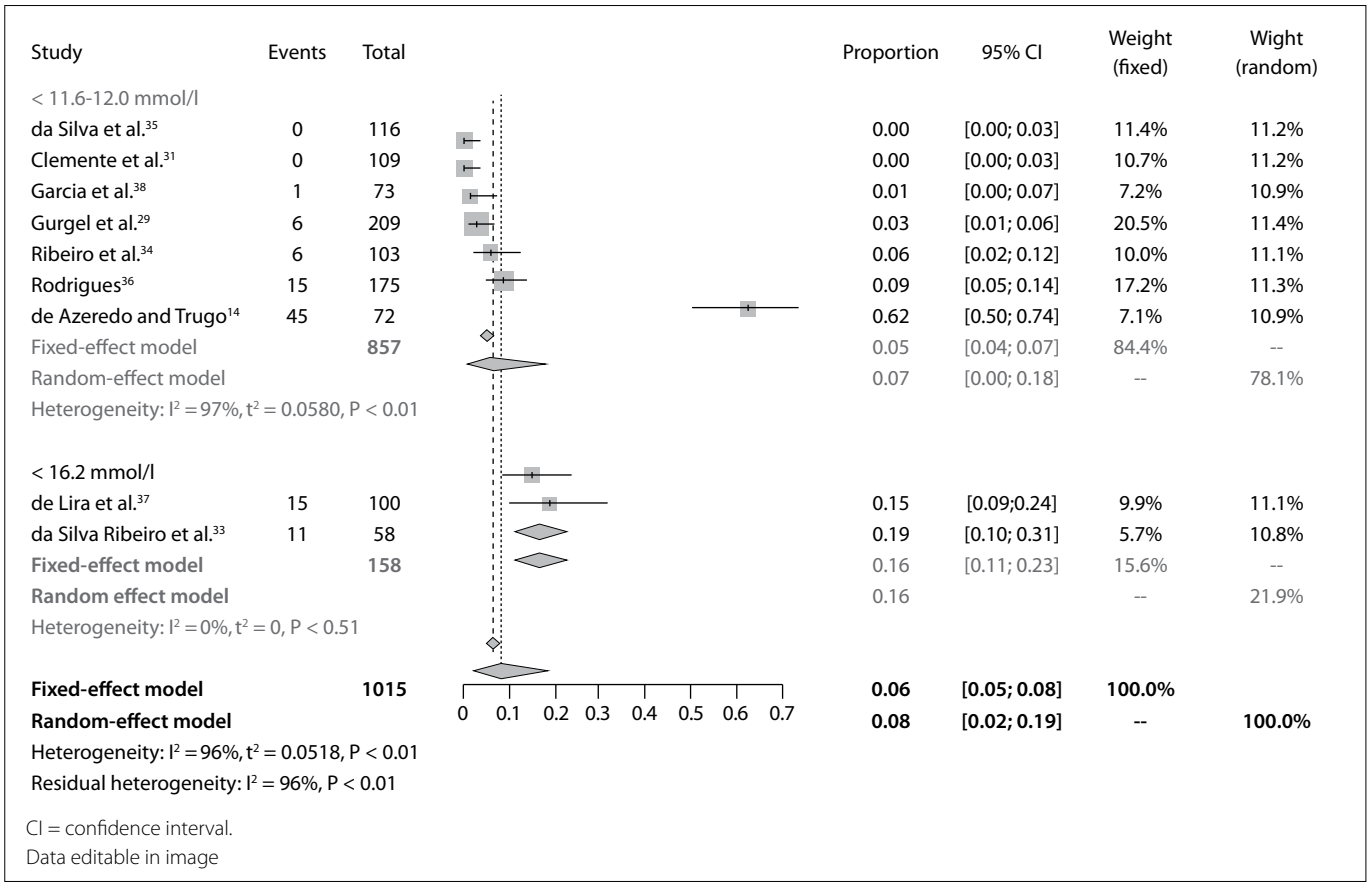

Figure 1. Forest plot for prevalence of vitamin E deficiency, according to alpha-tocopherol cutoff.

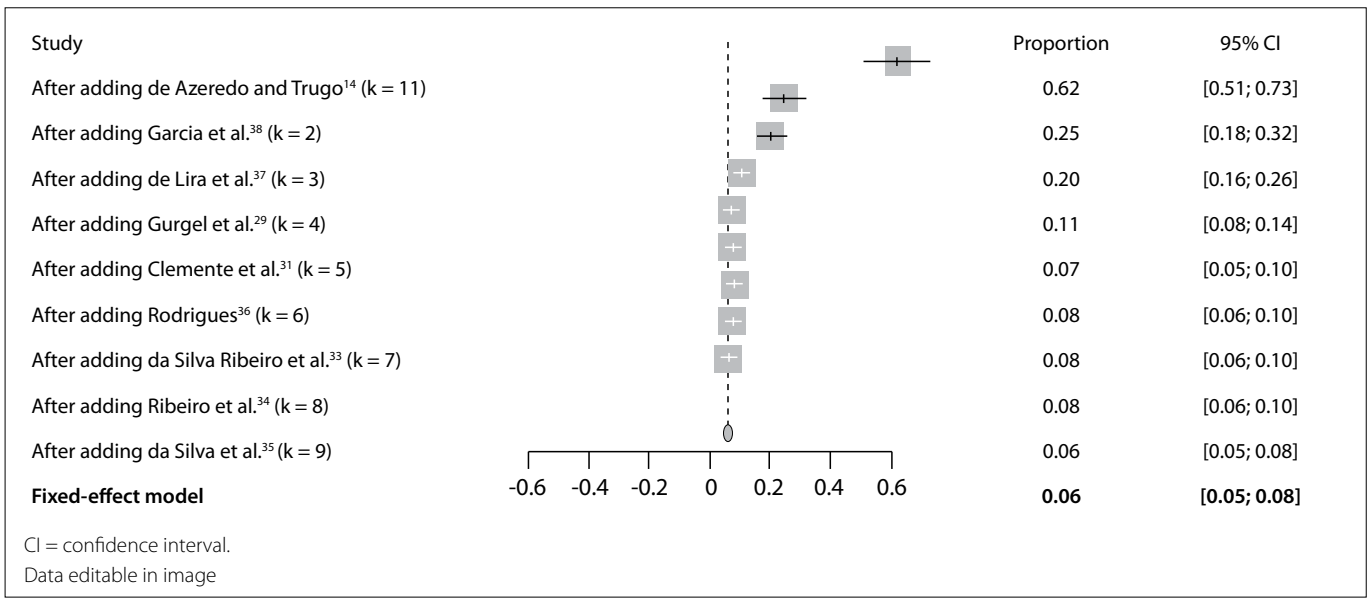

Figure 2. Forest plot for cumulative meta-analysis on prevalence of vitamin E deficiency, according to publication year.

deficiency of vitamins C and E could constitute a public health problem in Brazil, depending on the study and the cutoff for plasma alpha-tocopherol or ascorbic acid under consideration.

It is likely that breastfeeding women have lower vitamin C status due to transfer of vitamin C to the growing infant via breastmilk.[40] Maternal intake of vitamin C in the diet but not as a supplement has been shown to determine the concentration of vitamin C in breast milk,[41] and this was found to vary with season. Therefore, maternal ascorbic acid intake and education about healthy nutrition (consumption of vegetables and fruits) are important.

Furthermore, during pregnancy, placental transfer of vitamin E to the fetus is limited. Thus, breast milk is the only source of this nutrient for infants that are exclusively breastfed.[42] The composition of human milk depends on the stage of breastfeeding, time of the day, time since last meal, nutrition, maternal age, gestational age of the newborn and other individual maternal factors.[43] Therefore, it is important to diagnose deficiencies of vitamins C and E among breastfeeding women, since intake of these vitamins is an important way to supply the newborn with essential antioxidant protection and to stimulate immune system development.[43]

Indeed, insufficient evidence of deficiencies of vitamins C and E worldwide has led to a lack of definition of what constitutes adequate intake of these micronutrients. It has also led to use of different cutoffs for defining deficiency or insufficiency. As expected, in studies evaluating alpha-tocopherol (vitamin E), the higher the cutoff point was (alpha-tocopherol < 16.2 mmol/l), the greater the prevalence of deficiency also was (16%). This suggests that there is a need for studies to establish the cutoff taking into consideration the patients' clinical and physiological conditions (e.g. pregnant women, breastfeeding women or infants). It has, for instance, been found that maternal deficiency influenced the level of vitamin E in the umbilical cord, but not in the colostrum. This suggests that strategies for solving vitamin E deficiency should consider differences among pregnant and breastfeeding women.[33]

All the studies included here showed low reporting or methodological quality, thus producing findings with low confidence, mainly due to inappropriate sampling methods and sample sizes, which consequently did not provide representative samples of the base populations. High inconsistency was also identified, which further downgrades the confidence in the prevalence rates reported. These issues are common in observational studies.[17,44,45] This high inconsistency suggested that the studies should not be included in the same meta-analysis because of their different evaluation methods (e.g. the methods used to assess deficiency) or participant characteristics (e.g. age, ethnicity, educational level, per capita income or sociodemographic factors). In fact, most of the studies did not report the characteristics of the participants, which made it impossible to conduct robust analyses for exploring the heterogeneity, or to identify possible factors associated with deficiency or insufficiency of vitamins C and E.

Several options for vitamin supplements containing vitamins C and E are available in Brazil, and some of them are included in the Brazilian National List of Essential Medicines (RENAME).[46] Distribution of sachets containing a mixture of micronutrients forms part of the Brazilian strategy for strengthening baby feeding with micronutrients in powder (NutriSUS).[47] Moreover, policies for iron + folic acid[48] and vitamin A[49] supplementation for pregnant and breastfeeding women exist. Nonetheless, no national policy regarding supplementation with any other vitamin (e.g. C and E) exists.

On the other hand, little is known regarding the benefits of use of these supplements among pregnant women. A Cochrane systematic review found that routine supplementation with vitamin E in combination with other supplements, to prevent fetal

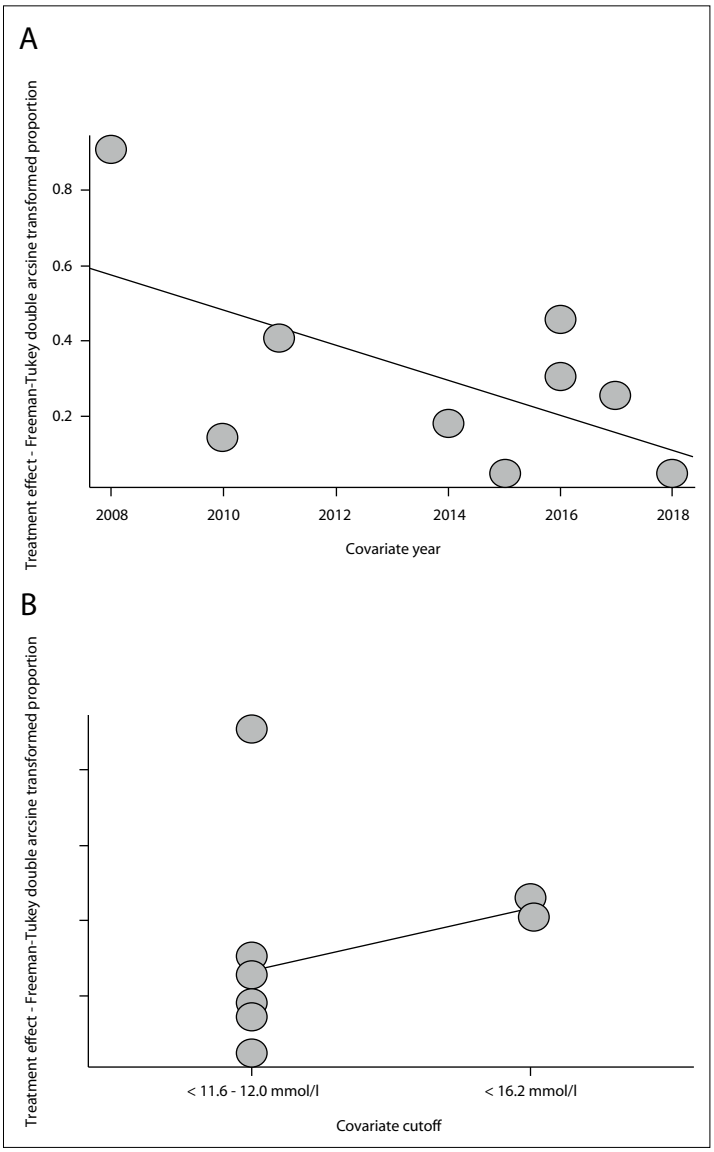

Figure 3. A) Meta-regression plot for publication year (vitamin E deficiency); B) Meta-regression plot for alpha-tocopherol cutoff.

death, neonatal death, premature birth, preeclampsia, premature rupture of membranes (at term or preterm) or fetal growth restriction, was not supported by the current data.[6] Another systematic review, which assessed interventions consisting of vitamin C supplementation alone or in combination with other supplements, found that there was no reduction in prevention of fetal or neonatal death, poor fetal growth, preterm birth or pre-eclampsia.[50] Therefore, it is important to assess the risks relating to deficiency of vitamins C and E, as well as the benefits from supplementation of these vitamins.

The risk of hypervitaminosis[51] or supplement-drug interactions has been documented.[52,53] Drug interactions with vitamins can be of particular importance and are well documented. These include the following situations: beta-blockers may present reduced absorption if used concurrently with vitamin C supplementation; mineral oil and antacids containing aluminum hydroxide can reduce the absorption of fat-soluble vitamins; vitamin C supplementation can inhibit the action of some antibiotics; use of proton pump inhibitors can cause vitamin C deficiency; and excessive vitamin E supplementation can reduce the absorption of vitamins A and K.[52,53] Therefore, care should be taken with regard to irrational use of supplements through self-medication or prescription. Indeed, robust evidence to assess the problem of vitamin deficiencies and their outcomes among women is needed before establishing potential strategies.

One limitation of this study, like in any systematic review, was that some studies may have been missed. To overcome this limitation, extensive investigation of the gray literature and manual searches to find unpublished studies were conducted, which found several studies that had not been retrieved through electronic searches. This high number of studies identified through manual search might be seen as a limitation of the search strategy. However, one hypothesis for explaining this occurrence is that the titles and abstracts of many studies may have been inadequately drafted in relation to the study subject or may not have been correctly indexed, which might have hindered retrieval. Lastly, another limitation was the absence of robust analysis on the potential factors associated with vitamin C and E deficiencies, due to poor reporting and the small size of the meta-analyses (studies and participants).

CONCLUSION

Although the studies identified in this systematic review showed poor reporting and poor methodological quality, the current evidence suggests that a mild-to-moderate problem exists regarding the prevalence of deficiencies of vitamin C (ranging from 0% to 40%) and vitamin E (5% to 16%), especially among breastfeeding women and in studies in Rio Grande do Norte. Thus, it seems that designing and implementing policies to address this problem is not seen as a national priority because the deficiency problem among women of childbearing age in Brazil is not accurately represented. Future studies should consider using standard cutoffs for plasma alpha-tocopherol and ascorbic acid, random probabilistic sampling, appropriate sample sizes and predefined subgroup analyses, in order to adequately inform the prevalences of deficiencies of vitamins C and E and associated factors among women of childbearing age (non-pregnant, pregnant and breastfeeding women), and to support potential healthcare policies.

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Authors' contributions: Lucchetta RC: conceptualization (lead), data curation (lead), formal analysis (lead), funding acquisition (lead), investigation (lead), methodology (lead), project administration (equal), software (lead), supervision (equal), validation (equal), visualization (lead) and writing-original draft (lead); Cavicchioli SA: data curation (supporting), investigation (supporting), visualization (supporting) and writing-review and editing (supporting); Gini ALR: data curation (supporting), investigation (supporting), visualization (supporting) and writing-review and editing (supporting); Forgerini M: visualization (supporting) and writing-review and editing (supporting); Varallo FR: visualization (supporting) and writing-review and editing (supporting); de Nadai MN: visualization (supporting) and writing-review and editing (supporting); Fernandez-Llimos F: visualization (supporting) and writing-review and editing (supporting); and Mastroianni PC: conceptualization (equal), funding acquisition (equal), project administration (equal), supervision (equal), validation (equal), visualization (equal) and writing-review and editing (lead). All authors actively contributed to discussion of the results from the study, and reviewed and approved the final version to be released

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Address for correspondence:
Patricia de Carvalho Mastroianni
Departamento de Fármacos e Medicamentos. Faculdade de Ciências Farmacêuticas. Universidade Estadual Paulista "Júlio de Mesquita Filho" – UNESP
Rodovia Araraquara-Jáu, km 1 – s/nº
Araraquara (SP) — Brasil
CEP 14801-902
Tel. (+55 16) 3301-6977
Fax. (+55 16) 3322-0073/3301-6960
E-mail: patricia.mastroianni@unesp.br

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Adding autogenic drainage to chest physiotherapy after upper abdominal surgery: effect on blood gases and pulmonary complications prevention. Randomized controlled trial

Mona Mohamed Taha[I], Ramy Salama Draz[II], Mohamed Mostafa Gamal[III], Zizi Mohamed Ibrahim[IV]

Princess Nourah bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia

[I]MD, PhD. Associate Professor, Department of Rehabilitation, College of Health and Rehabilitation Sciences, Princess Nourah bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia; and Assistant Professor, Department of Cardiovascular/Respiratory Disorders and Geriatrics, Faculty of Physical Therapy, Cairo University, Cairo, Egypt.
https://orcid.org/0000-0001-9080-5061

[II]MD, PhD. Assistant Professor, Department of Cardiovascular/Respiratory Disorders and Geriatrics, Faculty of Physical Therapy, Cairo University, Cairo, Egypt.
https://orcid.org/0000-0003-4089-323X

[III]PT, MD. Physiotherapist, Kasr Al-Ainy Teaching Hospital, Giza, Egypt.
https://orcid.org/0000-0002-8067-304X

[IV]MD, PhD. Assistant Professor, Department of Surgery, Faculty of Physical Therapy, Cairo University, Cairo, Egypt; and Associate Professor, Department of Rehabilitation, College of Health and Rehabilitation Sciences, Princess Nourah bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia.
https://orcid.org/0000-0001-6309-3484

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ABSTRACT

BACKGROUND: Hypoxemia and pulmonary complications are common after upper abdominal surgery (UAS).

OBJECTIVE: To examine whether inclusion of autogenic drainage (AD) in chest physiotherapy after UAS confers additional benefits in improving blood gases and reducing postoperative pulmonary complications (PPCs).

DESIGN AND SETTING: Randomized controlled study conducted at Kasr Al-Ainy teaching hospital, Egypt.

METHODS: A randomized controlled trial was conducted on 48 subjects undergoing elective UAS with high risk of developing PPCs. The study group received AD plus routine chest physiotherapy (deep diaphragmatic breathing, localized breathing and splinted coughing) and the control group received routine chest physiotherapy only. The outcomes included arterial blood gases measured at the first and seventh postoperative days, incidence of PPCs within the first seven days and length of hospital stay.

RESULTS: Baseline characteristics were similar between groups. In the AD group, SaO_2, PaO_2, $PaCO_2$ and HCO_3 significantly improved ($P < 0.05$) while in the physiotherapy group, only SaO_2 and PaO_2 significantly improved ($P < 0.05$). Nonetheless, significant differences in post-treatment SaO_2 and PaO_2 between the groups were observed. The overall incidence of PPCs was 16.66% (12.5% in the AD group and 20.8% in the physiotherapy group) (absolute risk reduction -8.3%; 95% confidence interval, CI, -13.5 to 29.6%), with no significant difference between the groups. The AD group had a significantly shorter hospital stay ($P = 0.0001$).

CONCLUSION: Adding AD to routine chest physiotherapy after UAS provided a favorable blood gas outcome and reduced the length of hospital stay. It tended to reduce the incidence of PPCs.

TRIAL REGISTRATION: ClinicalTrials.gov: NCT04446520.

INTRODUCTION

Surgery and postoperative care have become important in healthcare worldwide, given that nearly 234 million patients undergo operations every year.[1] In developed countries, the most common major surgical procedure is upper abdominal surgery (UAS).[2] After UAS, postoperative pulmonary complications (PPCs) contribute to poor patient outcomes, significant lengthening of hospital stay, increased readmissions and elevation of healthcare costs, and may constitute an important and significant cause of morbidity and mortality.[3] Eighty-five percent of PPCs occur during the first three days after surgery[4] and are partially caused by earlier pathophysiological reductions of lung volumes postoperatively.[5] If these conditions persist, they may lead to severe hypoxemia, atelectasis and pneumonia.[6]

The presence of preoperative risk factors like old age, malnutrition, smoking, obesity and clinical lung diseases increases the incidence of PPCs among subjects undergoing UAS. Other anesthetic and surgical factors like the duration and type of surgery also contribute to PPC development.[7]

Lunardi et al.[8] reported that after UAS, impairment of respiratory capacity occurred. This was correlated with a reduction in chest wall volume of 22% and breathing pattern modification due to a decline in the diaphragmatic contribution by 28% to 40%. Reduced lung volumes after surgery are associated with accumulation of pulmonary secretions, which can favor bacterial colonization and development of postoperative pneumonia.[9] Moreover, inability to cough and ineffective coughing by patients after surgery have been found to contribute to the basis of the pathophysiology for PPCs, as this can cause excessive accumulation of expectorations and elevate the risk

of developing pulmonary infections and obstructive atelectasis. Additionally, the decreases in alveolar ventilation and in clearance of bronchial secretions also reduce the clearance of carbon dioxide (CO_2), thus causing hypercarbia, acidosis and, usually, moderate hypoxemia.[10]

Since the beginning of the 20th century, chest physiotherapy has commonly been used for prevention and management of PPCs such as atelectasis, retained secretions, bronchopulmonary infection and pneumonia.[3] Postoperative chest physiotherapy improves lung volume and ventilation-perfusion matching, facilitates mucociliary clearance and reduces pain.[11]

Different alternatives for advanced airway clearance techniques have been developed to improve the efficiency of airway clearance and encourage patient autonomy. These have included autogenic drainage (AD),[12] which depends more on breathing pattern control by the individual to facilitate airway clearance.[13] AD consists of controlled tidal breathing that is practiced at different levels of lung volume. In this, the subject self-adjusts the force or velocity of the expiratory airflow at different levels of inspiration in order to reach the maximum possible airflow generated in the bronchi, without resulting in airway collapses during coughing.[12] AD has the advantage that it is tolerable and can be self-administered and performed from a seated position.[14]

Although there is widespread use of different chest physiotherapy methods after UAS, the impact of each technique on blood gases and prevention of PPCs has not been illustrated. Only limited clinical trials using the autogenic drainage technique after surgical procedures have been presented in the literature and there has not been any assessment of this technique in the population undergoing UAS.

OBJECTIVE

The aim of this study was to evaluate the effect of adding AD to routine chest physiotherapy, with regard to improving blood gases and decreasing the incidence of PPCs and length of hospital stay in the postoperative period, among subjects undergoing UAS.

METHODS

Design and sample

A randomized controlled trial was conducted on 60 obese subjects of both sexes who underwent UAS in Kasr Al-Ainy teaching hospital. This study was approved by the Institutional Review Board of the Faculty of Physical Therapy, Cairo University, under the number P.T.REC/012/001740, on October 1, 2017, and it was conducted in accordance with the principles of the Declaration of Helsinki. A verbal explanation of the trial was provided to eligible subjects and informed consents were obtained.

Subjects with ages from 50 to 60 years and body mass index (BMI) from 30 to 40 who underwent elective UAS were included in the study. In addition, the following procedure-related inclusion criteria were applied: expected duration of surgery ≥ 120 minutes; abdominal incision more than five centimeters above or extending above the navel; planned postoperative admission to the surgical ward; and anticipated length of hospital stay after surgery of more than six days. The exclusion criteria were situations in which subjects underwent any of the following procedures: laparoscopic surgery, lower abdominal surgery, emergency surgery, esophageal surgery or organ transplantation. In addition, subjects who were unable to follow the physiotherapy instructions, received preoperative physiotherapy or persisted with a requirement for invasive mechanical ventilation for more than 24 hours postoperatively were also excluded.

According to these inclusion criteria, the subjects were considered to be at high risk of developing PPCs because they had histories of cigarette smoking, long durations of surgery (> 120 minutes) and obesity (BMI > 27 kg/m²).[7] They were randomly assigned equally to two groups: the study group included 30 subjects who received routine chest physiotherapy (deep diaphragmatic breathing exercises, localized breathing exercises and splinted coughing) plus the AD technique; and the physiotherapy group included 30 subjects who received routine chest physiotherapy only.

Randomization of eligible participants who were present in the waiting list for surgery was done by means of sequentially numbered sealed opaque envelopes that contain allocation cards. These envelopes had been sealed by an independent administrator who did not participate in the trial. From these sealed opaque envelopes, an independent nurse selected the participant for group allocation. The allocation sequence was 1:1, and this was enabled through a web-based computer-generated blocked random number table (https://randomization.com).

Outcome measurements

The primary outcome measurements were changes to arterial blood gases through the following parameters: arterial oxygen saturation (SaO_2), partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), pH and bicarbonate (HCO_3). These were measured on the first and seventh days postoperatively, at room air temperature.

The secondary outcome measurements included: (A) the incidence of PPCs (pneumonia, hypoxemia and atelectasis) within the first seven hospital days, which was defined as development of one or more of the following: [1] pneumonia, which was indicated by the presence of new radiographic chest infiltration and two criteria from the following list: dyspnea, cough with purulent sputum, temperature > 38 °C, altered respiratory auscultation, leukocytosis > 14,000/ml or leucopenia < 3000/ml; [2]

hypoxemia, which was defined as peripheral oxygen saturation (SpO_2) ≤ 90%, with a requirement for administering or elevating supplemental oxygen to keep SpO_2 ≥ 90%; and [3] evidence of atelectasis from radiological evaluation, in association with dyspnea. (B) The number of days of the hospital stay, until discharge based on the physician's decision, was also assessed. The patients and the assessor of the outcome measurements were blinded to the group allocation.

Intervention

The treatment program was administered at a frequency of two sessions daily (in the morning and late afternoon) until the seventh postoperative day, starting from the first day. Early mobilization started from the first day.

AD treatment consists of maximum expiratory airflow with tidal breathing at various lung volumes, to mobilize expectoration while decreasing coughing episodes.[15] During the treatment session, the subjects were in a semi-reclining position (at a 45° angle). The treatment sessions consisted of three stages: (1) unsticking the secretions at low volume; (2) collection at medium volume; and (3) evacuation by breathing at high volume. When sufficient mucus had reached the upper airways, the mucus could then be expectorated by means of a cough or a huff.[16,17]

First, the physiotherapist placed his hands over the subject's chest to follow the breathing pattern and avoid paradoxical breathing. In the first stage, the subject started with diaphragmatic breathing at low lung volume with the following cycle: (a) inspiration slowly through the nose; (b) pause of three seconds between inspirations and expirations to permit the air to get behind the secretion; and (c) non-forced expiration through nose or mouth in a sighing manner. This cycle was then repeated at the same lung volume until secretions were felt or heard. In the second and third stage, this cycle was repeated at medium and high lung volumes. In the end, when the mucus was felt in the larger central airways, the subjects did 2-3 effective huffs or coughs with splinting of the incision site.[15] The cycles were then repeated until reaching a total session duration of 20 minutes.

The routine chest physiotherapy included deep diaphragmatic breathing exercises, localized breathing exercises and splinted coughing. One series of 10 repetitions of each exercise was performed with an inspiratory hold for three seconds and then relaxed expiration. The total session duration was 15 minutes.

Data analysis

Based on the primary outcome measurements, the sample size was calculated taking into account a minimum mean difference in oxygen saturation of about 1.8% and a standard deviation of 2, as used in a previous published study,[18] with a power of analysis of 80% and an alpha significance level of 0.05. From this calculation, it was determined that 20 participants would be required for each group. In order to allow for dropouts, a total of 60 subjects were recruited.

Continuous variables that were normally distributed were presented as the mean ± standard deviation (SD). Paired and unpaired-sample t tests were used for comparisons within and between the groups. The Kolmogorov-Smirnov test was used to test for normal distribution of the data. An independent chi-square test was used for comparisons of categorical variables. P-values less than 0.05 were deemed to be significant.

RESULTS

The flow of participants from recruitment to follow-up is shown in **Figure 1**. A total of 66 subjects were recruited and assessed for eligibility. Among these, 60 subjects were randomized equally between the two groups. Subsequently, a further six subjects were withdrawn from each group for a variety of reasons. The baseline data were comparable between the two groups, with no significant differences between the two groups in terms of demographic characteristics and clinical parameters at the pre-intervention assessment (P > 0.05), as demonstrated in **Table 1**.

Regarding the arterial blood gas parameters, the between-group analysis revealed that there were significant differences in post-treatment values for SaO_2 and PaO_2 (P = 0.0001 and P = 0.03, respectively), while no significant differences were observed with regard to HCO_3, $PaCO_2$, and PH (P > 0.05). The within-group analysis revealed that there were significant improvements in SaO_2, PaO_2, $PaCO_2$ and HCO_3, with percentages of 3.12%, 9.05%, 10.1% and 10.6%, respectively, in the AD group. In the physiotherapy group, significant improvements were observed only for SaO_2 and PaO_2, with percentages of 1.46 % and 5.14 %, respectively. These results are demonstrated in **Tables 2** and **3**.

As shown in **Table 4**, no significant difference in the incidence of PPCs between the groups was observed (P > 0.05), but lower frequency of PPCs in the AD group was observed. There was a significant difference between groups regarding the length of hospital stay, with a shorter hospital stay among the individuals receiving AD (P = 0.0001).

DISCUSSION

The aims of chest physiotherapy include improvement of ventilation and clearance of secretions from the airways.[19] Evaluation of different methods for chest physiotherapy is important in order to enable the possibility of selecting the most suitable method for every patient. It becomes necessary to standardize the practical approaches, in order to assist teams in making the most suitable decision, so as to favor the subjects' clinical outcomes. In the present study, we aimed to determine the effect of adding the AD technique to routine chest physiotherapy, in terms

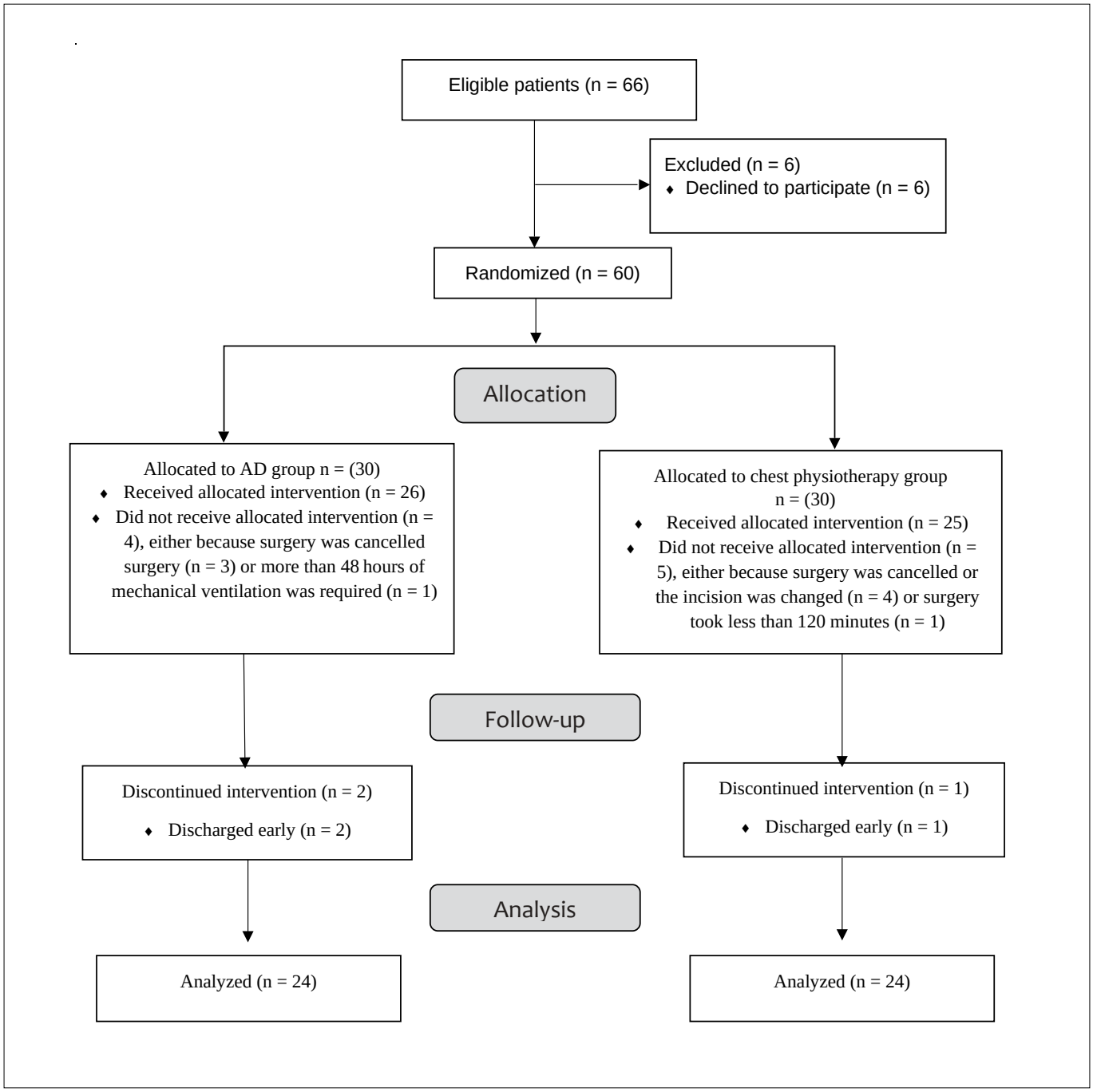

Figure 1. Flow of subjects through the study.

of improvement of gas exchange and reduction or prevention of pulmonary complications, in comparison with routine chest physiotherapy alone, among high-risk subjects undergoing UAS.

Several trials have assessed different airway clearance techniques as part of the physiotherapeutic management of ineffective cough in the postoperative period after abdominal surgery.[11,20,21] However, only limited studies using the AD technique in the postoperative period are available.

In the present study, both treatment groups revealed significant improvements in SaO_2 and PaO_2 but with higher percentages in the AD group. On the other hand, no significant difference in the incidence of PPCs was observed between the two groups, although the AD group had lower frequency of pulmonary complications, and the length of hospital stay was significantly lower in the AD group than in the routine chest physiotherapy group.

Piskin et al.[22] stated that chest physiotherapy increased oxygen saturation and returned the arterial blood gas values to normal limits. Chest physiotherapy is the main and most important treatment strategies for prevention of PPCs.[23]

The results from the present study are consistent with those of Duymaz et al.,[24] who demonstrated that, in subjects undergoing bariatric surgery, postoperative chest physiotherapy regulated their arterial blood gases, improved oxygen saturation and respiratory functions and reduced dyspnea levels. It improved SaO_2, PaO_2 and pH by 15%, 18% and 7% respectively, compared with the preoperative values.

Table 1. Baseline demographic and clinical characteristics of the study population. Values are in numbers (percentages) unless stated otherwise

Characteristics	AD group	Physiotherapy group
Subjects, n = 48		
Age, mean ± SD, years	53.79 ± 2.395	53.88 ± 2.173
Males, n (%)	15 (62.5)	14 (58.3)
Body mass index, mean ± SD, kg/m²	32.9125 ± 2.12888	32.7240 ± 1.78535
Clinical aspects		
Smoking history, n (%)		
Non-smoker	6 (25.0)	9 (37.5)
Current smoker	13 (54.2)	11 (45.8)
Ex-smoke	5 (20.8)	4 (16.7)
Subjects with comorbidities, n (%)		
Hypertension (n)	10 (41.7)	9 (37.5)
Diabetes (n)	11 (45.8)	13 (54.2)
COPD (n)	3 (12.5)	2 (8.3)
Surgical procedure, n (%)		
Cholecystectomy	6 (25)	7 (29.16)
Hernia repair	3 (12.5)	5 (20.38)
Colectomy	2 (8.33)	3 (12.5)
Gastrectomy	3 (12.5)	2 (8.33)
Hepatectomy	7 (29.16)	5 (20.38)
Pancreatectomy	3 (12.5)	2 (8.33)
Surgical duration, mean ± SD, min	240.83 ± 15.012	238.33 ± 9.52
Pain level, median (IQR)	4 (2-7)	4 (2-6)

AD = autogenic drainage; SD = standard deviation; COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

Moreover, Manzano et al.[18] showed, in an evaluation on immediate postoperative chest physiotherapy after UAS, that there was an effective improvement in oxygen-hemoglobin saturation without any increase in abdominal pain. Furthermore, in a study evaluating chest physiotherapy and mobilization versus mobilization alone, which were applied among 74 subjects who underwent bariatric surgery, chest physiotherapy improved postoperative respiratory functions, decreased dyspnea levels, increased oxygen saturation, regulated arterial blood gases and improved functional capacity and quality of life.[24] Additionally, Lunardi et al.[25] compared the effect of chest physical therapy versus no treatment on the incidence of PPCs in patients who underwent esophagostomy surgery. They found that chest physiotherapy reduced the incidence of PPCs (15% versus 37%; $P < 0.05$), shortened the duration of antibiotic treatment and thoracic drainage and reduced the frequency of re-intubation. Also, Rocha et al. found that conventional chest physiotherapy after bariatric surgery led to improvement of tidal volume and decreased the frequency of atelectasis.[20]

To the best of our knowledge, only limited clinical trials involving use of AD postoperatively are available in the literature. The results from the present study are supported by those of a study by Shingavi et al.,[26] who compared the active cycles of a breathing technique versus the AD technique after abdominal surgery. They found that both techniques improved chest expansion and peak expiratory flow rate, but that the active cycle of the breathing technique was more effective. Moreover, Spapen et al.[27] studied the effect of intrapulmonary

Table 3 . Comparison of post-treatment arterial blood parameters results between the two groups

Arterial blood gases parameters	AD group	Physiotherapy group	P-value
SaO_2 (%)	97.62 ± 0.87	95.29 ± 1.33	0.0001
PaO_2 (mmHg)	87.33 ± 4.33	84.29 ± 5.07	0.031
$PaCO_2$ (mmHg)	38.25 ± 5.87	40.27 ± 3.03	1.41
pH	7.39 ± 0.043	7.43 ± 0.072	0.086
HCO_3 (meq/l)	28.2 ± 4.3	26.6 ± 3.75	0.178

AD = autogenic drainage; SaO_2 = arterial oxygen saturation; PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide; HCO_3 = bicarbonate. Data are presented as means ± standard deviations; $P < 0.05$ was considered to be significant.

Table 2. Comparison of arterial blood gases parameters pre- and post-treatment in the two groups

Arterial blood gas parameters	AD group		MD	P- value	Physiotherapy group		MD	P- value
	Pre	Post			Pre	Post		
SaO_2 (%)	94.67 ± 1.27	97.62 ± 0.87	-2.958	0.0001	93.92 ± 1.86	95.29 ± 1.33	-1.375	0.0001
PaO_2 (mmHg)	80.08 ± 5.48	87.33 ± 4.33	-7.250	0.0001	80.17 ± 5.87	84.29 ± 5.07	-4.125	0.0001
$PaCO_2$ (mmHg)	42.55 ± 6.25	38.25 ± 5.87	4.3	0.0001	41.63 ± 7.3	40.27 ± 3.03	1.362	0.348
pH	7.40 ± .056	7.39 ± 0.043	.00458	0.764	7.39 ± .08	7.43 ± .072	-0.037	0.21
HCO_3 (meq/l)	25.5 ± 4.818	28.2 ± 4.3	-2.695	0.001	25.04 ± 2.92	26.6 ± 3.75	-1.562	0.083

MD = mean difference; AD = autogenic drainage; SaO_2 = arterial oxygen saturation; PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide; HCO_3 = bicarbonate. Data are presented as means ± standard deviations; $P < 0.05$ was considered to be significant.

Table 4. Incidence of postoperative pulmonary complications (PPCs) compared with length of hospital stay

Variable	AD group	Physiotherapy group	Difference between means or proportions (95% CI)	P- value
Mean length of hospital stay ± standard deviation (days)	7.33 ± 1.167	9.62 ± 1.610	-2.292 (-3.109 to -1.475)	0.0001
PPCs, n (%)	3 (12.5)	5 (20.8)	0.0833 (-0.135 to 0.296)	0.439
Atelectasis (n)	0	0		
Hypoxemia (n)	1	3		
Pneumonia (n)	2	2		

P < 0.05 was considered to be significant.

percussive ventilation physiotherapy plus assisted AD among critically ill patients on mechanical ventilation. Their patients received either intrapulmonary percussive ventilation physiotherapy plus assisted AD or conventional physiotherapy (chest wall vibrations, positioning, rib-springing, suction and aerosol therapy) or no physiotherapy. Intrapulmonary percussive ventilation plus AD tended to lower the incidence of Gram-negative infection associated with the ventilator, in comparison with the other groups.

A prospective cohort study evaluating 101 subjects postoperatively after UAS concluded that these individuals presented impaired cough effectiveness. On the first postoperative day, their peak cough flow was only 54% of the preoperative value. On the fifth postoperative day, their peak cough flow remained significantly decreased from the preoperative value (72% of that value).[3] Furthermore, excessive sputum may be present postoperatively, due to the action of anesthetic drugs and narcotic drugs, which reduces mucociliary clearing action, diminishes lung function, increases retained secretions and leads to hypoventilation, which consequently increases the respiratory effort.[28]

In addition, abdominal surgery and obesity cause restrictive breathing patterns.[20] Reductions in lung volume cause secretion accumulations in the airways, which are considered to be a risk factor for developing pneumonia and atelectasis. Reductions in vital capacity can also lead to atelectasis, with reduction of the partial pressure of oxygen and facilitation of alveolar collapse.[29]

Thus, there is a need for management of ineffective cough and administration of airway clearance therapy, which may possibly be provided through the improvement in blood gases and the lower incidence of postoperative complication in the AD group of the present study. AD as an airway clearance technique may be helpful in collateral airway opening through breathing with different volumes and instantaneous holding back, which leads to significant improvement in airway clearance, dyspnea, peak expiratory flow rate and mucus clearance.[30] Airway clearance treatment generally improves gas exchange, reduces the work of breathing and clears airway secretions.[31] Hence, removal of infected secretions in the airways can increase the ventilatory capacity and decrease direct inflammation of the airway epithelia.[32] Lastly, autogenic drainage as an airway clearance technique could be taught to patients undergoing UAS and could be self-administered to improve these patients' outcomes.

Limitations

The limitations of this study were the absence of a control group that did not receive any intervention and the fact that the length of time that the subjects stayed out of bed was not assessed. Another limitation was that the physiotherapist was not blind to the study groups.

CONCLUSION

From the results of this study, it can be concluded that adding the AD technique to routine chest physiotherapy after UAS provides improvement of blood gases, shortens the hospital stay and is accompanied by a lower percentage of pulmonary complications. Moreover, it is well tolerated by patients.

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Address for correspondence:
Mona Mohamed Taha
Department of Rehabilitation, College of Health and Rehabilitation Sciences,
Princess Nourah bint Abdulrahman University, Airport Rd,
PO Box 11421, Riyadh, Saudi Arabia
Tel. +966 0531352239
E-mail: monady2007@yahoo.com

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Fecal calprotectin levels used as a noninvasive method for screening for chronic gastritis in pediatric patients. A descriptive study

Fatma Demirbaş[I], Gönül Çaltepe[II], Hasan Abbasguliyev[III], Ayhan Gazi Kalaycı[IV]

Ondokuz Mayis University Faculty of Medicine, Samsun, Turkey

[I]MD. Physician, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ondokuz Mayis University Faculty of Medicine, Samsun, Turkey.
https://orcid.org/0000-0003-1788-2559

[II]MD. Professor, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ondokuz Mayis University Faculty of Medicine, Samsun, Turkey.
https://orcid.org/0000-0001-8525-6352

[III]MD. Postgraduate Student, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ondokuz Mayis University Faculty of Medicine, Samsun, Turkey.
https://orcid.org/0000-0002-1055-0925

[IV]MD. Professor, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ondokuz Mayis University Faculty of Medicine, Samsun, Turkey.
https://orcid.org/0000-0003-2104-6801

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ABSTRACT

BACKGROUND: Gastritis consists of inflammation of the gastric mucosa and is one of the main causes of dyspeptic symptoms in children.

OBJECTIVE: To investigate the presence of inflammation by evaluating fecal calprotectin (FC) in children diagnosed with chronic gastritis.

DESIGN AND SETTING: Descriptive study in Pediatric Gastroenterology Department of Ondokuz Mayis University Hospital in Turkey.

METHODS: Between January 2016 and July 2018, FC levels were compared retrospectively in children with chronic gastritis (histopathology-based diagnosis), patients with inflammatory bowel disease (IBD) and healthy children.

RESULTS: A total of 67 chronic gastritis patients (61.2% girls) with a mean age of 13.09 ± 3.5 years were evaluated. The mean FC levels were 153.4 μg/g in the chronic gastritis group, 589.7 μg/g in the IBD group and 43.8 μg/g in the healthy group. These levels were higher in chronic gastritis patients than in healthy individuals ($P = 0.001$) and higher in IBD patients than in the other two groups ($P < 0.001$). The FC level in the patients with chronic active gastritis (156.3 μg/g) was higher than in those with chronic inactive gastritis (150.95 μg/g) ($P = 0.011$). Among the patients with chronic active gastritis, the FC level was significantly higher in *Helicobacter pylori*-positive individuals than in negative individuals ($P = 0.031$).

CONCLUSION: We confirmed the association between increased FC and chronic gastritis. Elevated FC levels may be seen in patients with chronic active gastritis. In order to be able to use FC as a screening tool for chronic gastritis, further studies in a larger study group are needed.

INTRODUCTION

Gastritis, which consists of inflammation of the gastric mucosa against various factors, is one of the most important reasons for dyspeptic symptoms in children.[1] Children with gastritis frequently experience abdominal pain and other clinical symptoms. The diagnosis of chronic gastritis depends on histopathological findings.[2] It is defined as an inflammatory infiltrate in the lamina propria, within the epithelium and foveolar lumen.[3] Defects of mucosal protective barriers and disruption of the balance between the mucosal barriers and acid and pepsin levels play a role in the pathogenesis of gastritis.[4] Intense neutrophilic infiltration in chronic gastritis can lead to erosion of the cytoplasm and destruction of epithelial cells. This can lead to mucosal ulcers that can cause tissue loss at levels ranging from the superficial to the submucosal layers.[2]

Fecal calprotectin (FC) is a protein that is secreted from macrophages and neutrophils. It is used quantitatively to show intestinal inflammation.[5] It is 83% sensitive and 84% specific for distinguishing between organic and nonorganic diseases.[6] FC levels are high both in inflammatory bowel disease (IBD) and in non-IBD diseases, including in microscopic colitis, infectious colitis, cystic fibrosis, celiac disease and nonsteroidal anti-inflammatory drug-induced enteropathy, which cause increased macrophage and neutrophil levels in the intestinal mucosa.[7-12]

OBJECTIVE

Fecal calprotectin is widely used in diagnosing and following up IBD, but there are insufficient numbers of studies showing the relationship between FC and other upper gastrointestinal system diseases. The main objective of the present study was to compare the FC levels in children

with chronic gastritis (based on histopathological findings) with those in healthy children and children with IBD; and to determine the factors affecting the FC level.

METHODS

Study design

Between January 2016 and July 2018, in the Department of Pediatric Gastroenterology, Hepatology and Nutrition of our institution, 573 patients underwent endoscopy. These patients had come to our clinic with a complaint of chronic abdominal pain. In addition to physical examination and laboratory tests, their fecal calprotectin level was determined and abdominal ultrasound and abdominal X-ray were performed. Interventional procedures such as upper endoscopy and colonoscopy were performed in order to investigate the underlying etiology. Sixty-seven patients who were diagnosed with chronic gastritis (through histopathology-based diagnosis) and whose FC levels were assessed were included in this study.

The following individuals were not included in this study: patients for whom FC was not tested; patients who were not diagnosed histopathologically as having chronic gastritis; patients with upper endoscopy or pathology-verified mucosal lesions such as esophagitis, gastric ulcer, gastric polyp or duodenal ulcer; patients with chronic diseases; patients reacting positive for acute-phase disease; patients who were positive for infection in stool samples; patients with a history of drug use; and patients with a history of chronic disease.

The patients' demographic characteristics, physical characteristics (height Z score and weight Z score) and laboratory findings (white blood cells, thrombocytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin and hemoglobin) were recorded.

Endoscopy procedure

All the endoscopy procedures were performed by an experienced gastroenterologist. Gastric antrum, gastric corpus and incisura angularis biopsies were obtained from the patients during endoscopy. Patients with chronic gastritis were classified in accordance with the Sydney classification.

Hematoxylin-eosin preparations were initially used to examine the biopsy samples for the presence of *Helicobacter pylori*.[13] When the hematoxylin-eosin preparations revealed organisms in a biopsy specimen, situations of chronic active inflammation was then detected by using the modified Giemsa and toluidine blue stains. Chronic active gastritis was taken to be the presence of a mixed inflammatory infiltrate in the lamina propria, in the presence or absence of *Helicobacter pylori* organisms. Chronic inactive gastritis was taken to be the presence of dense populations of lymphocytes and plasma cells within the lamina propria, in the presence or absence of *Helicobacter pylori* organisms.[14]

There were two control group: one that included patients with IBD at the time of diagnosis by means of upper and lower endoscopy and the other that comprised healthy controls of the same ages as the patients, without any chronic disease or signs of infection.

Fecal calprotectin measurement

Three fecal specimens were collected from each child at least one week before endoscopy. These stool specimens were stored at 2-8 °C until tested. The FC evaluation kit was analyzed in accordance with the manufacturer's instructions (RIDA TUBE Calprotectin; R-Biopharm AG, Darmstadt, Germany). FC levels ≤ 50 μg/g were accepted as normal, and levels > 50 μg/g as abnormal.

Ethics

This study was approved by the ethics committee of our hospital (Clinical Research Ethics Committee decision number 2018/139; date: March 30, 2018. Written informed consent for all procedures was obtained from the parents or legal guardians of each child in the study.

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM Corporation, Armonk, New York, United States). The data were presented as the mean ± standard deviation, number (n) and percentage (%). The Shapiro-Wilk test was used to analyze the normal distribution assumption of the quantitative outcomes. Comparisons among the independent binary groups with normal distribution were made using Student's t test, and the analysis of variance (ANOVA) test was applied to hypervariable groups. The Mann-Whitney U test was used to compare pairs of groups of data that did not show normal distribution, and for over-variant groups. To compare the percentages of the qualitative data, the paired chi-square test and z-test were applied. P-values < 0.05 were considered statistically significant.

RESULTS

A total of 67 children with chronic gastritis were included in the study, comprising 41 girls (61.2%) and 26 boys (39%). Their mean age was 13.09 ± 3.5 years (range, 5-17.9).

All the patients were older than four years and they were all negative for stool infectious markers. The patients included had no evident history of any other disease, usage of any drugs, or positivity for inflammatory markers such as CRP and ESR.

Regarding the histopathological findings from the patients according to the Sydney classification, 38 patients (56.7%) had chronic active gastritis, 29 (43.3%) had chronic inactive gastritis,

28 (41.7%) had *Helicobacter pylori*-positive gastritis (n = 16 with chronic active gastritis and n = 12 with chronic inactive gastritis) and 39 (58.2%) had *Helicobacter pylori*-negative gastritis (n = 22 with chronic active gastritis and n = 17 with chronic inactive gastritis).

The mean FC level in the patients with chronic gastritis was 153.4 µg/g (range, 19.5-550); chronic active gastritis, 156.3 µg/g (range, 109-550); and chronic inactive gastritis, 150.95 µg/g (range, 19.5- 250). The FC levels were higher in patients with chronic active gastritis than in those with chronic inactive gastritis (P = 0.011).

The FC levels were significantly higher in *Helicobacter pylori*-positive patients with chronic active gastritis (157.1 µg/g) than in *Helicobacter pylori*-positive patients with inactive gastritis (152.3 µg/g) (P = 0.024). There was no significant difference in FC levels between chronic gastritis patients who were *Helicobacter pylori*-positive (154.7 µg/g) and *Helicobacter pylori*-negative (151.1 µg/g) (P = 0.486). However, among chronic active gastritis patients, the FC level was significantly higher in those who were *Helicobacter pylori*-positive than in those who were *Helicobacter pylori*-negative (P = 0.031) (**Table 1**).

Comparison of the gender, age, height Z score, body weight Z score, BMI Z score and laboratory findings from chronic gastritis patients showed that there was no statistically significant difference between FC levels > 50 µg/g (n = 42; 67%) and normal levels (**Table 2**).

Colonoscopy was performed later in all of the 42 children, in order to minimize false positivity of the test (due to IBD, drug intake or infectious diarrhea), and the results were found to be normal, both macroscopically and microscopically.

Comparison with the control groups

Among the IBD patients (n = 20), 12 (60%) were female and the mean age was 11.5 ± 3.5 years (range, 5-17.6). Thirteen patients (65%) had ulcerative colitis and 7 (35%) had Crohn's disease. The FC level of the IBD patients was evaluated at the time of diagnosis and the result was found to be 589.7 µg/g (range, 19.5-800).

Among the healthy children (n = 20), 11 were males (55%) and the mean age was 10.5 ± 3.3 years (range 5-15.1). The mean FC level in healthy children was 43.8 ± 25.4 µg/g (range, 19.5-144). There was no difference between the gastritis, IBD and healthy groups in terms of age and gender.

The FC level in the children with chronic gastritis was significantly higher than in the healthy group. (P = 0.001). Compared with the IBD patient group, the FC level was found to be significantly lower in the children with the chronic gastritis and healthy group (P < 0.001) (**Figure 1**).

DISCUSSION

Chronic gastritis is a chronic inflammatory process in the gastric mucosa and it is one of the most prevalent findings from endoscopy and histopathological examination.[15-16] In the present study, 67% of the patients with chronic gastritis had high FC levels. There are only limited numbers of studies evaluating the relationship between chronic gastritis and FC.[17-19] In the study by Manz et al.,[17] conducted on a total of 147 patients, the FC level was higher in patients with erosive gastritis than in normal patients. However, Montalto et al.[18] reported that there was no difference in FC levels between patients with gastritis (n = 61) (based on histopathological findings) and the healthy group.

Fecal calprotectin is a quantitative biomarker that detects inflammation of the gastrointestinal tract.[20-22] In the present study, the FC level in chronic gastritis patients was significantly higher than that of the healthy group. Colonoscopy was performed later on among the chronic gastritis patients with high FC levels, and the macroscopic and microscopic evaluation of these patients were normal. None of the patients were positive for stool infection markers, histories of chronic systemic disease, acute-phase reactants or drug usage. This supports the notion that the FC levels in this study represented an expression of chronic gastritis as the result of mucosal inflammation. The FC level was higher in the IBD patients than in the chronic gastritis patients. The higher FC levels in the IBD patients may be explained by the occurrence of more excessive inflammation, of greater severity, in the gastrointestinal tract than in the chronic gastritis patients, whose inflammation was limited to the gastric mucosa alone.

Table 1. Comparison of laboratory findings among patients with chronic active gastritis and chronic inactive gastritis

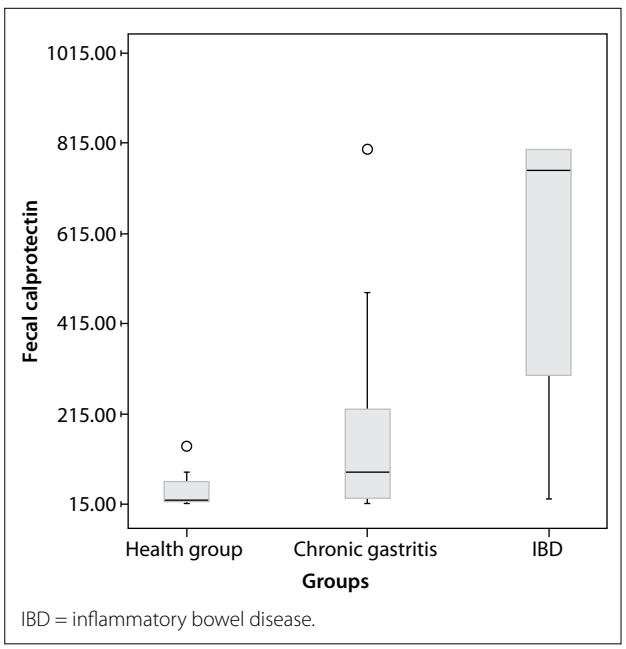
Total (n = 67)	Chronic active gastritis (n = 38)			Chronic inactive gastritis (n = 29)		
	HP (+) (n = 16)	HP (-) (n = 22)	P-value	HP (+) (n = 12)	HP (-) (n = 17)	P-value
Fecal calprotectin (µg/g)	157.1 (120-550)	153.4 (109-521)	0.031	152.3 (54-175)	149.6 (19.5-196)	0.423
C-reactive protein (mg/l)	9.4 ± 2.9	9.1 ± 3.1	0.416	7.8 ± 3.3	7.0 ± 2.8	0.343
Erythrocyte sedimentation rate (mm/h)	13.6 ± 3.2	12.9 ± 4.3	0.234	15.6 ± 3.8	15.2 ± 3.1	0.212
White blood cells (x 10^3/ul)	6.6 ± 2.9	6.1 ± 2.3	0.214	5.8 ± 2.8	5.6 ± 2.4	0.112
Hemoglobin (g/dl)	12.8 ± 0.6	12.7 ± 0.3	0.323	13.4 ± 1.6	13.1 ± 1.4	0.314
Albumin (g/dl)	4.6 ± 0.7	4.1 ± 0.9	0.447	4.8 ± 1.4	4.1 ± 1.8	0.178
Thrombocytes (x 10^3/ul)	386 ± 54	372 ± 46	0.349	329 ± 157	321 ± 168	0.456

HP = *Helicobacter pylori*.

Table 2. Comparison of demographic findings among patients with chronic gastritis

Total (n = 67)	FC > 50 μg/g (n = 42)	FC ≤ 50 μg/g (n = 25)	P-value
Age (year)	13.1 ± 4.08	13.1 ± 3.6	0.614
Gender (female/male)	27/15	14/11	0.606
Height Z score	-0.53 ± 0.9	-0.48 ± 0.8	0.696
Weight Z score	-0.63 ± 0.9	-0.53 ± 1.2	0.166
Hemoglobin (g/dl)	12.8 ± 0.5	13.0 ± 1.5	0.301
White blood cells (x 10^3/ul)	6.4 ± 2.8	5.7 ± 2.9	0.120
Thrombocytes (x 10^3/ul)	379 ± 46	325 ± 167	0.509
C-reactive protein (mg/l)	9.2 ± 3.2	7.4 ± 3.1	0.135
Erythrocyte sedimentation rate (mm/h)	13.1 ± 4.2	15.4 ± 3.5	0.872
Albumin (g/dl)	4.3 ± 0.5	4.5 ± 1.0	0.179

FC = fecal calprotectin.



IBD = inflammatory bowel disease.

Figure 1. Evaluation of fecal calprotectin between groups.

In this study, the FC level in the children with chronic active gastritis was higher than the level in the children with chronic inactive gastritis. The presence of neutrophils due to chronic inflammatory cells indicates the presence of chronic active gastritis.[13] The elevated FC levels in chronic active gastritis may be due to mucosal injury that is mediated by increased levels of mucosal macrophages and neutrophils. However, Montalto et al.[18] did not find any significant difference in FC levels between patients with chronic active gastritis and those with chronic inactive gastritis.

Helicobacter pylori infection is commonly acquired in childhood and affects one third of all children worldwide.[23] Its prevalence is low in developed countries but high in developing countries.[24] The standard method for diagnosing *Helicobacter pylori* infection is endoscopic biopsy of the gastric antrum.[25] In the present study, although there was no significant difference in FC levels between *Helicobacter pylori*-positive and *Helicobacter pylori*-negative patients, the FC levels of *Helicobacter pylori*-positive chronic active gastritis patients were significantly higher than those of *Helicobacter pylori*-negative chronic active gastritis patients. Sýkora et al.[19] found that the FC levels of patients with *Helicobacter pylori*-positive gastritis were normal, in comparison with healthy children. Summerton et al.[26] showed that in patients with upper gastrointestinal inflammation such as gastritis and duodenitis, their FC levels were normal. Additionally, in the present study, the FC levels were significantly higher in *Helicobacter pylori*-positive patients with chronic active gastritis than in *Helicobacter pylori*-positive patients with chronic inactive gastritis.

Helicobacter pylori infiltrates neutrophils, lymphocytes, monocytes, mast cells and eosinophils in the gastric mucosa.[13] The reason why significantly higher FC levels were observed only in *Helicobacter pylori*-positive patients with chronic active gastritis may have been because of greater severity of tissue damage caused by *Helicobacter pylori* in chronic active gastritis, through inducing neutrophil activation. In agreement with the data presented in the literature, our results in this study showed that the gastric inflammation was correlated with the *Helicobacter pylori* infection.[27]

There are, however, some limitations to this study. While the relationship between histopathological findings and FC was evaluated, the relationship between the patients' clinical symptoms and FC was not evaluated. Another limitation of this study was the low number of patients.

CONCLUSION

We found higher FC levels in patients with chronic active gastritis than in patients with chronic inactive gastritis. Additionally, the FC levels were higher in patients with chronic gastritis than in the healthy group and lower than in the IBD group. In the chronic gastritis patients, inflammation in the gastric mucosa caused a significant increase in FC level, compared with the healthy control group. However, the increment in FC levels in the chronic gastritis patients was lower than that of the FC levels in the IBD group, due to the lack of widespread involvement of the gastrointestinal tract inflammation in chronic gastritis. In the children with chronic abdominal pain and high FC levels, treatment of gastritis can be done firstly and then, if the FC level remains the same or rises, endoscopy with colonoscopy can be performed. Further studies in a larger study group are needed in order to be able to use FC as a screening tool for chronic gastritis.

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Address for correspondence:
Fatma Demirbaş
Department of Pediatric Gastroenterology, Hepatology and Nutrition,
Ondokuz Mayis University Faculty of Medicine
Kurupelit/Samsun 55200, Turkey
Tel. +905368302611
E-mail: fatmademirbas81@hotmail.com

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Relationship between frailty, social support and family functionality of hemodialysis patients: a cross-sectional study

Diana Gabriela Mendes dos Santos[I], Joice Marques Pallone[II], Carlene Souza Silva Manzini[III], Marisa Silvana Zazzetta[IV], Fabiana de Souza Orlandi[V]

Department of Gerontology, Centro de Ciências Biológicas e da Saúde (CCBS), Universidade Federal de São Carlos (UFSCar), São Carlos (SP), Brazil

[I]MD. Master's Student, Department of Nursing, Universidade Federal de São Carlos (UFSCar), São Carlos (SP), Brazil.
https://orcid.org/0000-0003-1572-5322

[II]BSc. Undergraduate Student, Department of Gerontology, Universidade Federal de São Carlos (UFSCar), São Carlos (SP), Brazil.
https://orcid.org/0000-0003-4955-6547

[III]PhD. Nurse, Department of Nursing, Universidade Federal de São Carlos (UFSCar), São Carlos (SP), Brazil.
https://orcid.org/0000-0001-6195-4252

[IV]MD, PhD. Associate Professor, Department of Gerontology, Universidade Federal de São Carlos (UFSCar), São Carlos (SP), Brazil.
https://orcid.org/0000-0001-6544-767X

[V]MD, PhD. Adjunct Professor, Department of Gerontology, Universidade Federal de São Carlos (UFSCar), São Carlos (SP), Brazil.
https://orcid.org/0000-0002-5714-6890

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ABSTRACT

BACKGROUND: The population with chronic kidney disease (CKD) is more predisposed to early development of frailty. Although the concept of frailty is well established from a physical point of view, it is not an exclusively physical syndrome. It can be characterized as an interaction of physical, psychological and social factors.

OBJECTIVE: To ascertain the relationship between frailty, social support and family functionality among CKD patients undergoing hemodialysis.

DESIGN AND SETTING: Correlational, cross-sectional and quantitative study conducted at a service in the interior of the state of São Paulo.

METHODS: This study included 80 patients with CKD who were on hemodialysis. The participants were interviewed individually, with application of the following instruments: sociodemographic and economic characterization, Tilburg Frailty Indicator, Medical Outcomes Study and Family APGAR. Females and white ethnicity predominated among the participants, and their mean age was 59.63 ± 15.14 years.

RESULTS: There was high prevalence of frailty (93.8%). Although there was a difference in scores for the dimensions of social support between the frail group and the non-frail group, only family functionality reached a statistically relevant difference. There was a significant correlation between physical frailty, social support and family functionality.

CONCLUSIONS: Presence of frailty is related to the social support and family functionality of patients with CKD undergoing hemodialysis.

INTRODUCTION

According to a Brazilian consensus, frailty consists of a state of physiological age-related vulnerability that is produced through reduction of homeostatic reserves and reduced capacity of the organism in response to negative health outcomes, such as hospital admissions, falls and functional loss, with increased likelihood of death.[1]

Despite being a complex syndrome, frailty can be reversed or mitigated through effective interventions, but for this to occur, it is recommended that screening for frailty should be done early, while patients are still in care.[2] Although the concept of frailty is well established from the physical point of view, it is not an exclusively physical syndrome. It also encompasses biopsychosocial factors that depend on a holistic view of frail individuals.[3,4]

The population with chronic kidney disease (CKD) has high incidence and prevalence of physical and cognitive impairment, and is more predisposed to early development of frailty.[5] In addition, the process of CKD, from diagnosis to treatment with hemodialysis, leads to several biopsychosocial changes in patients' lives.[6]

Mansur, Damasceno and Bastos carried out a study among 146 patients with CKD undergoing conservative treatment (CT), hemodialysis (HD) or peritoneal dialysis (PD), with the aim of assessing the prevalence of frailty and the factors associated with it.[7] They pointed out that frailty occurs frequently among patients with CKD undergoing conservative or dialysis treatment, even among those who are not elderly. In addition, a systematic review by Chowdhury et al. showed that frailty was associated with an increased risk of mortality and hospitalization.[8]

In view of this scenario, screening for frailty among patients with CKD is extremely important: not only for elderly individuals but also for younger ones. At early stages of kidney disease, individuals

may present frailty that, if untreated, may lead to falls, loss of quality of life, earlier hospitalizations and higher numbers of deaths.

In view of the above, the present study was conducted with the aim of answering the following questions: What is the level of frailty among patients with CKD undergoing hemodialysis? What social characteristics (material support, affective support, emotional support, positive social interaction support, information support and family functionality) are associated with frailty?

OBJECTIVE

Given the scenario presented, the aim of this study was to evaluate and ascertain the relationship between frailty, social support and family functionality among patients with CKD undergoing hemodialysis.

METHODS

Design

This study was characterized as correlational, cross-sectional and quantitative. This investigation was carried out in a renal replacement therapy unit in the municipality of São Carlos, in the interior of the state of São Paulo, Brazil, in 2019.

Sample

The unit where the study was carried out serves 180 patients. All patients who fulfilled the inclusion criteria (n = 150) were invited to participate in the study and those who accepted made up the sample of the present study, totaling 80 participants. The inclusion criteria were that the subjects needed to have a medical diagnosis of CKD, be under hemodialysis and have preserved oral communication. The exclusion criterion was presentation of dementia, according to the medical records.

Data collection

The data collection process took place as follows. An initial contact was made with the patients, at which the research was explained and they were invited to participate in the study. Patients who agreed to participate signed a free and informed consent statement. At their next hemodialysis session, and specifically in the first two hours (in which patients present with fewer hemodynamic changes), evaluations were started using a sociodemographic and economic characterization and the Tilburg Frailty Indicator, Medical Outcomes Study Social Support Scale and Family APGAR.

The Tilburg Frailty Indicator (TFI) has the aim of assessing frailty and is considered to be one of the best instruments for this purpose, since it has three dimensions (physical, psychological and social). It was developed by Gobbens et al. in the Netherlands and was adapted for use in Brazil by Santiago et al.[9,10] Its scores can range from 0 to 15 points, such that scores < 5 indicate frailty.

The Medical Outcomes Study Social Support Scale was developed by Shernoure and Stewart and was validated for use in Brazil by Andrade in 2001. It has the objective of evaluating social support.[11,12] It consists of 19 items that are subdivided into five dimensions of social support: material, affective, emotional, informative and positive social interaction. The total score from this instrument is obtained through scores for each domain ranging from 20 to 100 points. The closer to 100 that the score is, the higher the level of social support is. The responses to each question are scored as follows: never (1), rarely (2), sometimes (3), almost always (4) and always (5). These scores are added together in each dimension. For the Affective Social Support dimension alone, the score obtained should be divided by 15 and then multiplied by 100.[11]

Lastly, the Family APGAR has the aim of ascertaining whether there is any family dysfunction. This instrument was created by Smilkstein[13] and was adapted for use in Portuguese by Duarte.[14] It consists of five questions with four answer options: never (0 points), rarely (1 point), sometimes (2 points), almost always (3 points) and always (4 points). The total scores are interpreted as follows: high family dysfunction (1-8 points), moderate family dysfunction (9-12 points) and good family functionality (13-20 points).

Data analysis

The statistical treatment of the data was performed with the aid of the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM Corporation, Armonk, New York, United States). Descriptive analyses were performed and tables were prepared, containing central trend data (average, minimum and maximum) and dispersion measurements (standard deviation). The Kolmogorov-Smirnov test was performed, which showed that the data did not have normal distribution; hence, nonparametric tests were used.

Spearman's correlation coefficients were calculated to investigate relationships between continuous variables. The magnitude of correlations was classified as proposed by Levin and Fox (2004): weak (< 0.3); moderate (0.3 to 0.59); strong (0.6 to 0.9); or perfect (1.0).

To compare psychosocial variables, according to the level of frailty measured using the TFI (non-frail or frail), the Mann-Whitney test was used. The significance level adopted for the statistical tests was 5% ($P \leq 0.05$).

Ethical considerations

The protocol for this study was approved by the ethics committee of our institution (CAAE: 18828419.0.0000.5504, number 3.535.236; date: August 27, 2019) and all the subjects signed an informed consent statement.

RESULTS

This study included 80 patients undergoing hemodialysis treatment. Regarding frailty assessed through the Tilburg Frailty

Indicator instrument, 75 of the participants were considered frail. Among these frail patients, the following characteristics were more prevalent: female, white ethnicity, with a partner and retired. The subjects' average schooling was 6.63 years and they had had 4.51 years of hemodialysis. The most prevalent comorbidity was arterial hypertension, followed by diabetes mellitus (**Table 1**).

Among the non-frail patients (n = 5), males, white ethnicity and a steady partner were more prevalent. Their average education level was 7.20 years, the average length of time on hemodialysis was 4.76 years and all of them were retired. Among the comorbidities, four individuals were hypertensive (**Table 1**).

Social support was assessed using the Medical Outcomes Study Social Support Scale. Frail patients obtained lower scores for all dimensions of the Medical Outcomes Study Social Support Scale, in relation to non-frail patients. In spite of this, the averages found were relatively high, using the score range from 20 to 100 points as a parameter. Among the frail patients, the domain with the highest score was Material Support (84.16) and the one with the worst score was Positive Social Interaction Support (72.93). Among the patients considered non-frail, the domain with the highest score was Emotional Support (97.00) and the one with the worst score was Information Support (72.27) (**Table 3**).

To assess family functionality, the Family APGAR was used. It was found that frail participants scored lower than non-frail participants. Despite this, both groups showed good family functionality. Although there was a difference in scores for the dimensions of the Medical Outcomes Study Social Support Scale between the frail group and the non-frail group, only family functionality reached a statistically relevant difference (**Table 3**).

In the correlation analyses, frailty showed moderate correlations with material support, affective support, emotional support, positive interaction support, information support and family functionality, all with statistical significance (**Table 4**).

The physical dimension of the TFI instrument showed negative correlations of moderate magnitude with material support, emotional support, information support and family functionality. The psychological dimension of the TFI instrument presented negative correlations of moderate magnitude with emotional support, information support and family functionality (**Table 4**).

DISCUSSION

The sociodemographic characteristics found in the present study have also been pointed out in other investigations that are available in the literature, in Brazil and internationally. One of the characteristics that was distinct between the groups was sex, which was predominantly female in the frail group. According to a study by Fried et al., which included 5,317 elderly patients without CKD, women were more frail than men, regardless of age.[15]

Table 1. Sociodemographic categorical variables and economic characteristics. São Carlos (SP), Brazil, 2019 (n = 80)

Variable	Categories	Frail (n = 75)	Non-frail (n = 5)	P-value
Gender	Male	32	4	0.104
	Female	43	1	
Ethnicity	White	48	4	0.502
	Black	20	0	
	Brown	6	1	
	East Asian	1	0	
Marital status	With a fixed partner	48	4	0.760
	No fixed partner	26	1	
Occupation	Retired	52	5	0.708
	Absent*	10	0	
	Housewife	10	0	
	Others	2	0	
Comorbidities				
Diabetes	No	45	5	0.074
	Yes	30	0	
Hypertension	No	31	4	0.091
	Yes	44	1	
Other types of Comorbidities	No	68	4	0.441
	Yes	7	1	

*Absent from work, as approved by the National Institute of Social Security.

Table 2. Sociodemographic continuous variables and economic characteristics. São Carlos (SP), Brazil, 2019 (n = 80)

Variable	Mean	P-value
Age		
Frail (n = 75)	60.00	0.825
Non-frail (n = 5)	59.60	
Education level		
Frail (n = 75)	6.63	0.77
Non-frail (n = 5)	7.20	
Years on hemodialysis		
Frail (n = 75)	4.51	0.58
Non-frail (n = 5)	4.76	

Table 3. Descriptive statistics of the Tilburg Frailty Indicator (TFI), Family APGAR and Medical Outcomes Study Social Support Scale (MOS). São Carlos (SP), Brazil, 2019 (n = 80)

Instrument	Category	n	Mean	P-value
MOS				
Material support	Frail	75	84.16	0.278
	Non-frail	5	95.00	
Affective support	Frail	75	78.84	0.146
	Non-frail	5	96.00	
Emotional support	Frail	75	75.47	0.058
	Non-frail	5	97.00	
Positive social interaction support	Frail	75	72.93	0.058
	Non-frail	5	95.00	
Information support	Frail	75	75.27	0.034
	Non-frail	5	96.00	
APGAR	Frail	75	13.79	0.004
	Non-frail	5	19.60	

Table 4. Spearman's correlation of Tilburg Frailty Indicator (TFI) with Material Support (APM), Affective Support (APA), Emotional Support (APE), Positive Social Interaction Support (APISP), Information Support (API) and Family Functionality (APGAR). São Carlos (SP), Brazil, 2019 (n = 80)

		APM	APA	APE	APISP	API	APGAR
TFI total	r	-0.485	-0.559	-0.565	-0.481	-0.0543	-0.550
	P-value	**0.008**	**0.003**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Physical dimension	r	-0.307	-0.262	-0.392	-0.288	-0.366	-0.305
	P-value	**0,006**	**0.019**	**< 0.001**	**0.010**	**< 0.001**	**0.006**
Psychological dimension	r	-0.182	-0.220	-0.301	-0.246	-0.303	-0.385
	P-value	**0.006**	**0.019**	**< 0.001**	**0.010**	**< 0.001**	**0.006**
Social dimension	r	-0.106	-0.197	-0.226	-0.275	-0.264	-0.142
	P-value	**0.006**	**0.019**	**< 0.001**	**0.010**	**< 0.001**	**0.006**

Another study that corroborates our results is the one carried out by Shilipak et al., who compared 5,808 elderly patients with and without CKD and found higher prevalence of frailty among women, regardless of CKD status.[16] The most prevalent comorbidity in our study was arterial hypertension. This characteristic was also noted in the study by Mansur et al., among 61 patients with CKD who were receiving pre-dialysis treatment, of whom 56.1% had hypertension.[17]

The population with CKD has high incidence and prevalence of physical and cognitive impairment and is more predisposed to early development of frailty, which requires screening before old age is reached.[18,19] The high prevalence of frailty found in our study (93.8%) was also seen in a systematic review carried out by Chowdhury et al., in which the prevalence of frailty ranged from 7% among community-dwellers (CKD stages 1-4) to 73% in a cohort of patients on hemodialysis.[8]

Gesualdo conducted a study with the objective of identifying the factors associated with frailty among adults and elderly individuals with CKD who were undergoing hemodialysis. Most of the adults were found to be pre-frail: 54.84% according to Fried's frailty phenotype; and 58.06% according to the Tilburg Frailty Indicator. Most of the elderly subjects were frail: 64.44% and 73.33%, according to Fried's frailty phenotype and the TFI, respectively.[5]

This has also been seen in other investigations, such as the cross-sectional study conducted by Bessa, among 191 elderly people who comprised a non-probabilistic sample. In this population, 68.8% were women and the mean age was 75.8 years.[20] Regarding frailty, 50.0% of the participants were considered frail according to the Tilburg Frailty Indicator. Those findings corroborate the results from the present study, in which frailty was highly prevalent among our patients with CKD undergoing hemodialysis, according to the TFI instrument, comprising 93.8% of the sample.

The psychosocial alterations seen in our study were also observed in a study conducted by Mulasso et al., among 2010 elderly people in an Italian community, who aimed to investigate associations of frailty and psychosocial factors with autonomy in daily activities.[21] The objectives of their study were to evaluate differences in psychosocial factors between robust, pre-frail and frail individuals, and to investigate whether frailty showed any interactive effect with empirically identified groupings of psychosocial factors, with regard to autonomy in activities of daily living (ADLs). In the results, it was found that 30% of the individuals were robust, 55% pre-frail and 14% frail. Covariance analyses showed that there were differences in all psychosocial variables, in relation to frailty. That study demonstrated the relationship between physical frailty and social frailty and highlighted the importance of psychosocial factors in detecting frailty.

One of the social factors that can impact people's lifespan is social support. This can be evaluated and classified as perceived support or received support. According to Cramer, Henderson and Scott, perceived support relates to the people that the individual perceives as available in case of need, while received support is social support in the form in which it is received, even when the individuals who provide the support are not identified.[22]

Social support, in turn, is offered by the social network that encompasses the family and neighbors, among others. The family plays an essential role in individuals' social networks, and family rearrangements promote intergenerational coexistence. This experience can contribute positively to the social support received.[23] Thus, it is understood that each family has functionality and systematics that aim to fulfill and harmonize its essential functions, in a manner appropriate to the identity and tendencies of its members, through acting realistically in relation to the dangers and opportunities that prevail in the social environment.[10]

The association between family functionality and social support relationships is found in other studies, such as Park et al. These authors aimed to evaluate whether loneliness mediated the relationship between social involvement and depressive symptoms and to determine how age moderated the effect of mediation.[24] The data in this study came from a survey of adults living in the community aged 18 years or older in South Korea, from March to April 2017, in which a total of 1,017 respondents were divided into three age groups (18 to 44, 45 to 64 and 65 years or over). The mediating effect of loneliness was tested with regard to

each of three variables relating to social engagement (family network, network of friends and perceived community support) and depressive symptoms. The results showed age-related differences in mediation. The family network had a more pronounced effect in relation to loneliness in the oldest group, while the size of the network of friends significantly predicted loneliness among younger adults. The youngest and oldest groups felt less lonely when they had higher levels of community support; the middle age group was not influenced by the effects of mediation.

This study presented the limitation of selection of the sample by convenience. This makes it difficult to generalize the data. In addition, the imbalance between the frail and non-frail groups made it impossible to carry out logistic regression analyses.

CONCLUSION

Based on the proposed objectives and the results obtained, it can be concluded that that the presence of frailty was related to social support and family functionality.

Thus, it is important to highlight the need for early screening of frailty in this population. Moreover, there is a need to create public policies that meet the social and psychological demands of these patients, thereby preventing and managing injuries.

From the perspective of expansion of this investigation, longitudinal studies on monitoring the levels of physical and social frailty are desirable. Furthermore, differences in frailty factors between the forms of treatment of CKD should be investigated.

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Address for correspondence:
Fabiana de Souza Orlandi
Departamento de Gerontologia, Universidade Federal de São Carlos (UFSCar)
Rod. Washington Luiz, s/nº
São Carlos (SP) — Brasil
CEP 13565-905
Tel. (+55 16) 3306-6673
E-mail: forlandi@ufscar.br

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WALANT versus intravenous regional anesthesia for carpal tunnel syndrome: a randomized clinical trial

Aldo Okamura[I], Vinicius Ynoe de Moraes[II], Marcela Fernandes[III], Jorge Raduan-Neto[IV], João Carlos Belloti[V]

Hospital Alvorada Moema, United Health, São Paulo (SP), Brazil; and Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]MD. Doctoral Student and Hand Surgeon, Discipline of Hand and Upper Limb Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Hand Surgeon, Hand Surgery Service, Hospital Alvorada Moema, United Health, São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0115-2236

[II]MD, PhD. Hand Surgeon, Discipline of Hand and Upper Limb Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Hand Surgeon, Hand Surgery Service, Hospital Alvorada Moema, United Health, São Paulo (SP), Brazil.
https://orcid.org/0000-0002-4933-4007

[III]MD, PhD. Hand Surgeon, Discipline of Hand and Upper Limb Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Hand Surgeon, Hand Surgery Service, Hospital Alvorada Moema, United Health, São Paulo (SP), Brazil.
https://orcid.org/0000-0003-1646-6764

[IV]MD, PhD. Hand Surgeon, Discipline of Hand and Upper Limb Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Hand Surgeon, Hand Surgery Service, Hospital Alvorada Moema, United Health, São Paulo (SP), Brazil.
https://orcid.org/0000-0002-0476-8768

[V]MD, MSc, PhD. Full Professor, Discipline of Hand and Upper Limb Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Full Professor, Hand Surgery Service, Hospital Alvorada Moema, United Health, São Paulo (SP), Brazil.
https://orcid.org/0000-0003-3396-479X

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ABSTRACT

BACKGROUND: There are several anesthetic techniques for surgical treatment of carpal tunnel syndrome (CTS). Results from this surgery using the "wide awake local anesthesia no tourniquet" (WALANT) technique have been described. However, there is no conclusive evidence regarding the effectiveness of the WALANT technique, compared with the usual techniques.

OBJECTIVE: To evaluate the effectiveness of the WALANT technique, compared with intravenous regional anesthesia (IVRA; Bier's block), for surgical treatment of CTS.

DESIGN AND SETTING: Randomized clinical trial, conducted at Hospital Alvorada Moema and the Discipline of Hand Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.

METHODS: Seventy-eight patients were included. The primary outcome was measurement of perioperative pain through a visual analogue scale (VAS). The secondary outcomes were the Boston Questionnaire score, Hospital Anxiety and Depression Scale (HADS) score, need for use of analgesics, operating room times, remission of paresthesia, failures and complications.

RESULTS: The WALANT technique (n = 40) proved to be superior to IVRA (n = 38), especially for controlling intraoperative pain (0.11 versus 3.7 cm; P < 0.001) and postoperative pain (0.6 versus 3.9 cm; P < 0.001). Patients spent more time in the operating room in the IVRA group (59.5 versus 46 minutes; P < 0.01) and needed to use more analgesics (10.8 versus 5.7 dipyrone tablets; P = 0.02). Five IVRA procedures failed (5 versus 0; P = 0.06).

CONCLUSIONS: The WALANT technique is more effective than IVRA for CTS surgery.

TRIAL REGISTRY: NCT02986347. Clinical Question/ Level of Evidence: Therapeutic, II.

INTRODUCTION

In most countries, surgical treatment of carpal tunnel syndrome (CTS) is usually performed in hospitals, using the open (classical) surgical technique that is preferred by specialists.[1-3] Anesthetic technique preferences vary among surgeons. Intravenous regional anesthesia (IVRA), as described by Bier, is in widespread use: it is the second most popular technique among American specialists and the most popular in Brazil.[4,5] However, over the last decade, performance of this surgery using the "wide awake local anesthesia no tourniquet" (WALANT) technique has been described. This has proven to be a safe procedure with lower costs.[6-8]

Recent studies have compared surgical outcomes from CTS treatments, including the costs of WALANT versus general anesthesia; local anesthesia with adrenaline in association with sedation; and tourniquet application with monitored anesthetic care (MAC) and intravenous sedation. The conclusion from these studies was that local anesthesia was more effective and presented lower cost.[9-11] However, in evaluating the quality of evidence, we noticed that there was still a need for level I studies on this topic.

OBJECTIVE

The aim of this study was to randomly evaluate the effectiveness of two anesthesia methods for CTS: the WALANT technique and the IVRA technique.

METHODS

Ethics

This study was approved under institutional review board (IRB) number 61597316.4.0000.5505 on November 28, 2016. The trial protocol was registered *a priori* under the number NCT02986347 (http://clinicaltrials.gov).

Study design and setting

This was a randomized clinical trial with parallel groups (allocation ratio 1:1). It was conducted in accordance with the CONSORT statement for trial reporting. The study was conducted at two patient recruitment centers: Hospital Alvorada Moema and the Discipline of Hand Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil.

Inclusion criteria

Adult patients presenting with idiopathic CTS without prior hand surgery were included in this study. The diagnosis made through clinical evaluation and confirmed by means of electromyography.

A – The clinical criteria for diagnosing CTS were the presence of at least four of the following criteria, in accordance with CTS-6.[12]

1. Paresthesia in the territory of the median nerve.
2. Night paresthesia of the hand.
3. Decreased hand strength with thenar muscle hypotrophy.
4. Positive Tinel's sign at the wrist.
5. Positive Phalen test.
6. Loss of two-point discrimination, greater than 6 mm.

B – The indications for surgical treatment were either of the following:

1. Failure of conservative treatment for at least three months, use of night splint and one local corticosteroid injection.
2. Motor impairment detected through clinical examination and proven by means of an electromyographic test. The criteria that we used were the presence of sensory and motor involvement, stratified as moderate or severe CTS, as described by Padua.[13]

C – Patients were included if their pre-anesthesia evaluation categorized them as ASA I or II, in accordance with the American Society of Anesthesiologists (ASA) classification.

Exclusion criteria

The following individuals were excluded from this study:

1. Pregnant and postpartum women.
2. Patients who refused the terms of the research consent statement.
3. Patients who declared that they had previously undergone hand or wrist surgery.

Intervention

Out of the 85 patients eligible for this study, 78 were included and 72 (WALANT: 38; IVRA: 34) completed the 12-week follow-up. Four IVRA failures were found. The losses were balanced between the groups (WALANT, two losses; IVRA, four losses) **(Figure 1)**.

Preoperative care

The participants in both groups were admitted to the hospital approximately two hours before the surgical procedure and intravenously received 100 mg ketoprofen and 500 mg dipyrone diluted in 250 ml of saline solution in the contralateral limb, for preemptive analgesia. In patients with known sensitivity to these drugs, tenoxicam (20 mg) and tramadol (50 mg) were used as substitutes.

In the surgical suite, all patients were adequately positioned in the supine position, with a cardiac monitor and noninvasive blood pressure and pulse oximetry. No prophylactic antibiotic was used.

Intervention

WALANT technique

Anesthesia was administered by one of three hand surgery specialists who were already familiar with the WALANT technique.[5] At the time of admission to the surgical suite, each patient received a 10 ml to 15 ml infusion of an anesthetic solution. This solution was composed of 1% lidocaine, with epinephrine at proportions of 1:100,000.

Initially, 5 ml of the solution was slowly applied in the wrist flexion crease region between the median and ulnar nerves, just below the skin and subfascial plane. The needle was moved slowly while observing the swelling of the tissues, and was redirected to the radial side of the proximal palmar region for injection of another 2-3 ml of the solution into the subcutaneous layer. The remaining 3-7 ml was injected into the subdermal plane, anteriorly to the transverse carpal ligament. The approximate time taken for the injection was about five minutes, with care to keep the needle at a margin of 5 mm from the already anesthetized region. During infiltration of the solution, swelling of the tissues and pallor of the skin were observed. No exsanguination or tourniquet of the limb was used.

IVRA technique - intravenous regional anesthesia (Bier's block)

The IVRA technique was performed by the anesthesia team in accordance with to the following procedure: 1) Venous puncture and catheterization with a catheter as distal as possible in the limb to be operated; 2) Exsanguination with an elastic Esmarch bandage from distal to proximal; 3) A second Esmarch bandage was placed in the proximal portion of the arm; 4) Slow injection of 40 ml of lidocaine without epinephrine at 0.5% (maximum 3-4 mg/kg); 5) After injection, the arm was lowered to the level of the table and the intravenous cannula was removed; 6) The tourniquet was removed after the end of the surgery, and 30 minutes after injection of the anesthetic; 7) Removal of the tourniquet was performed slowly, while maintaining serial ischemic subocclusions, totaling three minutes for the procedure.[14]

Carpal tunnel syndrome surgery

Both groups underwent treatment using the same surgical technique. The surgery was performed by a hand surgery team with

more than 10 years of surgical experience. A longitudinal palmar incision was made, distal to the wrist flexion plantar fold, centered on the cubital edge of the ring finger in flexion, of length around 5 cm, followed by dissection plane by plane until all the transverse carpal ligament and proximal forearm fascia had been sectioned, followed by inspection of the carpal tunnel. We did not perform routine neurolysis.

Postoperative analgesia

During the in-hospital period, the participants in both groups received analgesia in accordance with the following protocol:

- Mild pain (up to 2.0 visual analogue scale [VAS] points): no medication.
- Moderate pain (between 2.1 and 5.0 VAS points): 500 mg of dipyrone intravenously, with a maximum dose of 4000 mg/day.
- Severe pain (5.1 to 9.0 VAS points): 50 mg of tramadol intravenously, with a maximum dose of 400 mg/day.
- Extreme pain (9.1-10 VAS points): 2 mg of morphine, with a maximum dose of 60 mg/day.

The patients were discharged 12 hours after the end of surgery.

Outcomes

The outcome assessments were performed by a blinded researcher who was not directly linked to the study. These evaluations took place within the following timeframes:

a. Office visit prior to surgery, on the date of scheduling the surgery.
b. Postoperative period: 15 minutes after tourniquet release, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 7 days, 14 days, 1 month and 3 months.

Primary outcome

Pain assessment was done through a visual analogue scale (VAS).[15] Pain was measured preoperatively and in the immediate postoperative period: 2 hours, 4 hours, 6 hours, 8 hours and 12 hours after completion of the surgery. The patients were instructed to measure their own pain level using the VAS. The score is determined by measuring the distance (mm) on the 100 mm line between the "painless" anchor and the patient's indication, thus providing scores from 0 to 100. We considered that

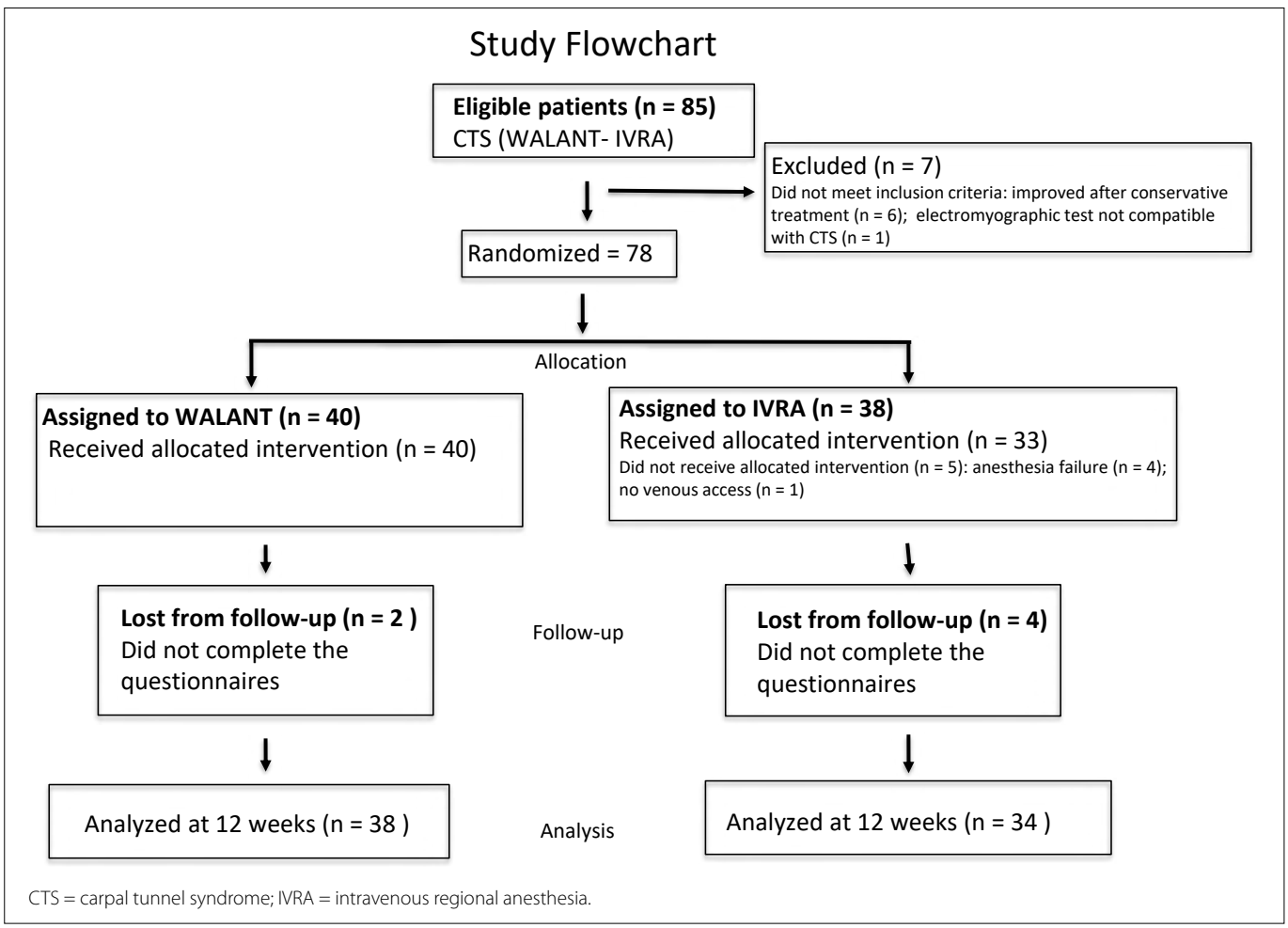

Figure 1. Study flowchart.

differences between measurements of more than two points were clinically relevant.[15]

Secondary outcomes

The following secondary outcomes were measured:

Use of analgesics - From hospital discharge until the patient's first return visit (seventh postoperative day), the number and type of analgesic drugs used by patients were recorded in relation to previous orientation.

Anxiety and depression - The Hospital Anxiety and Depression Scale (HADS) score[16,17] was assessed at the time of patient admission and at the first outpatient return (seventh postoperative day). HADS consists of 14 self-reported questions: seven of them referring to anxiety (HADS-A) and seven to depression (HADS-D). The scores range from 0 to 21 points for each subscale and a score of 9 or higher defines a likely diagnosis of anxiety and depression. With this cutoff point, the instrument presents sensitivity for anxiety of 93.7% and for depression of 84.6%; and specificity for anxiety of 72.6% and for depression, of 90.3%.[17]

Self-reported function - The Boston Carpal Tunnel Questionnaire (BCTQ)[18,19] was used for evaluations both preoperatively and postoperatively (three months). This is a disease-specific questionnaire for CTS that is self-administered. It evaluates the disease on two subscales: 1) severity of symptoms (SSS); and 2) functional status of patients (FSS) with CTS.

Paresthesia remission - After the surgical procedure and at the end of the first week and the third month of follow-up, an evaluation was made to verify remission of the paresthesia that patients had complained of preoperatively.

Complications and failures - All clinical events that occurred due to anesthesia and which required additional interventions not foreseen in this protocol were considered to be complications. We considered that failure of anesthesia had occurred when there was a need to change the anesthetic technique to which the patient had been allocated or when there was a need for surgical reintervention within the first three months after surgery. Patients who at some time presented complications or failures were given the usual necessary treatment and their results were computed within the group to which that had initially been allocated.

Sample calculation - We aimed to detect a minimum difference of two points (standard deviation, SD, of three points) on the VAS scale. This specification was derived from a systematic review that indicated that the minimum clinically important difference for VAS scales ranged from 0.8 to 4.0.[20] We considered an 80% power and alpha of 5%. Considering also an attrition loss of 10%, we derived a sample size of 78 patients for inclusion in the study.

Randomization and allocation - The randomization sequence was generated by means of software (http://www.randomizer.org). The allocation was performed using 78 opaque sealed envelopes marked only with numbering. These were opened by a person not directly involved in the study. Each envelope was only opened after a patient entered the surgical suite.

Statistical methods - We presented the data as means and standard deviations and proportions. As a method for confirming the effectiveness of randomization, the baseline data were compared when stratified according to the allocation group. The assumption of normality of the distribution was made by applying the Shapiro-Wilk test and by visual judgment. The chi-square test was used to analyze the results from both groups in relation to the categorical variables. Student's t test (parametric) or the Mann-Whitney U test was used to compare the groups in relation to the continuous variables. The significance level was set at 5%. The analysis was done in accordance with intention-to-treat principles.

RESULTS

The sample consisted mostly of women (97.2%), with a mean age of 51 years. The patients had had their disease for a mean time of 4.5 years and most cases were considered to be moderate, as staged using electromyography. Additional baseline data demonstrated that the randomization methods presented adequate performance (**Table 1**), which thus resulted in balanced groups.

Pain (VAS)

There were statistical differences between the groups at the following times: transoperative period, immediate postoperative period, 2 hours, 4 hours, 6 hours and 8 hours. Statistical differences with clinical relevance (> 2 VAS points) occurred in the immediate postoperative period and 2 hours after surgery (**Table 2**).

Table 1. Baseline data

Variable	WALANT (n = 38)	IVRA (n = 34)	P-value
Age (mean, SD)	51.6 (10.7)	51 (12)	0.84
Gender, female, n (%)	38 (100)	32 (94.1)	0.23
Affected side, n (%)	23 (60.5)	21 (61.7)	0.91
Dominant side, n (%)	36 (94.7)	32 (94.1)	0.90
Time with symptoms, years, (mean, SD)	5.3 (4.8)	4.4 (3.4)	0.77
Number of clinical criteria (mean, SD)	4.5 (0.7)	4.1 (0,5)	0.06
Electromyography, severe, n (%)	20 (52.6)	20 (58.8)	0.82
BCTQ pre (symptoms) (mean, SD)	37.3 (6.3)	37.7 (8.7)	0.81
BCTQ pre (function) (mean, SD)	25.1 (6.3)	24 (6.9)	0.49
Preoperative (mean, SD)	5.8 (2.8)	6 (2.1)	0.8
HADS (A) pre (mean, SD)	4.6 (3.5)	3.5 (3)	0.2

IVRA = intravenous regional anesthesia; SD = standard deviation; pre = preoperative; BCTQ = Boston Carpal Tunnel Questionnaire; HADS (A) = Hospital Anxiety and Depression Scale – anxiety subscale.

Operating room times

The duration of surgery for the WALANT group was 12.8 ± 3.8 minutes, while for the IVRA group it was 11 ± 3.2 minutes (P = 0.02). The WALANT group remained in the operating room for 46 ± 5.7 minutes, while the IVRA group was there for 59.5 ± 6.8 minutes (P < 0.01) (**Table 3**).

Drugs used in the first postoperative week

The WALANT group used 5.7 ± 9.81 dipyrone tablets in the first postoperative week, while the IVRA group used 10.8 ± 9.8 (P = 0.02). Regarding use of tramadol tablets, the WALANT group used on average 1.6 ± 3.3, while the IVRA group used 4 ± 8.0 (P = 0.066) (**Table 3**).

Patient-reported function

The evaluations of symptoms and function through the Boston Carpal Tunnel Questionnaire (BCTQ) before and after surgery were similar between the groups (**Table 3**).

Table 2. Pain scores

Pain (VAS)	WALANT (n = 38)	IVRA (n = 34)	P-value
Preoperative (mean, SD)	5.8 (2.8)	6 (2.1)	0.8
Postoperative, immediate (mean, SD)	0.11 (0.7)	3.7 (3.9)	**< 0.001****
Postoperative, 2 hours (mean, SD)	0.6 (1.8)	3.9 (2.4)	**< 0.001****
Postoperative, 4 hours (mean, SD)	1 (2.2)	2.9 (2)	**< 0.001***
Postoperative, 6 hours (mean, SD)	1.7 (2.1)	2.7 (2.1)	**0.02***
Postoperative, 8 hours (mean, SD)	1.35 (1.9)	2.2 (1.8)	**0.01***
Postoperative, 12 hours (mean, SD)	2 (2.2)	2.5 (2.2)	0.24

*Statistically significant (P < 0.05); **with clinical relevance.
VAS = visual analogue scale; IVRA = intravenous regional anesthesia; SD = standard deviation.

Table 3. Secondary outcomes

Variable	WALANT (n = 40)	IVRA (n = 38)	P-value
Operating room time, minutes (mean, SD)	46 (5.7)	59.5 (6.8)	**< 0.01***
Surgery time, minutes (mean, SD)	12.8 (3.8)	11 (3.2)	**0.02***
Dipyrone (n) (mean, SD)	5.7 (9.8)	10.8 (9.8)	**0.02***
Tramadol (n) (mean, SD)	1.6 (3.3)	4 (8)	0.066
BCTQ pre (function) (mean, SD)	25.1 (6.3)	24 (6.9)	0.49
BCTQ three months (symptoms) (mean, SD)*	11.6 (0.9)	12.2 (2)	0.16
BCTQ three months (function) (mean, SD)#	9 (1.1)	10.2 (2.1)	**0.007***
HADS (D) pre (mean, SD)	2.5 (3.3)	1.7 (2.2)	0.75
HADS (A) one week (mean, SD)	1.4 (1.9)	1.1 (1.4)	0.70
HADS (D) one week (mean, SD)	0.8 (1.6)	0.7 (1.2)	0.56
Failures, anesthesia n (%)	0	5 (13.1)	**0.02**
Complications, clinical n (%)	2 (5)	6 (15.7)	0.14

*Statistically significant (P < 0.05); #for the 3-month assessment, WALANT (n = 38) and IVRA (n = 34); IVRA = intravenous regional anesthesia; SD = standard deviation; pre = preoperative; BCTQ = Boston Carpal Tunnel Questionnaire; HADS (A) = Hospital Anxiety and Depression Scale – anxiety subscale; HADS (D) = Hospital Anxiety and Depression Scale – depression subscale.

In-hospital anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) showed that there was no significant difference from before to after the surgery between the groups studied **(Table 3)**.

Paresthesia after surgery

All the patients presented remission or significant improvement of paresthesia three months after the surgical procedure, without any difference between the groups **(Table 3)**.

Complications and failures

Five cases of anesthetic failure were recorded in the IVRA group. Two patients presented intense pain at the time of the cutaneous incision and two patient presented intense pain at the site of the tourniquet, with all of them requiring anesthetic intervention for intravenous sedation. One patient did not present any venous access to the limb that was to be operated on, and local anesthesia was chosen. No failures were found in the WALANT group **(Table 3).**

The clinical complications included one case in the WALANT group of surgical wound dehiscence after a fall from the patient's own height. This case evolved with healing after local care. "Pillar pain" occurred in three cases: one in the WALANT group and two in the IVRA group. All evolved with improved symptoms. One patient in the IVRA group with extreme pain returned for reevaluation in the emergency room, a few hours after hospital discharge, and required analgesia with morphine. Three patients had significant hematomas that needed postoperative clinical care **(Table 3).**

DISCUSSION

The study groups were homogeneous and were compatible with the standard epidemiology of CTS.[21] During the hospital stay, the pain measured on the visual analogue scale (VAS) was higher in the IVRA group in the immediate postoperative period and at 2 hours, 4 hours, 6 hours and 8 hours after surgery, with a statistical difference (P < 0.05). From the immediate postoperative period until the second hour after surgery, this difference was clinically relevant (> 2 points on the VAS), as indicated in the literature.[11] This was possibly due to the rapid dissipation of the anesthetic and short latency of IVRA anesthesia, with early recovery of sensory and motor functions after release of the tourniquet, while the WALANT group presented low levels of pain at these times, probably due to the longer half-life of the anesthetic (around 3 to 5 hours).[22,23]

The difference in the mean times spent by the participants in the operating room was 12 minutes (higher in the IVRA group). This was due to the need for additional procedures, such as access to the limb to be operated and also the need to only release the tourniquet after a minimum safety time of 30 minutes after intravenous infusion of the anesthetic. The mean duration of surgery in the WALANT group was 2.1 minutes longer than in the IVRA group, possibly due to the need for detailed intraoperative hemostasis and

due to the distortion of the anatomy resulting from the fluid and tissue edema in local anesthesia, a result that was in agreement with findings from other studies.[11,24]

The reported function (BCTQ), the anxiety and depression questionnaire (HADS) and the evaluation of the remission of paresthesia did not reveal any statistical difference between the groups, from before surgery to one month post-surgery. Thus, it could be inferred that the anesthetic techniques did not influence the final clinical result. We found that there was a statistical difference in the three-month assessment, but the numerical data suggested that it may not have been clinically relevant (9 versus 10.2 points).

The IVRA success rate reported in the literature is 96%-100%.[25] We obtained a failure rate (13%) that was above that reported in the literature. However, in analyzing the previous studies individually we found several sources of bias. It was common for the authors to observe that some patients also received supplementary medication in varying doses, such as fentanyl and propofol. However, they considered that IVRA was successful due to avoidance of conversion to general anesthesia because of insufficient analgesia.[26-29]

All the results found in our study were in agreement with the results from a randomized trial among 24 patients with bilateral CTS who were operated on one hand using WALANT and on the contralateral hand using the IVRA method. The outcomes were pain, expectations and feelings about the reoperation. The conclusion from that trial was that local anesthesia offered a better intraoperative and postoperative experience in relation to pain, and that the patients had a broad preference for WALANT.[30]

Although our results clearly demonstrated the superiority of the WALANT method, our study had limitations because it was a single-group experience, which did not allow a definitive conclusion to be reached regarding this subject. Our study sample may not have had enough power for all the secondary outcomes and also for the baseline data. No cost-effectiveness approach was investigated, and it was not possible to estimate the amount of resources saved through the WALANT technique. Nonetheless, recent data from trigger finger release procedures demonstrated that WALANT was cost-effective, which makes us believe that this pattern may be the same for CTS.[31]

CONCLUSIONS

The WALANT technique was more effective than IVRA in relation to pain control, operating room time, use of analgesic in the postoperative period and the failure rate, in open surgery for treating CTS.

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Address for correspondence:
Vinícius Ynoe de Moraes
R. Borges Lagoa, 786
São Paulo (SP) — Brasil
CEP 04041-050
Tel. (+55 11) 2337-4820
E-mail: vymoraes@gmail.com

Perfusion index: Could this be a new triage tool for upper gastrointestinal system bleeding in the emergency department? A prospective cohort study

Basak Toptas Firat[I], Muge Gulen[II], Salim Satar[III], Ahmet Firat[IV], Selen Acehan[V], Cem Isikber[VI], Adem Kaya[VII], Gonca Koksaldi Sahin[VIII], Haldun Akoglu[IX]

Adana Şehir Eğitim ve Araştırma Hastanesi, Adana Turkey

[I]MD. Emergency Physician, Department of Emergency Medicine, Adana City Training and Research Hospital, Adana, Turkey.
https://orcid.org/0000-0001-8327-8814

[II]MD, PhD. Associate Professor, Department of Emergency Medicine, Adana City Training and Research Hospital, Adana, Turkey.
https://orcid.org/0000-0002-5080-3501

[III]MD, PhD. Associate Professor, Department of Emergency Medicine, Adana City Training and Research Hospital, Adana, Turkey.
https://orcid.org/0000-0001-6080-4287

[IV]MD. Internal Medicine Physician, Department of Intensive Care Unit, Cukurova University School of Medicine, Adana, Turkey.
https://orcid.org/0000-0001-9182-7270

[V]MD. Emergency Physician, Department of Emergency Medicine, Adana City Training and Research Hospital, Adana, Turkey.
https://orcid.org/0000-0003-4390-6593

[VI]MD. Emergency Physician, Department of Emergency Medicine, Adana City Training and Research Hospital, Adana, Turkey.
https://orcid.org/0000-0002-9904-0189

[VII]MD. Emergency Physician, Department of Emergency Medicine, Adana City Training and Research Hospital, Adana, Turkey.
https://orcid.org/0000-0001-9529-1354

[VIII]MD. Emergency Physician, Department of Emergency Medicine, Adana City Training and Research Hospital, Adana, Turkey.
https://orcid.org/0000-0002-0550-3606

[IX]MD, PhD. Professor, Department of Emergency Medicine, Marmara University School of Medicine, Istanbul, Turkey.
https://orcid.org/0000-0002-1316-0308

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ABSTRACT

BACKGROUND: Many scoring systems for predicting mortality, rebleeding and transfusion needs among patients with upper gastrointestinal bleeding (UGIB) have been developed. However, no scoring system can predict all these outcomes.

OBJECTIVE: To show whether the perfusion index (PI), compared with the Rockall score (RS), helps predict transfusion needs and prognoses among patients presenting with UGIB in emergency departments. In this way, critical patients with transfusion needs can be identified at an early stage.

DESIGN AND SETTING: Prospective cohort study in an emergency department in Turkey, conducted between June 2018 and June 2019.

METHODS: Patients' demographic parameters, PI, RS, transfusion needs and prognosis were recorded.

RESULTS: A total of 219 patients were included. Blood transfusion was performed in 174 patients (79.4%). The PI cutoff value for prediction of the need for blood transfusion was 1.17, and the RS cutoff value was 5. The area under the curve (AUC) value for PI (AUC: 0.772; 95% confidence interval, CI: 0.705-0.838; $P < 0.001$) was higher than for RS (AUC: 0.648; 95% CI: 0.554-0.741; $P = 0.002$). 185 patients (84.5%) were discharged, and 34 patients (15.5%) died. The PI cutoff value for predicting mortality was 1.1, and the RS cutoff value was 7. The AUC value for PI (AUC: 0.743; 95% CI: 0.649-0.837; $P < 0.001$) was higher than for RS (AUC: 0.725; 95% CI: 0.639-0.811; $P < 0.001$).

CONCLUSION: PI values for patients admitted to emergency departments with UGIB on admission can help predict their need for transfusion and mortality risk.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a common and life-threatening reason for admission to emergency departments. Despite all improvements to diagnoses and treatments, the mortality rate is still 4%-14%, and the rebleeding rate is 10%-30%.[1-3] Many scoring systems that have been developed have been reported to be useful in predicting mortality, rebleeding and transfusion needs among patients with UGIB. Performing triage among patients with correct risk scores helps both to increase care efficiency and to identify patients with poor prognoses.[4]

One of the most widely used of these scores is the Rockall score (RS) system. The RS system is based on endoscopic and pre-endoscopic findings such as age, comorbidity, shock status, endoscopic diagnosis, and major new signs of bleeding.[5] The aim in using the RS is to be able to discharge low-risk patients by performing early endoscopy, thereby shortening their length of stay in the hospital and reducing treatment costs.[6] Furthermore, the RS has also been shown to predict the risks of rebleeding and mortality among hospitalized patients.[7]

The perfusion index (PI) is obtained by indirectly measuring pulsatile arterial flow in a specific area such as a hand or a finger, through a noninvasive method for ascertaining peripheral perfusion status. It is expressed as a percentage of the pulsatile current signal relative to the non-pulsatile current signal.[8] It is used in many scenarios within medical practice today.

Evaluating whether anesthesia is successful or not during general, epidural or local anesthesia provides further information for identifying critical patients in neonatal intensive care units.[9,10] Studies have shown that PI is more sensitive than oxygen saturation or pulse rate for predicting disease severity.[10,11] In addition to studies conducted in intensive care units, PI has previously

been studied in emergency departments to determine the severity of dehydration in patients with acute gastroenteritis and to predict occurrences of hypovolemic shock in trauma patients.[14,15] However, the clinical significance of PI in patients with UGIB has not been adequately studied.

OBJECTIVE

In this study, we aimed to compare the predictive strength of RS and PI with regard to the need for transfusion and prognosis among patients presenting with UGIB who were admitted to an emergency department.

METHODS

This was a cohort study and was conducted prospectively. Patients with UGIB who were admitted to the emergency department of a tertiary-level hospital in Turkey between June 1, 2018, and June 1, 2019, were included in the study. The study was started after receiving approval from the Cukurova University Medical Faculty Non-Interventional Clinical Research Ethics Committee, through its meeting number 77 and decision 6, dated May 4, 2018.

Patients

A total of 219 patients were included in this study. The following inclusion criteria were used: (1) cases of upper gastrointestinal bleeding, presented with complaints of hematemesis, melena, hematochezia, dizziness, syncope or blood from nasogastric tube aspiration; (2) cases of gastrointestinal bleeding confirmed by means of upper gastrointestinal endoscopy; (3) age ≥ 18 years. The following situations were taken to be exclusion criteria: (1) endoscopy could not be performed (unavailability, refusal or intolerance); (2) UGIB was not detected on endoscopy; (3) lower gastrointestinal tract bleeding was detected on colonoscopy; (4) coinfection with UGIB or (5) incomplete medical records.

Sample size

The sample size was estimated by means of the G*Power for Mac OS X software (version 3.1.9.2; Universität Dusseldorf, Germany). Accordingly, with a type-1 error of 5%, type-2 error of 5% (power 95%) and two-sided analysis, the sample size was determined as 168 patients. Considering the possibility of protocol bias, addition of 10% to the number of patients in each arm was planned. Hence, 185 was determined as the minimum number of volunteers to be included.

Data collection and measurements

The patients' age, gender, comorbidities, laboratory parameters, PI, RS, endoscopy findings, amount of transfusion performed, length of hospital stay, development of rebleeding, surgical requirements and prognosis were recorded in the data collection form.

Blood transfusion decisions were planned according to the patients' hemodynamic status and blood hemoglobin levels. The hemoglobin threshold for transfusion was 7 g/dl, with a target range for the post-transfusion hemoglobin level of 7 to 9 g/dl.[16] The target hemoglobin level was > 9 g/dl in patients with cardiovascular disease and 8 g/dl in patients with portal hypertension. Red blood cell transfusion was considered if hemodynamic instability was observed despite appropriate fluid resuscitation, even if the hemoglobin level was normal.[16,17]

The RS, including age, shock status, comorbidities and endoscopic parameters, was calculated for each patient at the time when first admitted to the emergency department. This scoring system divides patients into low, medium and high-risk categories regarding rebleeding and mortality: 0-2 points constitute the low-risk category; 3-4 points, medium-risk; and ≥ 5 points, high-risk (minimum 0, maximum 11).[5,6]

The PI was measured in the supine position, noninvasively from the patient's index fingers with the aid of a probe coupled to a Masimo Radical-7 Pulse CO-Oximeter (Masimo Corporation, Irvine, United States), at the time of admission. PI was measured for two minutes (baseline value) after signal stabilization.

Primary outcome

The primary outcome for this study was the mortality rate observed during the hospital stay. The secondary outcomes were the need for red blood cell transfusion and the length of hospital stay.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software, version 22 (SPSS Inc, Chicago, Illinois, United States) was used for the statistical evaluation of the data obtained in the study. Descriptive statistics, consisting of the mean and standard deviation, were calculated for variables with normal distribution; and the minimum, maximum, median and 25%-75% percentiles were presented for variables that did not show normal distribution.

Categorical variables were compared using the chi-square test when the variables were normally distributed. Student's t test was used for comparisons of pairs of groups. The Mann-Whitney U test was used when the variables were not normally distributed. Pearson's correlation analysis was used to explain relationships between pairs of parametric numerical variables. The receiver operating characteristic (ROC) curve was used to evaluate the accuracy of the RS and PI in measuring hospital mortality and the need for transfusion. The Youden index, taken from the point of highest sensitivity and specificity on the ROC curve, was used to determine the cutoff value.

In investigating diagnostic test accuracy, the sensitivity and specificity parameters were calculated with 95% confidence

intervals (CI) and were presented in a table. Binomial logistic regression analysis was used to reveal independent variables for predicting the prognosis. P-values < 0.05 were taken to be statistically significant.

RESULTS

Population characteristics

During the study period, 361 patients presented with gastrointestinal bleeding. Among these, 142 patients were excluded for the following reasons: patients with lower GIS bleeding (n = 84); endoscopy was refused or intolerance was shown (n = 26); presentation of infection (n = 32). Thus, in the end, 219 patients were included in the study based on the inclusion criteria. 69.9% (n = 153) of these patients were male and 30.1% (n = 66) were female. The mean age of the patients was 64.14 ± 17.2 years (minimum 22 to maximum 95 years).

The most common symptom was hematemesis, in 43.8% of the patients included. The most common comorbidity was coronary artery disease, in 34.7%. Among the medications thought to cause bleeding, the most commonly used drug was antiaggregant, used by 37.4%. The most common endoscopic diagnosis was a duodenal ulcer (43.4%). Endoscopic hemostasis therapy was applied to 73.3% of all the patients. The most common endoscopic procedure performed was sclerotherapy (63%). Only red blood cell transfusion was performed, in 51.5% of the patients (n = 113), and both erythrocyte and fresh frozen plasma transfusion were performed in 27.8% (n = 61) of the patients.

While 84.5% (n = 185) of the patients were discharged, 15.5% (n = 34) died. It was found that 15.1% (n = 33) of the patients had rebleeding during their follow-up. While 63.6% (n = 21) of the patients who experienced rebleeding died, 36.4% (n = 12) were discharged (P < 0.001). Surgery was required in 4.1% of all the patients (n = 9) at the time of admission. While four patients who need surgery died, five patients were discharged (P = 0.014). The characteristic features of the patients according to their transfusion needs and prognosis are presented in **Table 1**.

Table 1. Characteristics of patients according to the requirement for transfusion and hospital mortality

	Transfused patients n = 174	Non-transfused patients n = 45	P-values	Survivors n = 185	Non-survivors n = 34	P-values
Age (years) median ± SD	66.0 ± 16.2	56.8 ± 19.6	**0.005**	63.1 ± 17.5	69.6 ± 15.2	**0.046**
Sex, n						
Female	58	8	**0.046**	52	14	0.155
Male	116	37		133	20	
Symptoms, n						
Hematemesis	72	24	0.178	78	18	0.264
Melena	56	16	0.726	63	10	0.694
Syncope	12	1	0.476	13	0	0.228
Hematochezia	11	1	0.467	8	4	0.96
Dizziness	22	3	0.429	23	2	0.384
Other	13	2	0.741	14	1	0.476
Comorbidity, n						
CAD	64	12	0.224	65	11	0.846
HT	53	9	0.196	53	9	1.00
Malignancy	18	0	**0.028**	7	11	**< 0.001**
CLS	8	5	0.148	12	1	0.697
CKD	8	3	0.700	8	3	0.383
COPD	4	3	0.154	5	2	0.298
DM	32	7	0.827	36	3	0.220
No comorbidity	47	21	**0.018**	61	7	0.223
Vital signs and laboratory parameters						
MAP (mmHg)	79.5 ± 15.9	85.3 ± 15.6	**0.031**	81.8 ± 14.8	74.9 ± 20.6	0,073
Pulse (beat/min)	97.5 ± 19.7	92.3 ± 15.7	0.09	95.5 ± 17.9	101.4 ± 23.6	0,175
Hemoglobin (g/dl)	8.4 ± 2.3	12.0 ± 2.1	**< 0.001**	9.3 ± 2.6	8.4 ± 2.7	0,103
BUN (mg/dl)	52.7 ± 32.3	34.2 ± 16.3	**< 0.001**	46.7 ± 27.7	60.6 ± 41.5	0,070
Creatinine (mg/dl)	1.3 ± 1.3	1 ± 0.9	**0.001**	1.1 ± 0.9	2 ± 2.0	**0,020**
Lactate (mmol/l)	3.0 ± 2.7	2.0 ± 1.0	**< 0.001**	2.4 ± 1.6	5.1 ± 4.4	**0.001**

Continue...

Table 1. Continuation

	Transfused patients n = 174	Non-transfused patients n = 45	P-values	Survivors n = 185	Non-survivors n = 34	P-values
Medications, n						
No medications	63	23	0.087	77	9	0.126
Antiaggregant	70	12	0.12	72	10	0.339
NSAID	31	11	0.395	36	6	1.00
Anticoagulant	19	4	1.00	18	5	0.368
Steroid	2	1	0.50	2	1	0.399
Other medications*	111	22	0.087	108	25	0.126
Endoscopic findings, n						
Duodenal ulcer	79	16		88	7	
Gastric ulcer	53	18		59	12	
Esophageal varicose veins	15	6		17	4	
Esophageal erosion	10	3	0.625	9	4	**0.007**
Gastric erosion	7	2		6	3	
Gastric cancer	7	0		4	3	
Angiodysplasia	2	0		0	1	
Esophageal cancer	1	0		2	0	
Endoscopic hemostasis, n						
Sclerotherapy	55	19		68	6	
Sclerotherapy + heater probe	43	7		43	7	
Band ligation	11	5		13	3	
Sclerotherapy + hemoclips	6	3	0.282	7	2	**0.042**
APC	4	2		4	2	
Sclerotherapy + APC	5	0		2	3	
No endoscopic hemostasis	50	9		48	11	
Perfusion index median [25%-75% percentile]	0.86 [0.40-1.50]	1.60 [1.20-2.70]	**< 0.001**	1.1 [0.60-1.70]	0.41 [0.18-0.90]	**< 0.001**
Rockall scores median [25%-75% percentile]	6 [5-7]	5 [3-7]	**0.002**	6 [4-7]	7 [6-8]	**< 0.001**
Rebleeding, n	33	0	**0.002**	12	21	**< 0.001**
Surgery need, n	9	0	0.119	5	4	**0.014**

CAD = coronary artery disease; HT = hypertension; CLS = chronic liver disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; MAP = mean arterial pressure; BUN = blood urea nitrogen; NSAID = non-steroidal anti-inflammatory drug.
*Antihypertensive, antidiabetic, bronchodilator, antidepressant drugs; APC: Argon plasma coagulation.
Bold text indicates a statistically significant difference with a P-value < 0.05.

Perfusion index and Rockall scores with predictions for outcomes

It was found that the patients' red blood cell transfusion needs showed a statistically significant but weak negative correlation with the PI value (r = -0.363; P < 0.001) and a statistically significant and weak correlation with the RS (r = 0.292; P < 0.001).

For patients whose hemoglobin value was above 7 on admission, the mean PI of those who needed transfusion (n = 126) during their follow-up was 1.3 ± 1.1, and the mean PI of those who did not need transfusion (n = 45) was 1.9 ± 1. The PI level of the patients who needed a transfusion was statistically significantly lower (p = 0.001).

The ROC analysis graph to determine the need for red blood cell transfusion, comparing RS and PI in the patient group, is shown in **Figure 1**. In the analytical evaluations made, it was determined that the area under curve (AUC) value for the PI (AUC: 0.772; 95% CI 0.705 -0.838; P < 0.001) was higher than that of the RS (AUC: 0.648; 95% CI 0.554-0.741; P = 0.002). When the threshold

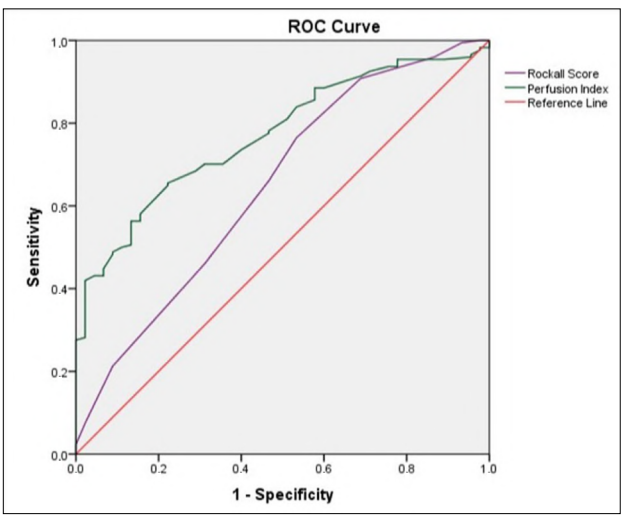

Figure 1. Receiver operating characteristic (ROC) curves showing comparisons of perfusion index and Rockall score for predicting need for red blood cell transfusion.

value determined for predictability of the need for red blood cell transfusion was taken as 1.17 for PI, its sensitivity was calculated as 77.8% and specificity as 66.5%; while the sensitivity was 76.4% and specificity was 46.7% when 5 was taken as this value for RS.

The mean number of days of hospitalization for discharged patients was 5.3 ± 3.8 (minimum: 1; maximum: 23), and the mean number of days of hospitalization for patients who died was 10.4 ± 9.5 (minimum: 1; maximum: 40). There was a statistically significant difference in the number of days of hospitalization between discharged and dead patients (P < 0.001). It was determined that the patients' hospitalization time was statistically significant but weakly correlated with RS (r = 0.293; P < 0.001), and that the higher this score was, the longer the hospitalization period also was. However, a statistically significant but very weak negative correlation was found between the PI (r = -0.160; P = 0.018) and hospitalization periods.

The ROC analysis graph, which was produced to determine the predictive mortality properties of PI and RS, is shown in **Figure 2**. In the analytical evaluations conducted, it was determined that the AUC value for PI (AUC: 0.743; 95% CI: 0.649-0.837; P < 0.001) was higher than the value for RS (AUC: 0.725; 95% CI: 0.639-0.811; P < 0.001). When the threshold value determined for predicting mortality was taken as 1.1 for PI, its sensitivity was calculated as 57.8% and specificity was 85.3%; while the sensitivity was 70.6% and specificity was 62.2% when the cutoff was taken as 7 for RS.

Logistic regression analysis determined that the presence of malignancy (odds ratio, OR: 6.34; 95% CI: 1.979-20.305; P = 0.002), creatinine values > 1.4 mg/dl (OR: 1.406; 95% CI: 1.068-1.852; P = 0.015) and lactate values > 2 mmol/l) (OR: 1.328; 95% CI: 1.137-1.550; P < 0.001) were independent variables that predicted hospital mortality. However, this analysis did not show PI (OR: 0.774; 95% CI: 0.41-1.337; P = 0.323) as a statistically significant parameter in determining mortality.

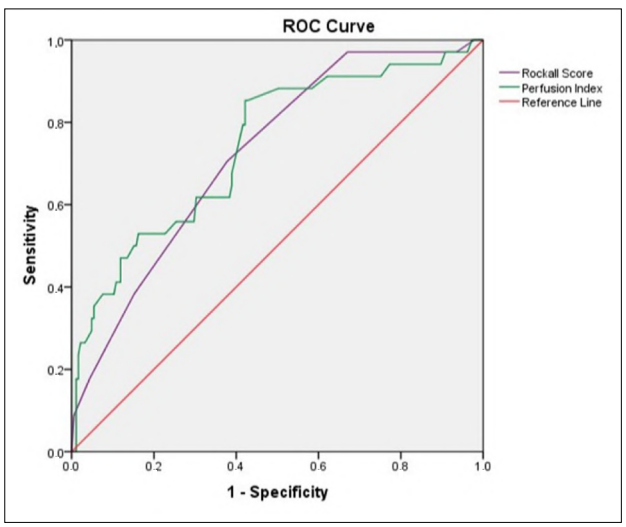

Figure 2. Receiver operating characteristic (ROC) curves showing comparisons of perfusion index and Rockall score for predicting hospital mortality.

DISCUSSION

In our study, the ability of PI to predict the need for transfusion and mortality among patients with UGIB who were admitted to the emergency department was compared with the proven RS. Low PI in UGIB patients was found to be a good indicator of the ability to predict transfusion needs and mortality. We found that when PI was lower than 1.17, the need for erythrocyte suspension increased, and if it was lower than 1.1, the mortality increased significantly.

PI is obtained by dividing pulsatile arterial blood flow by the non-pulsatile flow signal, measured from an area such as the finger or toe using infrared rays.[11] Its significant advantages are that it is noninvasive and provides continuous monitoring at the bedside that is repeatable and easy to measure.[18] Redistribution of blood flow caused by increased vasoconstriction during hemorrhagic hypovolemia, or circulatory failure associated with low cardiac output, results in reduced skin perfusion.[19] While vasoconstriction occurring in peripheral tissues causes a decrease in pulsatile arterial blood flow, the rate decreases because the non-pulsatile component does not decrease, which thus causes a decrease in PI.[11] Hemoglobin and hematocrit levels are not reliable enough to predict the amount of bleeding and should not be used to rule out the presence of hypovolemic shock.[20]

Peripheral vasoconstriction caused by acute blood volume changes may be an early indicator of shock and the need for transfusion, given the rapid response to this that is seen through the PI.[15,21] In a study evaluating the strength of the PI for predicting hypovolemic shock in trauma patients, when the cutoff value for the PI was taken as "1", its sensitivity for predicting the need for transfusion was found to be 78% and its specificity, 97.6%.[15] In a study in which the severity of dehydration was determined by means of the PI, among patients with acute gastroenteritis admitted to the emergency department, the PI was found to be statistically significantly lower in the moderate/severe dehydration group (PI: 1.8 (1.4-2.1)) than in the mild dehydration group (PI: 2.3 (2-2.7)).[14] The studies conducted showed that PI could predict hypovolemia at normal blood pressure levels during the pre-shock phase.[22]

In our study, in patients with hemoglobin values above 7 on admission to the emergency department, the mean PI (1.3 ± 1.1) of the patients in need of transfusion was statistically significantly lower than the PI value of those who did not receive transfusion (1.9 ± 1). Our study also showed that PI measurement in UGIB

patients could be a useful parameter for determining the need for blood transfusion. When the cutoff value of the PI was taken to be 1.17, the sensitivity was 77.8% and the specificity was 66.5%, in terms of predicting the need for transfusion. Also, according to the ROC analysis, the AUC value of PI (AUC: 0.772; P < 0.001) was found to be higher than the AUC value of RS (AUC: 0.648; P = 0.002). Therefore, we think that a low PI value may be a triage tool that will enable early detection of patients with UGIB as an effective means of triage, especially in crowded emergency departments.

Current guidelines recommend using risk stratifications to identify high-risk UGIB patients undergoing aggressive resuscitation, thereby reducing mortality and morbidity.[23] Risk scores help predict occurrences of mortality during the hospital stay, the frequency of rebleeding, the need for transfusion and the need for hemostatic procedures through endoscopy.[1-3,24] In a study comparing the RS with other risk scores, the AUC value (AUC: 0.624; P < 0.05) for the RS of patients who needed transfusion was similar to that of our study (AUC: 0.648; P = 0.002).[24] In the same study, when the cutoff value for the RS was taken as 6, the sensitivity was 42.9% and the specificity was 90.5%, for predicting mortality.[24]

In our study, in terms of predicting mortality, the sensitivity was calculated as 70.6% and the specificity was 62.2% when the cutoff value for RS was taken as 7; while the sensitivity was 57.8% and the specificity was 85.3% when the cutoff value for PI was taken as 1.1. Also, according to the ROC analysis that was conducted to predict mortality, the AUC value for PI (AUC: 0.743; P < 0.001) was found to be higher than that of RS (AUC: 0.725; P < 0.001).

A good risk scoring system should have high sensitivity and specificity for predicting relevant outcomes, should contain easy-to-access variables, should be easy to calculate and remember and should distinguish low-risk patients from high-risk patients.[25] Although there are many scoring systems for patients with UGIB, there is no scoring system with all of these properties. The PI has the capacity to provide continuous noninvasive monitoring regardless of laboratory parameters, in places where large numbers of patients are admitted to emergency departments and where many critical patients receive interventions at the same time. It may therefore facilitate management of critical patients with UGIB. Although there are many studies in the literature comparing risk scoring systems for use among patients with UGIB, there is also no study on the perfusion index. Our study is the first study in the literature with this feature.

Limitations

There are some limitations to our study. First, this study was conducted at a single center in a regional referral hospital; hence, our results cannot be applied generally. Second, the decisions regarding transfusion needs were made based on clinical judgment by an individual clinician, which might have caused variability. The outcome measured in this study was whether the patient was transfused, which is different from whether the patient really needed a transfusion. Cases with hemoglobin levels between 7 and 9 could have been inappropriate for transfusion.

CONCLUSION

The PI value of a patient admitted to the emergency department, with UGIB on admission, can help predict this patient's need for transfusion and predict mortality. The PI has the critical advantage that it provides easy access, is noninvasive and fast and enables continuous monitoring at the bedside in the emergency department. Therefore, it can be a useful triage tool for UGIB patients admitted to crowded emergency departments. We think that prospective studies conducted with new scoring systems, in which risk scores that have proven their benefits are combined with PI, may help predict the need for transfusion and mortality.

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Address for correspondence:
Muge Gulen
Department of Emergency Medicine,
Adana Şehir Eğitim ve Araştırma Hastanesi, 01370, Yuregir, Adana, Turkey
Telephone Number: +90 506 488 55 78
E-mail: muge-gulen@hotmail.com

Years of life lost due to premature deaths associated with air pollution: an ecological time-series study

Luiz Fernando Costa Nascimento[I], Luciana Cristina Pompeo Ferreira Vieira[II],

Department of Energy, São Paulo State University (UNESP), Guaratinguetá, Brazil

[I]MD, PhD. Researcher, Postgraduate Program on Mechanical Engineering, Department of Energy, Universidade Estadual de São Paulo (UNESP), Guaratinguetá, Brazil.
http://orcid.org/0000-0001-9793-750X

[II]MSc. Doctoral Student, Postgraduate Program on Mechanical Engineering, Department of Energy, Universidade Estadual de São Paulo (UNESP), Guaratinguetá, Brazil.
https://orcid.org/0000-0002-4285-8449

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Particulate matter.
Air pollutants.
Value of life.

AUTHORS' KEYWORDS:
DALY.
Financial costs.
Years of life lost.

ABSTRACT

BACKGROUND: Exposure to air pollutants is associated with hospital admissions due to cardiovascular diseases and premature deaths.

OBJECTIVE: To estimate years of life lost (YLL) due to premature deaths and their financial costs.

DESIGN AND SETTING: Ecological time-series study carried out in São José dos Campos, Brazil, in 2016.

METHODS: Data on deaths among residents of this city in 2016 were assessed to estimate the financial cost of premature deaths associated with air pollution. The diagnoses studied were ischemic heart disease, congestive heart failure and cerebrovascular disease, according to YLL. The fractions attributable to deaths associated with air pollutant exposure and to each potential year of life lost were calculated using negative binomial regression with lags of 0-7 days between exposure and outcome. Nitrogen dioxide, particulate matter (PM_{10}) and ozone concentrations were included in the model and adjusted for temperature, humidity and seasonality.

RESULTS: Exposure to particulate matter was significant at lag 3 days. There were 2177 hospitalizations over the study period, with 201 deaths (9.2%). Premature deaths led to 2035.69 years of life lost. A 10 $\mu g/m^3$ increase in PM_{10} concentrations was correlated with 8.0% of the hospitalizations, which corresponded to 152.67 YLL (81.67 for males and 71.00 for females). The cost generated was approximately US$ 9.1 million in 2016.

CONCLUSION: In this first study conducted in a medium-sized Brazilian city, using the YLL methodology, we identified an excess expense attributable to air pollution.

INTRODUCTION

In Brazil, in 2016, about US$ 1 billion were spent on hospitalizations due to circulatory system diseases. This comprised over one million hospitalizations with more than 90,000 deaths. In the state of São Paulo, there were more than 250,000 hospitalizations and just over 20,000 deaths, thus generating expenditure of approximately US$ 200 million. In São José dos Campos, a city located in the state of São Paulo, about US$ 3 million were spent on 3,000 hospitalizations, with around 300 deaths.[1]

The factors associated with this morbidity and mortality included physical inactivity, active and passive smoking, hypercholesterolemia and exposure to air pollutants.

Studies have shown positive associations between exposure to air pollutants and presence of cardiovascular diseases. In one study covering the years 2003-2007, the effects of exposure to sulfur dioxide (SO_2) were found to be significantly associated with mortality due to circulatory diseases, with a relative risk of 1.04 (95% confidence interval, CI: 1.01-1.06).[2] In another study, an association was found between exposure to environmental pollutants and hospitalizations due to stroke, and it was shown that a 12% increase in the risk of hospitalization (relative risk, RR = 1.137; 95% CI: 1.014-1.276) was associated with a 10 $\mu g/m^3$ increase in the concentration of particulate matter with aerodynamic diameter less than 10 μ (PM_{10}).[3]

In Presidente Prudente, a city in the western region of the state of São Paulo that is surrounded by large areas of sugar cane plantations, straw-burning after the harvest is still practiced. This increases the safety of cane cutters, but causes the release of particulate material and gases, in particular NO_2. These pollutants have been correlated with hospitalizations due to cardiovascular diseases.[4]

An association between exposure to fine particulate matter ($PM_{2.5}$) and hospitalizations due to vascular diseases was identified in another medium-sized city in the state of São Paulo. It was

calculated that an excess of 650 hospitalizations, with a cost of US$ 600,000, was caused through an increase in the concentration of this pollutant ($PM_{2.5}$) by 10 μg/m³.[5]

A study carried out in Canada using data from 2003 to 2007 also identified a significant association between exposure to nitrogen dioxide (NO_2) and carbon monoxide (CO) and occurrences of hemorrhagic and ischemic strokes, with relative risks of 1.46 and 1.36. This association showed dose-response behavior with highest risk values in the fourth and fifth quintiles of NO_2 concentration.[6]

Exposure to air pollution due to particulate matter contributes to cardiovascular morbidity and mortality, such that exposure to $PM_{2.5}$ for a few hours would increase the RR of cardiovascular mortality by approximately 0.4% to 1.0% due to an increase of 10 μg/m³ at lag 1 day. Long-term exposure (some years) would increase the relative risk by between 1.06 and 1.76.[7]

In an extensive review on 76 studies published between 2000 and 2018, Bazyar et al.[8] showed that exposure to air pollutants increased the relative risk or chance (odds ratio, OR) of the need for emergency care in emergency rooms and also of mortality due to cardiovascular diseases such as acute myocardial infarction and hypertension. In another extensive review on 41 studies, higher risk of death due to cardiovascular diseases through exposure to particulate matter was identified.[9]

Positive associations between exposure to pollutants and hospitalizations leading to premature death were identified in a study conducted in Skopje, Republic of North Macedonia, using the Disability Adjusted Life Years (DALY) methodology.[10] Using this same approach, the economic impact of premature deaths associated with particulate matter concentrations in 29 Brazilian metropolitan regions was evaluated. A total of 20,050 deaths were found, resulting in a cost of US$ 1.7 billion annually.[11] Also in Brazil, Abe and Miraglia estimated that savings of US$ 15.1 billion per year would be achieved in the city of São Paulo, if the $PM_{2.5}$ concentration were to be reduced in accordance with the standards recommended by the World Health Organization (WHO). This would also prevent about 5,012 premature deaths, i.e. 266,486 years of life lost.[12]

All the studies conducted so far in Brazil have been in major metropolises. Thus, there are no studies in medium-sized cities in Brazil.

OBJECTIVE

The aim of this study was to estimate the cost of years of life lost (YLL) due to premature deaths in the city of São José dos Campos, Brazil, that were associated with exposure to PM_{10}.

METHODS

Place of study

São José dos Campos is a city located in the southeastern region of Brazil between the cities of São Paulo and Rio de Janeiro (23° 11' S and 45° 53' W). It occupies an area of 1,099 km², has a population of approximately 700,000 inhabitants and has 12 hospitals. This city is an industrial, commercial and service center serving the eastern part of the state of São Paulo and the southern part of the state of Minas Gerais, with a total regional population of approximately two million inhabitants. Some important research centers are installed in this city, such as the National Institute for Space Research (INPE), Technological Institute of Aeronautics (ITA) and São Paulo State University (UNESP). The human development index (HDI) of São José dos Campos is 0.81. The Dutra highway, which is considered to be the most important highway in Brazil, crosses the city and has a flow of approximately 80,000 vehicles per day, including large numbers of heavy vehicles and buses.

Statistical analysis

This was an ecological time-series study on data relating to hospitalizations due to circulatory system diseases (International Classification of Diseases, 10th edition [ICD-10], chapter X) among residents of São José dos Campos, São Paulo, aged 30 years and over, of both sexes. Information covering the entire year of 2016 was obtained from the DATASUS[13] website. The data on this website originated from hospital admission authorizations contained in hospital information systems and referred to all municipalities in the state of São Paulo. These data comprise not only accounting information but also information of epidemiological interest such as age, sex, date of admission, diagnosis according to ICD-10 and type of hospital discharge (dead or alive).

The independent variables evaluated in the present study were NO_2, PM_{10} and O_3 pollutant concentrations, minimum temperature and relative humidity. These data were obtained from the São Paulo State Environmental Agency (CETESB), which has three monitoring stations in the municipality of São José dos Campos.[14]

The data for the year 2016 were inserted in a spreadsheet for analysis. This analysis used negative binomial regression, instead of Poisson regression, to avoid overdispersion due to possible significant differences between the mean values of hospitalizations and their variance. The model was adjusted for temperature and relative humidity and controlled for day of the week and long-term trend. The analysis used lags of 0 to 5 days between exposure to the pollutant and the outcome.

The negative binomial regression coefficients (βi) with their respective standard deviations were transformed into relative risk (RR) of hospitalization with a confidence interval of 95%, for lags of zero to five days between exposure and outcome, as the effects of this exposure may be evident either on the same day or some days after exposure (lag 0 to lag 5) (**Figure 1**).

Increases in risk were considered in terms of an increase of 10 μg/m³. This was done using the expression (exp (β * DC)), where DC is the increase in concentration of 10 μg/m³. Significant

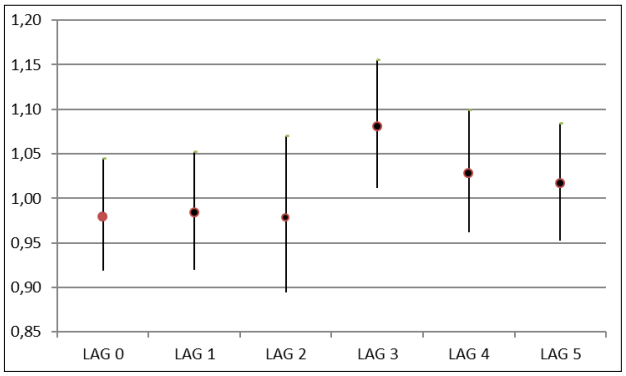

Figure 1. Relative risk with respective 95% confidence intervals, according to a 10 µg/m³ increase in particulate matter concentration, from Lag 0 to Lag 5 days.

values (P-value < 0.05) were identified as the lag that provided the proportional attributable risks (PAR) of the given increase in RR, using the expression PAR = [1-1/RR]. From this, the population attributable fraction (PAF) was estimated using the expression PAF = PAR * N, where N is the number of deaths.

Hospitalizations were included in three groups. Ischemic heart disease (ICD-10 categories I-20 to I-25) (Group 1), congestive heart failure (I-50) (Group 2) and cerebrovascular disease (I-60 to I-64) (Group 3), which corresponded to 70% of all deaths, were selected from among causes in ICD-10 Chapter X. The premature deaths from these diseases were determined, and the financial cost of these premature deaths was calculated using the DALY methodology.

The DALY method is a summary measurement of health expressed by means of a standard indicator in time units (years). It is obtained as the sum of two components: years of life lost (YLL) due to premature death (associated with a specific outcome) in relation to the estimated life expectancy; and years lived with disability (YLD), i.e. the time spent in an unhealthy condition. This method is consistent with the ideals from outcomes such as disease, injury or risk factors, as described by Murray and Lopez.[11]

The YLL component of DALY is obtained through equation 1, as follows:

$$YLL = \frac{KCe^{ra}}{(r+\beta)^2}\left[e^{-(r+\beta)(L+a)}\left[-(r+\beta)(L+a)-1\right]-e^{-(r+\beta)a}\left[-(r+\beta)a-1\right]\right]+\frac{1-K}{r}\left(1-e^{-rL}\right) \quad (1)$$

Where:
r = discount rate (r = 0.03); K = weight-age modulation factor (K = 1); C = constant (0.1658); a = age at death event; L = life expectancy pattern at age a; and β = weight-age function parameter (β = 0.04).

The variable "a" refers to the age of the individual at the time of death, while the variable L refers to the pattern of life expectancy at age a. These were obtained from the Brazilian Institute for Geography and Statistics (IBGE). For each interval, the value at its onset was considered: for example, for a case within the age range 45-50 years the value was set at 32.2 years for males and 37.0 for females, regardless of age.

These two variables provided the data on the events analyzed that needed to be entered in order to estimate the number of years of life lost due to a given disease. This formula was programmed and developed in an Excel spreadsheet in which the original database was aggregated for calculation. An implementation was introduced in order to make life expectancy comparisons at the age of death considering the same spreadsheet file, thus providing a single output. This output consists of each individual YLL calculation for each event. A value of € 50,000 (euros) was assigned to each individual YLL.

The total number of YLL was obtained by summing the individual YLL results due to pollution-attributable disease mortality, i.e. the part of YLL that was due to the effects of atmospheric pollution within the outcome, using the calculation given in the formula. Thus, YLL due to pollution was obtained via the following formula:

$$YLL_{pol} = \Sigma\ YLL * PAF \quad (2)$$

Where:
YLL_{pol} = YLL attributable to air pollution
Σ YLL = sum of all individual YLL in the parsed database

The significance level was taken to be alpha = 0.05. This study was conducted using data publicly available from the official source, from which it was not possible to identify the subjects. Therefore, there was no need to submit the study protocol for approval by a research ethics committee.

RESULTS

This study included 2,177 hospitalizations among individuals aged 30 years and over of both sexes: 1,332 men (61.2%) and 845 women (38.8%). Their diagnoses related to cardiovascular disease groups, as mentioned in the Methods. The daily average number of hospitalizations was 4.8 (standard deviation SD = 2.5), with a range from 0 to 13. There were 201 deaths (9.2% of the hospitalizations): 106 among the males (52.7% of the deaths) and 95 among the females (47.5% of the deaths). Among the males, the proportion of deaths was 7.96%; and among the females, 11.24%. The mortality rate for these three groups of diseases was 29.3 deaths per 100,000 inhabitants.

Table 1 shows the descriptive analysis results from the variables. For the number of hospitalizations, the variance was 11.76, which therefore justified the use of negative binomial regression.

Table 1. Descriptive analysis on atmospheric variables, with mean values and their respective standard deviations (SD) and minimum and maximum values (Min-Max), São José dos Campos (SP), 2016

	Mean (SD)	Min–Max
NO_2* (μg/m³)	40.0 (20.4)	4-119
PM_{10}** (μg/m³)	22.4 (12.4)	4-78
O_3*** (μg/m³)	60.8 (21.6)	14-120
Temperature (°C)	27.3 (4.4)	15.8-36.8
Relative humidity (%)	48.5 (13.5)	19-88

*Nitrogen dioxide; **particulate matter with aerodynamic diameter less than 10 μ; ***ozone.

The modeling coefficients with only one pollutant (unipollutant model) provided by the negative binomial approach are shown in **Table 2**. The analysis used a multipollutant model and it was only possible to identify significant exposure to PM_{10} at lag 3 days (P-value = 0.021). The relative risk associated with this exposure, in terms of an increase in PM_{10} concentration of 10 μg/m³ was RR = 1.081 (95% CI: 1.012-1.155). This represented an excess risk of around 8.1% (**Table 3**).

The results obtained, and the respective percentages, according to the aggregated groups of diseases, are shown in **Table 4**. It could be seen that the highest percentage of deaths occurred in group 3. On the other hand, there was no significant difference (P-value > 0.05) in YLL values between males and females.

The total YLL value was 2035.69 years; the mean value per individual was 9.88 (± 6.18) with values varying between 2.52 and 26.65. The YLL for males was estimated as 1089.02 years (53.5%). According to sex, the average YLL was 9.81 (SD = 6.02) for males and 9.96 (SD = 6.40) for females, with no significant differences.

The YLL values according to sex and diagnosis group are shown in Table 4. The highest YLL value was for group 3 (10.58 ± 6.39) and the lowest was for group 2 (8.54 ± 5.53), but without a significant difference. There were 549.96 YLL within the age range 30 to 50 years (27.02%).

The PAR value for this RR was (1 – 1/1.081) à 0.075. Thus, the resultant PAF value (i.e. the product of total YLL and PAR) was 2035.69*0.075 à 152.67. Out of the total of 2035.69 YLL, 152.67 YLL (81.67 YLL for males and 71.00 for females) were attributed to this increase, with costs of approximately € 7.63 million (approximately US$ 9.16 million) in 2016.

Table 2. Coefficients and their standard errors, in brackets, provided through analysis on three pollutants separately. São José dos Campos (SP), 2016

Lag*	PM_{10}	NO_2	O_3
Lag 0	0.001162	0.001875	0.001378
	(0.002339)	(0.001295)	(0.001688)
Lag 1	0.001796	0.001831	0.002084
	(0.002310)	(0.001283)	(0.001661)
Lag 2	0.001613	0.000535	-0.000220
	(0.002321)	(0.001299)	(0.001688)
Lag 3	0.004117	0.000013	0.000703
	(0.002268)	(0.001299)	(0.001680)
Lag 4	0.000843	-0.000538	-0.000099
	(0.002302)	(0.001291)	(0.001664)
Lag 5	0.001432	-0.000120	0.000713
	(0.002280)	(0.001288)	(0.001672)

*Lag = number of days between exposure and outcome.

Table 3. Regression coefficients (Coeff) and respective standard errors (SE) for PM_{10} pollutant (multipollutant model) on all days of the lag structure analyzed, São José dos Campos (SP), 2016.

Lag*	Coeff	SE
Lag 0	-0.002080	0.003286
Lag 1	-0.001635	0.003414
Lag 2	-0.002210	0.004573
Lag 3	0.007781#	0.003382#
Lag 4	0.002765	0.003408
Lag 5	0.001615	0.003290

*Lag = number of days between exposure and outcome; #P-value < 0.05.

Table 4. Multivariate analysis on the variables of type of hospital discharge, mean age, sex and DALY values according to hospitalization groups: ischemic heart disease (Group 1), congestive heart failure (Group 2) and cerebrovascular disease (Group 3). São José dos Campos (SP), 2016

	Group 1	Group 2	Group 3	P-value
Hospital discharge				
Alive	1203 (97.6%)	395 (86.8%)	378 (77.1%)	< 0.01
Dead	29 (2.4%)	60 (13.2%)	112 (22.9%)	
Mean age in years (SE)	62.3 (10.6)	67.0 (12.1)	64.8 (14.3)	< 0.05
Sex				
Male	801 (65.0)	241 (53.0)	290 (59.2)	< 0.01
Female	431 (35.0)	214 (47.0)	200 (40.8)	
YLL#				
Male	10.12 (6.75)	9.07 (6.43)	10.04 (5.80)	NS
Female	9.67 (6.29)	8.10 (4.72)	11.48 (7.23)	

#mean and standard error (SE); YLL = years of life years; NS = not significant

DISCUSSION

Until now, no studies quantifying the cost of premature deaths associated with exposure to air pollutants had been conducted in a Brazilian medium-sized city, particularly with regard to particulate matter using the YLL DALY component. The costs of these premature deaths were of the order of US$ 9.1 million in the year 2016.

In this study, it was possible to quantify 2035.69 years of life lost, with 1089.02 YLL attributable to males and 946.67 YLL to females. The female response to the risk of death among women represented by the substantial proportion found in this study had already been pointed out in two other studies.[16,17]

Studies conducted in Brazil have already shown the costs of hospitalizations associated with exposure to all air pollutants. With a reduction in pollutant concentrations, there is a reduction in the costs of these hospitalizations to the National Health System (Sistema Único de Saúde, SUS). It was found in São José do Rio Preto, state of São Paulo, that a reduction in the $PM_{2.5}$ concentration would lead to avoidance of around 600 hospitalizations, with cost savings of around US$ 550,000.[6] This was also demonstrated in studies conducted in Cuiabá, state of Mato Grosso, with savings of about US$ 30,000 regarding hospitalizations among children[15] and around US$ 100,000 regarding hospitalizations among the elderly[16] due to respiratory diseases. For cardiovascular diseases, it was possible to estimate a reduction of US$ 150,000 in Taubaté.[17] Regarding the reduction in $PM_{2.5}$ concentrations, there would be a reduction of 256 hospitalizations and cost savings of approximately US$ 60,000 in São José do Rio Preto.[18]

A study carried out in Skopje, Republic of North Macedonia, on hospital admissions due to respiratory diseases in 2012, identified around 1200 premature deaths, costing between € 570 million and €1470 million, when the $PM_{2.5}$ concentration was 49.2 μg/m³. Lowering $PM_{2.5}$ levels to the European Union recommended limit of 25 μg/m³ would decrease these deaths by 45%.[7] The $PM_{2.5}$ concentration in Skopje corresponded to around 80 μg/m³ in PM_{10} values, i.e. much higher than the values recorded in São José dos Campos. The YLL values were obtained using the AirQ+ software, which quantifies the health impact of exposure to air pollutants and was developed by WHO.

A study was conducted in 29 Brazilian metropolitan regions using the DALY methodology, to assess the economic impact of premature deaths associated with air pollution. A total of 20,050 deaths were considered to be due to exposure to particulate matter, and these generated a cost of US$ 1.7 billion annually.[11] In that study, deaths from all causes that occurred among subjects of both sexes aged 30 years or over were considered, and it was determined that these deaths corresponded to approximately 250,000 YLL. This was 100 times greater than what we calculated in our study, but it is difficult to compare the data because all deaths were included in that study, whereas we included only a few diagnoses.

In São Paulo, Brazil, the health impact associated with air pollution was assessed for the years 2009 to 2011. It was determined that reducing the concentrations of particulate matter and ozone would prevent more than 5,000 premature deaths, which corresponded to a gain of 266,486 life years, with savings of US$ 15.1 billion per year. For a reduction in the average $PM_{2.5}$ level in São Paulo of 5 μg/m³, about 1,724 deaths would be prevented and there would be savings of US$ 4.96 billion.[12] It is also difficult to make comparisons with the results from that study, since the diagnoses of cardiovascular diseases were different, in addition to differences in study duration (three years for that study) and in the population studied. Nonetheless, the results from that study also showed that reductions in particulate matter concentrations would lead to decreases in the number of deaths, with an important reduction in costs for the healthcare system.

In Kuwait, where PM_{10} concentrations are of the order of 170 μg/m³, the AirQ+ software was used to show that reducing these concentrations could increase life expectancy in the group of subjects aged 30 years or over.[19]

According to Gao et al., in a review of the DALY method, it could be seen from the existing studies that use of DALY was advantageous in relation to conventional environmental impact assessments for quantifying and comparing the risks from environmental pollution. However, they concluded that further studies were still needed in order to standardize the assessment methods relating to the effect on health of various pollutants under various circumstances, prior to calculating DALY.[20]

In Guangzhou City, China, between 2004 and 2007, the YLL through cardiovascular mortality due to exposure to air pollution was estimated. It was calculated that a 10 μg/m³ increase in NO_2, SO_2 and PM_{10} would resulting in daily average YLL corresponding to 248, 87.5 and 73.7 for deaths from cardiovascular disease (CVD), stroke and ischemic heart disease (IHD) respectively. The effects of air pollutants on YLL were immediate and lasted for two days.[21]

This study may have some limitations. Among these, it was developed using secondary data: even though these data came from an official source (DATASUS), they may have contained misdiagnoses, since the main purpose of DATASUS is to record financial information. In addition, the hospitalization data referred only to occurrences within the public system through SUS, thus excluding private hospitalizations or occurrences though health plans or health insurance operators. Furthermore, factors such as passive smoking, dietary habits and lifestyle were not considered because they are not available through DATASUS. The time period used in this study was one year only.

CONCLUSIONS

Despite these possible limitations, this study not only presented unpublished data from a medium-sized city in Brazil but also quantified the cost of premature deaths due to some cardiovascular diseases. If these deaths were avoided, the cost savings could be allocated to other healthcare needs in the city. In addition, it was possible to estimate the importance of YLL in an important economically active age group.

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Address for correspondence:
Luiz Fernando Costa Nascimento
Av. Ariberto Pereira da Cunha, 333
Guaratinguetá (SP) — Brasil
CEP 12516-410
Tel. (+55 12) 3123-2161
E-mail: fernando.nascimento@unesp.br

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Changes in serum albumin and liver enzymes following three different types of bariatric surgery: six-month follow-up. A retrospective cohort study

Mohadeseh Hassan Zadeh[I], Negar Zamaninour[II], Hastimansooreh Ansar[III], Ali Kabir[IV], Abdolreza Pazouki[V], Gholamreza Mohammadi Farsani[VI]

School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran

[I]Undergraduate Student, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran.
http://orcid.org/0000-0002-4291-2986

[II]PhD. Nutritionist, Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran.
http://orcid.org/0000-0002-6697-3943

[III]PhD. Nutritionist, Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran.
http://orcid.org/0000-0002-6768-4203

[IV]MD, MPH, PhD. Associate Professor, Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran.
http://orcid.org/0000-0001-9496-4705

[V]MD. Associate Professor of Surgery, Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran; and Associate Professor, Center of Excellence of European Branch of International Federation for Surgery of Obesity, Tehran, Iran.
http://orcid.org/0000-0003-1706-4177

[VI]MD, MPH, PhD. Assistant Professor, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran; and Assistant Professor, Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran.
http://orcid.org/0000-0003-2033-9100

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ABSTRACT

BACKGROUND: Few reports have examined the effects of Roux-en-Y gastric bypass (RYGB), one-anastomosis gastric bypass (OAGB) and sleeve gastrectomy (SG) on changes to serum albumin (Alb) and liver enzyme levels.

OBJECTIVE: To compare short-term post-surgery changes in serum Alb, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALKP) levels. Body composition changes were also measured and compared among three groups.

DESIGN AND SETTING: Retrospective cohort study conducted in Tehran, Iran.

METHODS: 151 OAGB, RYGB and SG patients referred to the obesity clinic of Hazrat-e Rasool General Hospital, Tehran, Iran, were evaluated. Physical characteristics and biochemical parameters were measured pre-surgery and then after three and six months.

RESULTS: Through repeated measurements to determine intragroup changes, significant changes in serum AST ($P = 0.003$) and ALT ($P < 0.001$) were observed in follow-ups. However, Alb levels did not change ($P = 0.413$). Body fat, fat-free mass and muscle mass decreased significantly in each group ($P < 0.05$). In a univariate general linear model for determining intergroup changes, SG showed greater decreases in ALT and AST at three and six months ($P < 0.05$) and in ALKP at six months ($P = 0.037$), compared with OAGB. There were no significant differences in Alb levels. Also, RYGB had a greater effect on reducing fat percentage (three months, $P = 0.011$; six months, $P = 0.059$) and fat mass (three months, $P = 0.042$) than OAGB.

CONCLUSION: SG and RYGB may be superior to OAGB in reducing liver enzymes and body fat, respectively. However, Alb levels showed no significant differences.

INTRODUCTION

The worldwide prevalence of obesity has tripled in the past four decades,[1] which may have led to higher incidence of some major health problems, such as type 2 diabetes (T2DM), high blood pressure, cardiovascular disease (CVD), degenerative arthritis and sleep apnea.[2] Trends have also shown that non-alcoholic fatty liver disease (NAFLD), which is seen in more than of 80% of patients with obesity, is becoming the most common cause of liver dysfunction.[3]

Bariatric surgery is considered not only to form a treatment for obesity, but also to be a means for improving related illnesses.[4] Roux-en-Y gastric bypass (RYGB) is considered to be the gold standard for bariatric surgery.[5] However, sleeve gastrectomy (SG) and one-anastomosis gastric bypass-mini-gastric bypass (OAGB-MGB) surgeries have challenged RYGB recently.[6,7]

Nonetheless, despite successful results from treating obesity and related complications using these techniques, there are concerns surrounding their restrictive and/or malabsorptive outcomes, which may be associated with long-term adverse consequences.[8-10] These include protein malnutrition, manifested as albumin (Alb) levels of less than 3.5 g/dl, which may be associated with death, myocardial infarction and sepsis.[11-13] In a number of previous studies, hypoalbuminemia after OAGB-MGB, RYGB and SG was reported.[14-16] The current study was conducted in order to improve previous research data. Furthermore, no similar domestic study had compared the three types of surgery regarding Alb levels.

Liver failure is another complication after rapid weight loss post-bariatric surgery that was previously reported.[17] Moreover, decreased liver transaminase levels were observed in other studies.[18]

OBJECTIVE

Because of these contradictory findings and the lack of similar studies in Iran, the aim of this study was to investigate and compare changes in serum Alb and liver enzyme levels following three types of bariatric surgery. A secondary aim was to measure and compare body composition changes between groups.

METHODS

Patients and study design

This retrospective cohort study was conducted among 151 laparoscopic OAGB-MGB, SG and RYGB surgery patients within the past six months, among those referred to the obesity clinic of Hazrat-e Rasool General Hospital, Tehran, Iran (which is a Center of Excellence of the European Branch of the International Federation for Surgery of Obesity), between April 2018 and June 2019. Patients were enrolled in this study if they were aged 18-65 years and had preoperative body mass index (BMI) ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with major comorbidities such as T2DM, hypertension, CVD or dyslipidemia. Patients with a history of abdominal surgery and pregnancy after obesity surgery were excluded. Data on these patients relating to their condition pre-surgery and three and six months' post-surgery were obtained from the National Iranian Obesity Surgery Database, which is the largest such database in Iran. This study was approved by the Health Ethics Committee of the Research Council of Tehran University of Medical Sciences (Ethics number: IR.TUMS.VCR.REC.1397.308; on July 23, 2018). A written informed consent form was received from all patients.

Data collection

Basic information

Demographic information (age, sex, education and marital status), anthropometric indices (weight, height, BMI, waist and hip) and comorbidities (dyslipidemia, diabetes, hypertension and cardiovascular disease) were collected and recorded in the database by a qualified specialist. Height was measured, without shoes, to the nearest 0.5 cm using a Seca stadiometer (Seca 700, Hamburg, Germany). Body weight was measured with the patient wearing light clothing and no shoes, using a Seca scale (Seca 700, Hamburg, Germany). BMI and percentage total weight loss (%TWL) were calculated using the following formulas, respectively: BMI = weight (kg)/height^2 (m); and %TWL = [(initial weight) – (postoperative weight)]/[(initial weight)] * 100. Waist and hip circumferences were measured using a nonelastic measuring tape, without imposing any pressure on the individual's body, at the top of the iliac crest and at the largest part of the buttocks, respectively, to a precision of 0.1 cm.

Biochemical measurements

Fasting blood samples were taken to measure serum levels of albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALKP), hemoglobin (Hb), hematocrit (Hct) and platelets (PLT). All measurements were made using standard laboratory methods.

Body composition measurements

A body composition analyzer (Tanita BC-418, Tanita Corp., Tokyo, Japan) was used to estimate fat range (%), fat mass (kg), fat-free mass (kg), muscle mass (kg), visceral fat (level) and body water (kg and %).

Dietary intake and physical activity assessment

A 24-hour dietary recall questionnaire (two workdays and one weekend day) was used to assess the dietary intake of each patient[19] in their pre and postoperative states. Physical activity (PA) was assessed preoperatively and also six months postoperatively, by means of the International Physical Activity Questionnaire (IPAQ).[20]

Surgical technique

In SG surgery, about 80% of the stomach is removed from 3-5 cm of the pylorus. For gastric resection, a linear stapler is applied alongside a 36 (Fr) calibrating bougie to achieve a gastric volume of 50-100 cm^3. The OAGB-MGB procedure technique has previously been reported.[21] In the RYGB procedure, a small gastric pouch with a volume of 30-60 cm^3 is created and connected to the Roux limb, with a length of 75-100 cm. The length of the biliopancreatic limb varies between 75 and 100 cm.

Statistical analysis

The sample size of 144 individuals (48 per group) was estimated by considering a two-sided $\alpha = 0.05$ and 80% power ($\beta = 0.2$). Due to the possibility of dropouts, the sample size was then increased by about 10%. Thus, 158 patients were enrolled by means of convenience sampling.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM Corp., Armonk, New York, United States). Descriptive statistics were presented as mean ± standard deviation, or as frequencies and percentages. Repeated-measurement analysis was used to assess dependent variable changes over time (at the times of 0, 3 and 6 months) within each of the groups (SG, RYGB and OAGB-MGB). The differences in means relating to 0-3 and 0-6 months were compared between the groups by means of a univariate general linear model (GLM).

Comparison and analysis of patients' dietary intake and their physical activity levels at two separate times (baseline and six months post-surgery) between the groups was performed

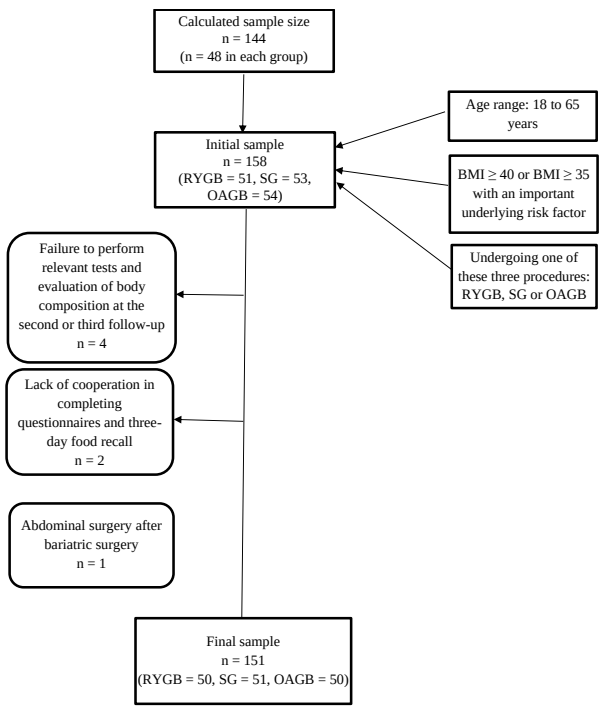
using an analysis of variance (ANOVA) test; the paired-sample t test was also used in intragroup analyses on dietary intake and physical activity levels. P-values < 0.05 were considered statistically significant.

RESULTS

Over the period from April 2018 to June 2019, among 158 eligible patients, 151 were included in the study (50 in the OAGB-MGB and RYGB groups, and 51 in the SG group) (**Figure 1**).

Basic patient characteristics

In the study population, there were almost five times as many females as males (84.1% versus 15.9%). There was no difference among the three groups in terms of female or male gender (P = 0.369). The mean age was highest among the RYGB patients (43.04 ± 8.31 years) (P = 0.017). Also, the patients in the three groups were significantly different in terms of their educational levels (P < 0.001) and marital status (P = 0.003). At six months post-surgery, none of the participants reported smoking or alcohol consumption. Significantly, the number of participants with diabetes in the OAGB-MGB group was about four and three times higher than the SG and RYGB groups, respectively (P = 0.004). No statistical difference in any other comorbidities was found between the groups. The descriptive patient characteristics are shown in **Table 1**.



OAGB-MGB = one-anastomosis gastric bypass-mini-gastric bypass; SG = sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass.

Figure 1. Flow chart of sample size.

Physical activity and dietary intake

Analysis on physical activity revealed that all the patients had light activity (less than 600 metabolic equivalent (MET)-minutes/week) before surgery. However, six months post-surgery, the majority of the patients (96%) had moderate activity: 600-1500 MET-minutes/week.

Detailed information on the mean intake of energy and macronutrients is presented in **Table 2**. The total energy and macronutrient intakes at six months post-surgery were significantly lower than before surgery (P < 0.05). A one-way ANOVA test showed that there were no significant differences in terms of energy and macronutrient intakes among the SG, OAGB-MGB and RYGB groups at baseline (P > 0.05), but that significant differences existed between the three groups six months after surgery (**Table 2**). The Tukey post-hoc test revealed that energy and carbohydrate, protein and fat intakes were significantly higher in the OAGB-MGB group than in the SG group six months after surgery, with significance levels of 0.002, 0.010, 0.044 and 0.010, respectively.

Anthropometric indices, body composition and biochemical parameters

At the three-month follow-up, the mean percentage total weight loss (%TWL) after OAGB-MGB, SG and RYGB was 17.47% ± 4.39%, 18% ± 73% ± 4.55% and 19.56% ± 5.15%, respectively. The OAGB-MGB, SG and RYGB groups lost an average of 26.32% ± 5.13%, 26.59% ± 6.43% and 27.71% ± 4.64% of their total weight by the time of six months post-surgery, respectively. The %TWL differences at three and six months among the three groups were not statistically significant (P = 0.085 at three months and P = 0.805 at six months). The trends of changes in biochemical measurements, anthropometric and body composition, at different time points in the three surgery groups are reported in **Table 3**. According to the one-way repeated-measurement ANOVA results, the serum ALT levels were reduced significantly (P < 0.001) in all three groups. Additionally, significant changes in AST were noted (P = 0.003). However, the Alb and ALKP concentrations did not change significantly within the groups at various time points (P = 0.413 and P = 0.053, respectively). Moreover, the anthropometric parameters (weight, BMI, waist and hip) and body composition parameters (fat stores, muscle mass and fat-free mass) significantly decreased (P < 0.001) over the six-month period following surgery.

Influence of OAGB-MGB, SG and RYGB on physical and blood parameters

The differences in the means of the anthropometric, body composition and biochemical parameters at three and six months after the three different types of bariatric surgery are presented in **Table 4**. Using univariate analysis from the general linear model

Table 1. Basic descriptive characteristics of the patients

Characteristics		OAGB-MGB (n = 50)	SG (n = 51)	RYGB (n = 50)	P-value
Age, years (SD)		39.54 (9.29)	37.73 (10.42)	43.04 (8.31)	0.017*
Gender, n (%)	Female	41 (82)	41 (80.4)	45 (90)	0.37
	Male	9 (18)	10 (19.6)	5 (10)	
Education, n (%)	Illiterate	0 (0)	1 (2)	0 (0)	0.000*
	1-6 years of education	4 (8)	15 (29.4)	12 (24)	
	7-12 years of education	31 (62)	13 (25.5)	31 (62)	
	12+ years of education	15 (30)	22 (43.1)	7 (14)	
Marital status, n (%)	Married	38 (76)	30 (58.8)	39 (78)	0.003*
	Single	8 (16)	18 (35.3)	3 (6)	
	Divorced	4 (8)	3 (5.9)	8 (16)	
Alcohol consumption[$] n (%)	Yes, n (%)	3 (6)	9 (17.6)	3 (6)	0.08
	No, n (%)	47 (94)	42 (82.4)	47 (94)	
Smoking[§], n (%)	Yes, n (%)	4 (8)	8 (15.7)	3 (6)	0.21
	No, n (%)	46 (92)	42 (82.4)	47 (94)	
Comorbidities, n (%)	Diabetes	15 (30)	4 (7.8)	5 (10)	0.004*
	Dyslipidemia	11 (22)	9 (17.6)	11 (22)	0.90
	HTN	8 (16)	8 (15.7)	12 (24)	0.48
	CVD	1 (2)	0 (0)	2 (4)	0.35

OAGB-MGB = one-anastomosis gastric bypass-mini gastric bypass; SG = sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass; SD = standard deviation; BMI = body mass index; HTN = hypertension; CVD = cardiovascular diseases.

[§]Those who smoked tobacco in the past 30 days. [$]Those who consumed alcohol in the past 30 days.

*P-value less than 0.05 was considered statistically significant.

Table 2. Nutrient composition of diets before and six months after three types of surgeries

	OAGB-MGB		SG		RYGB		P-value*	
	Preoperative	6 months postoperative	Pre-operative	6 months postoperative	Preoperative	6 months postoperative	Preoperative	6 months postoperative
Energy (kcal)	2036.25 ± 868.82	719.57 ± 239.31	2173.58 ± 620.89	525.57 ± 308.37	2162 ± 275.54	594.89 ± 274.71	0.51	0.003
Carbohydrate (g)	292.67 ± 138.39	88.95 ± 32.58)	301.46 ± 78.19	65.36 ± 46.96	315.88 ± 56.04	74.41 ± 36.26	0.51	0.013
Fat (g)	63.26 ± 35.38	24.20 ± 13.67	75.09 ± 30.04	17.07 ± 11.56	69.97 ± 17.00	18.97 ± 10.14	0.13	0.011
Protein (g)	77.92 ± 31.51	39.23 ± 15.68	81.99 ± 46.87	31.14 ± 18.17	77.25 ± 23.41	34.98 ± 15.47	0.78	0.057

Data expressed as mean ± SD. *P-value result from ANOVA. P-values less than 0.05 were considered statistically significant.

OAGB-MGB = one-anastomosis gastric bypass-mini gastric bypass; SG = sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass.

Table 3. Trends of serum and physical measurements at various time points in three types of surgical procedure

	OAGB-MGB			SG			RYGB			P-value*
	Preoperative	3 months postoperative	6 months postoperative	Preoperative	3 months postoperative	6 months postoperative	Preoperative	3 months postoperative	6 months postoperative	
Weight (kg)	120.1 ± 22.34	98.85 ± 17.57	88.26 ± 16.16	121.6 ± 18.36	98.51 ± 13.5	89 ± 13.87	118.26 ± 17.38	94.93 ± 13.87	86.10 ± 12.48	< 0.001
BMI (kg/m²)	45.91 ± 6.95	39.06 ± 10.11	33.77 ± 5.30	45.23 ± 5.97	36.69 ± 4.67	33.14 ± 4.83	45.01 ± 4.91	36.16 ± 4.23	32.81 ± 3.95	< 0.001
Waist (cm)	117.52 ± 13.62	100.91 ± 11.28	93.23 ± 10.01	115.93 ± 9.58	97.43 ± 8.52	93.81 ± 8.27	116.64 ± 9.86	98.23 ± 7.87	91.79 ± 8.43	< 0.001
Hip (cm)	134.17 ± 11.61	118.94 ± 11.26	111.44 ± 9.18	135.62 ± 7.98	119.65 ± 7.62	113.81 ± 9.15	136.76 ± 8.99	120.86 ± 9.02	112.14 ± 9.25	< 0.001
Fat range (%)	45.19 ± 8.64	40.68 ± 6.94	35.05 ± 8.09	46.79 ± 5.51	40.69 ± 6.11	36.48 ± 6.99	47.58 ± 4.59	40.59 ± 5.96	35.38 ± 6.99	< 0.001
Fat mass (kg)	55.01 ± 14.01	40.12 ± 11.13	31.15 ± 10.34	56.71 ± 12.31	40.21 ± 10.62	32.76 ± 11.72	56.59 ± 11.13	38.69 ± 81.88	30.45 ± 8.59	< 0.001
Fat free mass (kg)	64.21 ± 13.94	58.13 ± 11.74	56.65 ± 11.13	64.07 ± 9.80	57.77 ± 7.77	55.72 ± 7.61	62.04 ± 11.05	56.25 ± 9.14	54.94 ± 8.64	< 0.001
Visceral fat (level)	16.46 ± 5.68	11.78 ± 3.75	8.98 ± 3.41	15.96 ± 4.03	11.09 ± 3.14	8.78 ± 3.10	15.90 ± 4.13	10.72 ± 2.61	8.40 ± 2.59	< 0.001
Muscle mass (kg)	60.97 ± 13.33	55.16 ± 11.30	53.79 ± 10.68	60.83 ± 9.41	54.88 ± 7.47	52.93 ± 7.33	58.87 ± 10.55	53.39 ± 8.73	52.17 ± 8.29	< 0.001
Body water (%)	47.00 ± 10.20	42.50 ± 8.62	41.47 ± 8.15	46.88 ± 7.24	42.25 ± 5.74	40.73 ± 5.62	45.41 ± 8.09	41.19 ± 6.69	40.23 ± 6.32	< 0.001
Body water (kg)	39.53 ± 4.24	43.41 ± 5.08	47.62 ± 6.02	39.04 ± 4.01	43.48 ± 4.49	46.55 ± 5.14	38.37 ± 3.36	43.71 ± 4.42	47.53 ± 5.17	< 0.001
Hb (mg/dl)	13.44 ± 1.54	13.38 ± 1.37	13.12 ± 1.41	13.72 ± 1.41	13.98 ± 1.31	13.89 ± 1.40	13.45 ± 1.31	13.32 ± 1.41	13.03 ± 1.39	0.015
HCT (%)	40.79 ± 4.22	40.21 ± 5.66	39.49 ± 3.65	41.51 ± 3.59	43.08 ± 6.72	41.62 ± 3.83	40.79 ± 3.25	40.85 ± 9.20	39.61 ± 3.94	0.091
PLT (10³/mm³)	276.96 ± 69.88	244.63 ± 78.97	257.41 ± 71.13	297.57 ± 65.21	255.65 ± 65.14	266.35 ± 72.79	299.49 ± 78.57	256.33 ± 69.35	266.49 ± 67.74	< 0.001
Alb (g/l)	4.27 ± 0.36	4.32 ± 0.52	4.21 ± 0.37	4.42 ± 0.40	4.37 ± 0.41	4.35 ± 0.38	4.31 ± 0.39	4.28 ± 0.33	4.28 ± 0.51	0.41
SGOT (U/l)	18.56 ± 6.51	25.86 ± 13.61	20.23 ± 8.05	27.40 ± 22.90	21.99 ± 9.38	18.56 ± 5.42	22.11 ± 15.25	22.86 ± 12.16	19.05 ± 5.70	0.003
SGPT (U/l)	23.38 ± 3.51	28.45 ± 16.36	19.65 ± 10.58	34.22 ± 27.97	25.24 ± 16.37	17.70 ± 7.86	26.30 ± 17.22	25.55 ± 17.01	18.85 ± 7.82	< 0.001
ALKP (U/l)	187.60 ± 54.99	184.00 ± 45.53	198.48 ± 47.43	170.28 ± 59.76	153.16 ± 50.10	155.35 ± 56.23	191.38 ± 60.32	182.09 ± 49.04	193.20 ± 54.35	0.053

OAGB-MGB = one-anastomosis gastric bypass-mini gastric bypass; SG = sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass; BMI = body mass index; Hb = hemoglobin; Hct = hematocrit; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ALKP = alkaline phosphatase; BUN = blood urea nitrogen; Alb = albumin.

Data are expressed as mean ± standard deviation. *P-values are results from repeated-measurement one-way analysis of variance. P-values less than 0.05 were considered statistically significant.

(GLM), the effects of confounding variables were controlled for, including age, gender, education level, marital status, alcohol consumption and diabetes, as dependent variables.

Regarding mean differences in dependent variables and operations as fixed factors in the univariate model, there were no significant differences in albumin levels among the groups post-surgery (P > 0.05). Despite the postoperative fluctuations in the serum levels of liver enzymes (AST, ALT and ALKP) that were observed in both the OAGB-MGB and the RYGB group, all of these enzymes in the SG group showed significant decreasing trends during the study. Interestingly, SG was significantly more effective than OAGB-MGB in lowering AST (P = 0.003 at three months and P = 0.015 at six months), ALT (P = 0.005 at three months and P = 0.015 at six months) and ALKP (P = 0.037 at six months). Additionally, significant differences were found among the three groups in terms of the fat range percentage at both times (P = 0.014 and P = 0.036 at three and six months, respectively). Interestingly, RYGB, in comparison with OAGB-MGB, had a greater effect on fat range reduction (P = 0.011 at three months; P = 0.059 at six months). Moreover, fat mass reduction at three months post-surgery was highest in RYGB patients, and there was a considerable difference with OAGB-MGB in pairwise comparisons (P = 0.042).

DISCUSSION

This study focused on changes in serum Alb levels and liver enzymes in 151 patients who had undergone RYGB, OAGB-MGB or SG. Significant changes in serum AST and ALT levels were noted during the follow-up. Additionally, in the intergroup

Table 4. Results from univariate general linear model (GLM) for the mean differences in variables at three and six months after surgery

		OAGB-MGB (n = 50)	SG (n = 51)	RYGB (n = 50)	P-value
Diff-Weight (kg)	0-3	-21.25 ± 7.56	-23.09 ± 7.59	-23.33 ± 8.11	0.13
	0-6	-31.84 ± 9.44	-32.60 ± 9.93	-32.16 ± 8.46	0.46
Diff-Waist (cm)	0-3	-16.10 ± 8.07	-15.72 ± 5.87	-18.37 ± 8.40	0.096
	0-6	-26.76 ± 14.14	-23.41 ± 10.60	-24.35 ± 7.77	0.52
Diff-Hip (cm)	0-3	-15.77 ± 7.80	-15.99 ± 8.10	-16.27 ± 7.70	0.84
	0-6	-23.60 ± 7.22	-24.16 ± 11.48	-24.20 ± 8.85	0.81
Diff-BMI (kg/m²)	0-3	-6.86 ± 9.69	-8.54 ± 2.59	-8.85 ± 2.77	0.096
	0-6	-12.14 ± 3.15	-12.08 ± 3.44	-12.19 ± 2.69	0.68
Diff-Fat range (%)	0-3	-4.51 ± 7.13	-6.10 ± 2.77	-7.00 ± 3.63	0.01[b]
	0-6	-10.14 ± 8.42	-10.31 ± 4.04	-12.21 ± 4.40	0.04[b]
Diff-FM (kg)	0-3	-14.89 ± 6.59	-16.61 ± 5.32	-17.90 ± 8.02	0.035[b]
	0-6	-23.86 ± 8.48	-23.95 ± 11.73	-26.14 ± 8.89	0.28
Diff- FFM (kg)	0-3	-6.08 ± 3.48	-6.30 ± 3.32	-5.79 ± 3.33	0.91
	0-6	-7.55 ± 4.32	-8.35 ± 4.10	-7.11 ± 3.67	0.86
Diff-MM (kg)	0-3	-5.80 ± 3.23	-5.95 ± 3.16	-5.48 ± 3.17	0.93
	0-6	-7.18 ± 4.02	-7.90 ± 3.88	-6.70 ± 3.47	0.87
Diff-VF	0-3	-4.68 ± 2.77	-4.86 ± 2.01	-5.18 ± 3.03	0.19
	0-6	-7.48 ± 3.73	-7.18 ± 2.70	-7. 50 ± 3.45	0.24
Diff-TBW (%)	0-3	-4.50 ± 2.51	-4.61 ± 2.43	-4.22 ± 2.94	0.10
	0-6	-5.53 ± 3.16	-6.15 ± 3.01	-5.18 ± 3.08	0.84
diff-BW (kg)	0-3	3.88 ± 2.29	4.47 ± 2.04	5.34 ± 2.90	0.006[b]
	0-6	8.09 ± 3.86	7.51 ± 2.97	9.16 ± 3.48	0.025[a]
diff-Alb (g/l)	0-3	0.05 ± 0.51	-0.04 ± 0.53	-0.03 ± 0.47	0.40
	0-6	-0.07 ± 0.54	-0.06 ± 0.52	-0.03 ± 0.57	0.70
diff-SGOT (U/l)	0-3	7.30 ± 13.09	-5.41 ± 18.36	0.75 ± 17.77	0.005[c]
	0-6	1.67 ± 8.70	-8.69 ± 21.91	-3.06 ± 16.99	0.02[c]
diff-SGPT (U/l)	0-3	5.07 ± 15.15	-8.98 ± 22.31	-0.76 ± 20.43	0.006[c]
	0-6	-3.73 ± 13.14	-16.23 ± 26.94	-7.45 ± 18.00	0.017[c]
diff-ALKP (U/l)	0-3	-3.40 ± 51.54	-18.08 ± 57.42	-9.29 ±51.04	0.16
	0-6	11.32 ± 52.87	-13.91 ± 56.47	3.70 ± 60.10	0.041[c]

Data are expressed as mean ± standard deviation. OAGB-MGB = one-anastomosis gastric bypass-mini-gastric bypass; SG = sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass; Diff = mean difference; (0-3) = mean difference in variables three months after surgery, compared with preoperative time; (0-6) = mean difference in variables six months after surgery, compared with preoperative time; BMI = body mass index; BMR = basal metabolic rate; FM = fat mass; FFM = fat-free mass; MM = muscle mass; VF = visceral fat level; TBW = total body water; BW = body water; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; Alb = albumin; ALKP = alkaline phosphatase. P-values are results from univariate GLM and are significant at the 0.05 level. [a,b,c]Pairwise comparison adjustment for multiple comparisons: Bonferroni; [b]Significant difference between OAGB-MGB and RYGB; [a]Significant difference between SG and RYGB; [c]Significant difference between SG and OAGB-MGB.

comparison, SG showed a significant effect towards reducing both transaminases at both time points, and on ALKP levels at six months, compared with OAGB-MGB. Changes in serum Alb levels were not significantly different among the three groups.

Weight loss-induced improvements in liver enzyme levels among patients receiving bariatric surgery (non-adjustable or adjustable banding, vertical banded gastroplasty or gastric bypass) have previously been reported.[18] Bariatric surgery reduces transaminase levels[22] by reducing liver fat and inflammation, and also by improving insulin resistance following appetite loss and calorie restriction.[23] Despite the reported importance of weight loss in relation to reduction of liver enzymes, the present study revealed that SG played a vital role in reducing liver enzymes compared with the two other surgical methods, especially OAGB-MGB; a downward trend of weight was observed in all three groups, with no statistically significant differences. The presence of a lower number of patients with diabetes in the SG group (7.8%) than in the RYGB group (10%), and particularly lower than in the OAGB-MGB group (30%), might explain this finding. It is worth noting that, in the clinic of the present study, the main reason given for performing a higher proportion of OAGB-MGB surgeries among patients with diabetes was its greater effectiveness in lowering blood sugar, compared with other types of surgery.[24,25] This is supported by a previous study that indicated that SG resulted in greater liver enzyme improvement, compared with RYGB.[26] However, no data comparing SG and OAGB-MGB were available. Several mechanisms have been proposed for explaining the increased levels of liver enzymes after OAGB-MGB:

1. Worse fatty liver levels following OAGB-MGB, with increased levels of liver enzymes.[27] In this regard, diagnostic evaluation of hepatic steatosis seems to be an important factor. However, in the clinic of the present study, no routine evaluation of liver steatosis and fibrosis was performed within the short-term postoperative assessments, which was in accordance with the guidelines of the American Society for Metabolic and Bariatric Surgery (ASMBS)[28] (0, 3 and 6 months).
2. Liver enzyme levels can also be increased through growth of intestinal bacterial flora, which leads to production of hepatotoxic macromolecules that are transported to the liver through the portal vein. In vulnerable livers facing nutritional challenges, this can lead to liver damage.[29]
3. Malabsorption and malnutrition after OAGB-MGB seem to be an underlying mechanism involved in increased liver enzyme levels.[30] In this regard, we assessed the patients' dietary intake, although we did not study the link between liver enzymes and markers of malnutrition, except albumin.

In this context, no significant changes in serum Alb levels were noted in any group of the present study. Additionally, the intergroup comparison of mean difference of Alb at three and six months after surgery did not show any statistically significant difference. This result was in agreement with some previous findings.[31,32] However, Jammu and Sharma found that the prevalence of hypoalbuminemia was lower in a SG group and higher in an OAGB-MGB group. Those authors suggested that being vegetarian, having diabetic nephropathy, having alcoholic or nonalcoholic fatty liver disease and presenting long bypass limb length were possible causes of albumin deficiency. However, their long-term follow-up (maximum 87 months and minimum 20 months), in comparison with the short follow-up of the present study (six months) may explain this discrepancy. Likewise, the 24-hour dietary recall analysis of the present study showed that energy and protein intake in malabsorptive surgery groups (especially OAGB-MGB) were higher than in the SG group. No exact measurement of dietary protein intake was made in Jammu and Sharma's study: their patients were only recorded as having a high-protein diet based on self-reported statements.

Significant reductions in anthropometric and body composition parameters were observed in all three groups. The greatest reduction in body fat range and fat mass at six months post-surgery was observed in the RYGB group. This reduction was significant, compared with the OAGB-MGB group.

Weight loss and decreases in BMI and waist, and hip circumference have previously been reported after bariatric surgery.[33] However, the downward trend of anthropometric indices was not significantly different among the three groups. Additionally, there was no statistical difference in %TWL between three groups. This result was also consistent with previous findings, which showed that SG may be correlated with malabsorptive bariatric surgery aimed at weight loss.[34] However, some inconsistencies have also been observed.[35] The main reason for the same %TWL and BMI loss between the three groups seems to have been patient-tailored surgery, as decided by the surgeon.

Loss of body fat reserves, along with fat-free mass and muscle mass wasting, was found in all groups, which concurs with similar post-bariatric surgery studies.[36] This may relate to significant restrictions of energy and macronutrient intake (**Table 2**). Additionally, the fat range percentage and fat mass in the RYGB group were lower than in the other two groups, especially the OAGB-MGB group, while the reductions in fat-free mass and muscle tissue after the three types of surgery did not differ significantly. This was contrary to the findings of Arble et al. (2018),[37] who showed that both RYGB and OAGB-MGB surgeries had positive effects on fat reduction, compared with SG, and that there was no significant difference in body fat loss between RYGB and OAGB-MGB. Also, no change in muscle tissue was observed by Arble et al. after surgery, compared with a control group. These inconsistencies may have been due to differences in study designs (human versus animal study).

Additionally, the role of physical activity in maintaining muscle mass cannot be ignored.[38,39] Physical activity in all study groups improved from mild to moderate after surgery. However, concurrent food intake reductions were also observed in all groups. The OAGB-MGB group had higher energy and macronutrient consumption than the other groups, while the weight change among the groups was statistically similar. This suggests that OAGB-MGB patients may experience greater decreases in nutrient absorption than RYGB and SG patients. A rat study also showed that the OAGB-MGB group was more malabsorbent, showing greater protein and calorie excretion than the RYGB group. Likewise, slightly higher food intake in the OAGB-MGB group was observed, which was attributed to the increased expression of orexigenic peptides (neuropeptide Y and N-acetyl-γ-glutamyl-phosphate) in the rat hypothalamus.[40]

One of the strengths of the present study was that changes in liver enzymes, serum Alb, body composition parameters, dietary intake and physical activity were simultaneously evaluated in three surgical groups. However, the sample selection from a single obesity clinic in Hazrat-e Rasool General Hospital may have been a limitation (nonetheless, patients are referred nationally, and thus the results may be generalized with minimum bias). Furthermore, the lack of dietary measurement and physical activity at three months post-surgery was another limitation. Additionally, due to the retrospective nature of the data sources, we could not control for some specific variables, such as the preoperative severity of steatosis and steatohepatitis, by either direct or indirect means.

CONCLUSION

The findings from this study provide support regarding the ability of SG to reduce the serum levels of AST, ALT and ALKP; and the ability of RYGB to reduce body fat, compared with OAGB-MGB surgery, within short-term follow-up. However, all of these types of surgery were found to be equally effective regarding serum albumin changes and %TWL at the six-month follow-up. This study may lead to greater insights into the various surgical procedures for patients with different blood parameters and body composition conditions.

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Authors' contributions: Hassan Zadeh M: data curation (equal), investigation (lead), methodology (supporting), resources (equal), visualization (supporting) and writing-original draft (lead); Zamaninour N: conceptualization (supporting), data curation (equal), investigation (equal), methodology (lead), project administration (equal), resources (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (lead); Ansar H: formal analysis (equal), software (equal) and writing-original draft (equal); Kabir A: formal analysis (lead), software (equal), supervision (equal) and writing-review and editing (equal); Mohammadi Farsani G: conceptualization (equal), project administration (lead) and supervision (lead); and Pazouki A: data curation (supporting), resources (supporting) and supervision (supporting). All authors provided critical feedback and helped shape the research, analyzes and manuscript

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Address for correspondence:
Gholamreza Mohammadi Farsani
Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), No: 44 Hojjatdoost Alley, Naderi St., Keshavarz Blvd., Tehran, Iran
Tel. +98-21-88955742 — Fax. +98-21-88984861
E-mail: mohammadigh53@gmail.com

Colonization of methicillin-resistant Staphylococcus aureus among healthcare students: an integrative review

Erika Morganna Neves de Oliveira[I], Ana Raquel Batista de Carvalho[II], Adriano Menis Ferreira[III], Luana Kelle Batista Moura[VI], Andreia Rodrigues Moura da Costa Valle[V], Daniela Reis Joaquim de Freitas[VI], Maria Eliete Batista Moura[VII]

Nursing Postgraduate Program, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil; Nursing Postgraduate Program, Universidade Federal de Mato Grosso do Sul, Três Lagoas (MG), Brazil; and Department of Dentistry, Centro Universitário Santo Agostinho, Teresina (PI), Brazil

[I]MSc, PhD. Nurse, Nursing Postgraduate Program, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil.
https://orcid.org/0000-0001-8588-6290

[II]MSc. Doctoral Student, Nursing Postgraduate Program, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil.
https://doi.org/0000-0001-5287-1084

[III]PhD. Nurse and Professor, Nursing Postgraduate Program, Universidade Federal de Mato Grosso do Sul (UFMS), Três Lagoas (MS), Brazil.
https://orcid.org/0000-0002-4054-768X

[IV]PhD. Dentist and Professor, Department of Dentistry, Centro Universitário Santo Agostinho, Teresina (PI), Brazil.
https://orcid.org/0000-0003-4917-7598

[V]PhD. Nurse and Professor, Nursing Postgraduate Program, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil.
https://orcid.org/0000-0002-2706-0711

[VI]PhD. Biologist and Professor, Department of Microbiology, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil.
https://orcid.org/0000-0002-5632-0332

[VII]PhD. Nurse and Professor, Nursing Postgraduate Program, Universidade Federal do Piauí (UFPI), Teresina (PI), Brazil.
https://orcid.org/0000-0001-9988-1992

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ABSTRACT

BACKGROUND: Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is a worldwide concern given its presence even in non-hospitalized healthy individuals, such as university students.

OBJECTIVE: To identify in the literature the prevalence of colonization by MRSA among healthcare students.

DESIGN AND SETTING: Integrative review of the literature conducted in Universidade Federal do Piauí.

METHOD: A search for primary studies was performed in the following databases: Medical Literature Analysis and Retrieval System on-line; Cumulative Index to Nursing and Allied Health Literature; Web of Science; Scopus; and LILACS.

RESULTS: This review included 27 studies that demonstrated MRSA infection prevalence ranging from 0.0 to 15.3% among students.

CONCLUSION: The prevalence of colonization of MRSA among healthcare students is high, and the nasal cavity was cited as an important reservoir location for these microorganisms.

INTRODUCTION

Staphylococcus aureus is considered to be a persistent member of the human endogenous microbiota and has historically been associated with important and serious cases of infection. It has the ability to rapidly develop resistance to antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) is considered to be a paradigm for bacterial infections, since it is associated with high rates of morbidity and mortality.[1-3]

In assisting carriers of bacterial infections or colonized or infected patients, or in handling contaminated objects, healthcare workers' hands can become contaminated. These workers may subsequently transmit the microorganism to other patients. However, this situation is not exclusive to the hospital environment. Clinically manifested diseases in the community or in professionals and/or patients may lead to situations in which some individuals are asymptomatic carriers, also called colonized individuals or simply carriers, when the disease is present in the host organism without causing apparent manifestations.[1,4] In the United States and Taiwan, the prevalence of strains acquired in the community is 52%, thus exceeding the proportion of strains acquired in hospital environments.[5] There have also been reports of cases of MRSA acquired in the community.[6,7]

Healthcare students play an important role in the epidemiology and pathogenesis of *Staphylococcus aureus* infection and can act as a source of dissemination both in the community and in hospital environments, and for carrying bacteria from one of these environments to another.[1]

In Brazil, this topic has been little addressed, but it is known that the presence of MRSA among students has been gradually spreading.[1] Hence, it has become relevant to summarize the knowledge of MRSA that has resulted from research on this subject.

OBJECTIVE

The objective of this study was to identify in the literature the prevalence of colonization by methicillin-resistant *Staphylococcus aureus* among healthcare students.

METHODS

Research design

This study was an integrative review of the literature, incorporating a method of searching for secondary data.[8] To preserve methodological rigor, the following steps were taken to conduct this review: formulation of the research question; idealization of sampling plan and data collection strategies; extraction of relevant data from studies included in the review; and, finally, analysis and interpretation of the data.[8]

The research question was elaborated in accordance with the PVO strategy (P – population; V – variable of interest; O – outcome). Thus, in line with the objective of the study, the following structure was used: P - healthcare students; V – methicillin-resistant *Staphylococcus*; O – prevalence.[9] Therefore, the following question was asked: "What evidence is available in the literature regarding the prevalence of methicillin-resistant *Staphylococcus aureus* colonization among healthcare students?"

Data collection period

Searching for and selection of studies took place between the months of November 2019 and January 2020 and were carried out by two independent reviewers. Any divergences were resolved by a third reviewer.

Selection criteria

After the search stage, original articles were selected, based on reviewing their titles and abstracts, in accordance with the following inclusion criteria: original articles covering the population of undergraduate students in the field of healthcare who experienced clinical activities that brought them into direct contact with patients.

The full text of each article was then read, with a view to choosing studies that answered the research question. Through this process, articles involving high school or technical students, those that did not comply with selection criteria mentioned above, those that did not answer the research question and those that were duplicates were excluded, as also were opinion articles, theoretical reflections, dissertations and book chapters.

Data collection

The following databases were selected: Medical Literature Analysis and Retrieval System online (MEDLINE) via National Library of Medicine National Institutes of Health (PubMed); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Web of Science; Scopus; and Literatura Latino-americana e do Caribe em Ciências da Saúde (LILACS) via Biblioteca Virtual em Saúde (BVS).

The descriptors and keywords used in the search were applied in accordance with particularities of each database. They were obtained by consulting the Descritores em Ciências da Saúde (DeCS), Medical Subject Headings (MeSH) and titles from CINAHL. During the search, descriptors were cross-referenced with each other using the Boolean operators "or" and "and". Descriptors were inserted in the English language, since all journals indexed in these databases have descriptors in English in their articles; with the exception of BVS, in which descriptors were inserted in English and Portuguese. To expand the search, there was no limitation on the time of publication or language. **Table 1** shows the descriptors used in this study and summarizes how the search was carried out.

Table 1. Descriptors used in the search strategy for primary articles. Teresina (PI), Brazil, 2020

Data Source
Descriptors and Keywords
BVS
Estudantes OR Estudantes de Ciências da Saúde OR Estudantes de Enfermagem OR Estudantes de Farmácia OR Estudantes de Medicina OR Aluno OR Alunos OR Estudante OR Enfermeiras Estudantes OR Alunos de Enfermagem OR Estudante de Enfermagem OR Enfermeiros Estudantes
Staphylococcus aureus
Resistência à meticilina
PubMed/ WEB OF SCIENCE/ SCOPUS
"Students" OR "Students, Health Occupations" OR "Students, Nursing" OR "Students, Pharmacy" OR "Students, Medical" OR Students, Dental" OR "Health Occupations Students" OR "Health Occupations Student" OR "Student, Nursing" OR "Nursing Student" OR "Nursing Students" OR "Pharmacy Students" OR "Student, Pharmacy" OR "Pharmacy Student" OR "Medical Students" OR "Student, Medical" OR "Medical Student" OR "Dental Students" OR "Student, Dental" OR "Dental Student"
"Staphylococcus aureus"
"Methicillin Resistance" OR "Resistance, Methicillin" OR "Methicillin-Resistant" OR "Methicillin Resistant"
CINAHL
Students, Health Occupations
Staphylococcus aureus
Methicillin-Resistant Staphylococcus Aureus

Data processing and analysis

The studies thus found were exported to the Endnote reference manager software, version 20 (Clarivate Analytics, Philadelphia, United States), in order to identify duplicates and gather together all publications. In addition, the reference lists of these articles were consulted in order to find any additional studies. The selection of studies followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[9] (**Figure 1**).

For data analysis and extraction, a data collection instrument that had been validated by Ursi was chosen for this study and was adapted for use in it.[10] Furthermore, the protocol for this review was previously assessed by experts in the method used. After fully evaluating the texts, a descriptive analysis on the results found was carried out, in which a synthesis of all the studies included in the review was presented, along with comparisons between them.

RESULTS

The final sample for this review comprised 30 primary articles, which were characterized taking into account the authors, year of publication, country, objective and main results (**Table 2**). These studies were published in the years 2010, 2012, 2013, 2014, 2015, 2016, 2017, 2018 and 2019.[3,5,7,11-37]

Regarding the locations of the studies, they were carried out in Brazil, Malaysia, Colombia, China, Palestine, Spain, Brunei, India, Turkey, Czech Republic, Saudi Arabia, Madagascar, Pakistan, Nepal, Tanzania, South Korea, Iran, Ireland, Jordan, Italy, Nigeria, Poland and Ethiopia.[3,5,7,11,12,14-22,24-37]

The populations addressed by the researchers of these 30 studies were nursing students, medical students, health science students and dental students.[3,5,7,12-18,20,21,23-25,27,29-30,33-37] Two studies involved students from more than one undergraduate course.[11,22,28]

To detect colonizing microorganisms, samples were collected using the technique of swab smears from nasal specimens, in all of these studies except for four studies, in which specimens were collected from more than one anatomical site.[3,5,7,15-17,18-27-30,33-37]

Regarding the prevalence of MRSA, the student population in some studies was divided into groups before exposure to healthcare and after such exposure.[14,19,21,23,26] The percentages found are shown in **Table 3**.

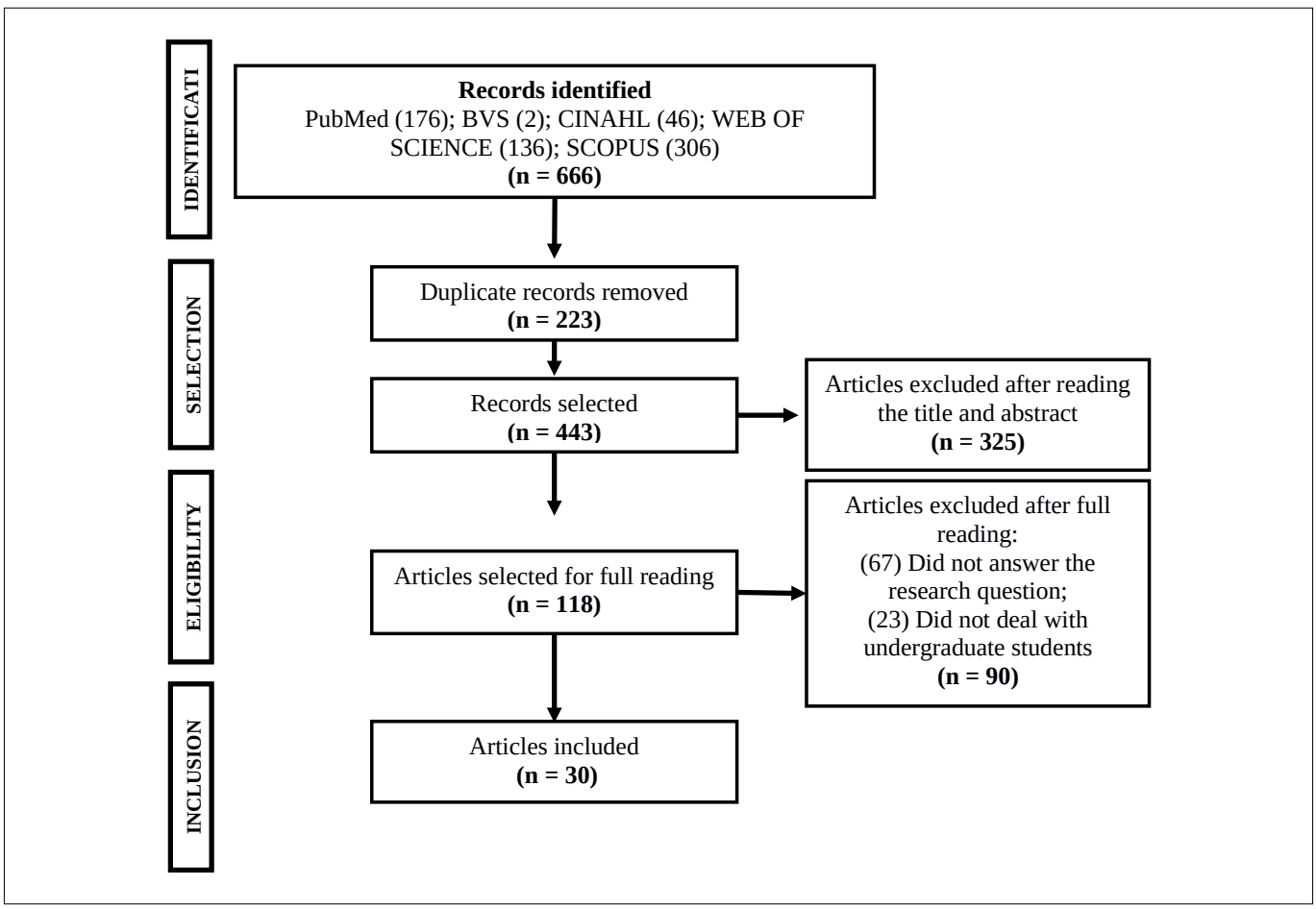

Figure 1. Study selection flowchart. Teresina (PI), Brazil, 2020.

Table 2. Characterization of studies included in this review (n = 30). Teresina (PI), Brazil, 2020

Article	Authors/Year	Location	Objective	Site
A1	Prates et al.[11] 2010	Brazil	To determine the prevalence of nasal transportation of *S. aureus* in university students.	Nostrils
A2	Syafinaz et al.[12] 2012	Malaysia	To determine the prevalence of *S. aureus* nasal carriers among medical students.	Nostrils
A3	Bettin et al.[13] 2012	Colombia	To investigate the nasal transportation of Panton-Valentin leukocidin-positive *S. aureus* strains, categories of transportation and risk factors associated with colonization, in medical students.	Nostrils
A4	Chen et al.[14] 2012	China	To investigate whether clinical exposure in the hospital affects MRSA nasal transportation among medical students.	Nostrils
A5	Sabri et al.[16] 2013	Palestine	To investigate the prevalence of nasal transportation of *S. aureus* and MRSA.	Nostrils
A6	López-Aguilera et al.[15] 2013	Spain	To determine the prevalence of nasal carriers of sensitive and methicillin-resistant *S. aureus* and evaluate knowledge of and adherence to hand hygiene among students.	Nostrils
A7	Mat Azis et al.[17] 2014	Malaysia	To evaluate the transportation of *S. aureus* and its persistence in students of health sciences.	Nostrils
A8	Malik et al.[18] 2014	Brunei	To determine the prevalence of the status of nasal carrier of *S. aureus* and MRSA among healthy young people.	Nostrils
A9	Krishnamurthy et al.[19] 2014	India	To examine the influence of exposure to the hospital environment on MRSA transportation, MRSA antimicrobial resistance patterns and presence of genes that encode five determinants of extracellular pathogenicity.	Nostrils, throat and hand palms
A10	Demirel et al.[20] 2014	Turkey	To investigate the prevalence of methicillin-sensitive (CA-MSSA) and resistant (CA-MRSA) *S. aureus*, including inducible sleepers (ID-MRSA), in *S. aureus* and MRSA strain genotypes from nasal cultures.	Nostrils
A11	Renushri et al.[21] 2014	India	To assess the influence of exposure to the hospital environment on MRSA transportation.	Nostrils and throat
A12	Ribeiro et al.[22] 2014	Brazil	To identify *S. aureus* and MRSA in university students.	Nostrils and palm hands
A13	Holý et al.[24] 2015	Czech Republic	To investigate the prevalence of nasal transportation of *S. aureus* and MRSA in healthy people aged 18–26 years. To find out whether the prevalence of nasal transportation strains of *S. aureus* and MRSA varies over the years of studies. To compare general medical students from year 1 and year 5 for nasal transportation of *S. aureus* and MRSA strains.	Nostrils
A14	Zakai et al.[23] 2015	Saudi Arabia	To identify MRSA nasal carrier status among medical students during their clinical rotations.	Nostrils
A15	Collazos Marín et al.[25] 2015	Colombia	To establish the genetic diversity of *S. aureus* isolates and detect the presence of mecA gene in isolated strains in asymptomatic medical students who were in their clinical rotation phase in a hospital.	Nostrils
A16	Petti et al.[26] 2015	Italy	To evaluate the MRSA carrier rate in a sample of dental students.	Nostrils, throat and palm hands
A17	Hogan et al.[3] 2016	Madagascar	To examine the prevalence and clonal epidemiology of nasal *S. aureus* and MRSA among healthcare professionals and non-medical university students.	Nostrils
A18	Javaeed et al.[27] 2016	Pakistan	To assess the prevalence of MRSA transportation in healthy medical students.	Nostrils
A19	Subri et al.[28] 2016	Malaysia	To determine the prevalence of nasal colonization of *S. aureus* and its susceptibility to antibiotics among pre-clinical and clinical physicians and nursing students.	Nostrils
A20	Ansari et al.[29] 2016	Nepal	To evaluate the rate of nasal colonization of *S. aureus*, its methicillin-resistant strains and risk factors in medical students before clinical exposure.	Nostrils
A21	Okamo et al.[30] 2016	Tanzania	To determine the prevalence of *S. aureus* and MRSA nasal transportation among medical students, and the antimicrobial susceptibility of isolated profiles of *S. aureus*, and to verify the association of *S. aureus* nasal transportation with demographic and clinical characteristics.	Nostrils

Continue…

Table 2. Continuation

Article	Authors/Year	Location	Objective	Site
A22	Baek et al.[31] 2016	South Korea	To determine the prevalence rate of nasal colonization by MRSA among dental students and identify the characteristics of the strains isolated.	Nostrils
A23	Radhakrishna et al.[32] 2016	India	To establish the prevalence and pattern of S. aureus antibiograms, with special emphasis on MRSA among students of the second year.	Nostrils
A24	Abroo et al.[7] 2017	Iran	To investigate the prevalence, antimicrobial susceptibility and molecular factors characteristic of CA (community acquired) MRSA among two groups of college students (medical and non-medical).	Nostrils
A25	Budri et al.[33] 2018	Ireland	To investigate co-located nasal *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS), recovered from healthy medical students in a preclinical year and the transportation of genes and common elements to both species that may contribute to the evolution of *S. aureus* and MRSA.	Nostrils
A26	Al-Tamimi et al.[34] 2018	Jordan	To investigate the prevalence, standard antimicrobial susceptibility, antibiotic resistance genes and risk factors of medical students with MRSA.	Nostrils
A27	Suhaili et al.[35] 2018	Malaysia	To evaluate the antimicrobial susceptibility profile of *S. aureus* strains isolated from university students and to determine the prevalence of resistance to constitutive and inducible clindamycin, in which the latter would be capable of causing therapeutic failure due to false in vitro susceptibility to clindamycin.	Nostrils
A28	Onanuga et al.[36] 2019	Nigeria	To determine the antibiogram and the virulent characteristics of nasal *S. aureus*, accessing its profile of resistance to antibiotics and potential pathogens in healthy students at the University of the Niger Delta, Bayelsa State, Nigeria.	Nostrils
A29	Szymanek-Majchrzak et al.[37] 2019	Poland	To evaluate and compare the level of colonization of *S. aureus* (MRSA or MSSA) among medical students and evaluate the sensitivity of the strains.	Nostrils
A30	Efa et al.[5] 2019	Ethiopia	To determine the nasal transportation of MRSA and its antimicrobial susceptibility patterns among medical students at the Jimma University Medical Center (JUMC), southwestern Ethiopia.	Nostrils

DISCUSSION

Worldwide, occurrence of healthcare-associated infections (HAI) is one of the main public health problems, with severe human and economic repercussions. According to the Centers for Disease Control and Prevention (CDC), MRSA infections have outperformed HIV as the leading cause of morbidity and mortality in the United States.[38]

Studies have revealed high prevalence of MRSA in patients and healthcare professionals with exposure to the healthcare system.[23,38,39] However, the results systematized in the present study revealed that presence of MRSA has also been reported among non-hospitalized healthy individuals, such as undergraduate students, ranging from 0.0% to 15.3%.[14,25,26]

Data in the literature have highlighted occurrences of MRSA infection in healthy populations that live in agglomerations or experience such conditions but which have little or no contact with healthcare services, as is the case of undergraduate students within the field of healthcare.[1,40] This was observed in the present study, thus indicating that MRSA infection was present in students who were not exposed to hospital environments. This may indicate the presence of community-acquired MRSA strains.[1] It needs to be borne in mind that in the studies discussed here, students who had been hospitalized within the last few months had been excluded, considering that hospitalization could be a confounding factor for occurrences of MRSA.

Identification of high frequencies of MRSA in students before they were exposed to experiences of clinical care is a matter for concern. It indicates that there is a need for effective infection prevention and control policies, in relation to hygiene and surveillance.[5]

Clinical practice among students in the field of healthcare is part of the teaching-learning process. In relation to this process, there is exposure to occupational risks, especially through recognition of the variability of care provided to patients.[1,5] In this regard, studies that have addressed the prevalence of MRSA among students after exposure to hospital environments can provide evidence that exposure to MRSA in hospitals can play a critical role in achieving nasal colonization by MRSA.

According to the literature, the nostrils are the main colonization site for *Staphylococcus aureus*, whose prevalence reaches, on average, 40% in the adult population.[1,5-6] Possibly for this reason, the nasal

Table 3. Prevalence of methicillin-resistant *Staphylococcus aureus*, according to the studies included in this review

	General students	Students before clinical exposure	Students after clinical exposure
A1	2.4%	-	-
A2	0.0%	-	-
A3	1.61%	-	-
A4	2.2%	1.9%	2.4%
A5	9.0%	-	-
A6	2.1%	-	-
A7	3.3%	-	-
A8	-	0.0%	-
A9	6.8 %	4.0%	9.0%
A10	3.0%	-	-
A11	8.2%	4.0%	11.8%
A12	1.9%	-	-
A13	0.0%	-	-
A14	15.3%	0.0%	6.7%
A15	14.3%	-	-
A16	3.2%	3.1%	0.0%
A17	1.3%	-	-
A18	5.5%	-	-
A19	0.0%	-	-
A20	-	4.0%	-
A21	0.3%	0.0%	0.3%
A22	3.1%	-	3.1%
A23	6.1%	-	-
A24	13.1%	-	-
A25	2.1%	2.1%	-
A26	4.1%	-	-
A27	8%	-	-
A28	7.1%	-	-
A29	0.1%	-	-
A30	8.4%	-	-

cavity was the site most chosen by researchers for sample collection in their studies, thus showing the importance of the upper airways in transmission and acquisition of pathogenic microorganisms. The throat and palms are also important reservoirs for MRSA.[19,21,22,26]

It is known that students in the field of healthcare, as they progress through the curriculum with increasing complexity of care practices, whether in hospitals or other healthcare delivery environments, become carriers of microbes. In this, acquisition of *Staphylococcus aureus* is considered to be a major concern, especially with regard to MRSA.[1]

Thus, MRSA rates in students may increase according to their clinical exposure, as well as from isolated occurrences. In another study, there was greater potential for virulence in samples from groups working in clinics.[5] This aspect of infection could not be analyzed in the present study, since the studies included in this review were cross-sectional, which did not allow the study sample to be monitored.

The prevalences found need to be analyzed with caution, considering that occurrences of infections caused by MRSA may differ according to the scenarios within which they occur. This may be due to measures that are taken to control infection and may be dependent on effective implementation.[5] Likewise, the MRSA rate also varies in different locations.[27,41]

This study presented some limitations due to the choice of databases and keywords. Use of the CINAHL database may have restricted the search, as it is a specific database for the field of nursing. In addition, the choice of databases and keywords may have camouflaged studies on the same topic that were not indexed in the same database. Hence, it can be suggested that similar investigations should be conducted, with cross-referencing of other databases, in order to investigate Brazilian scientific production on colonization by *Staphylococcus aureus* among healthcare students.

CONCLUSION

The prevalence of colonization by methicillin-resistant *Staphylococcus aureus* among healthcare students is high, and the nasal cavity was cited in this study as an important reservoir for these microorganisms.

Efforts need to be made to implement standards and routines that are designed to limit the spread of MRSA strains among students, given that once MRSA has become established within a community, its eradication and control is difficult. Furthermore, in view of the high morbidity and mortality and exponential growth of series of microbial resistance, implementation of control strategies is prudent.

Therefore, education on infection control measures in undergraduate healthcare courses is of great importance, as also is implementation of adequate and effective infection control programs to reduce the prevalence of MRSA.

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Address for correspondence:
Erika Morganna Neves de Oliveira
Universidade Federal do Piauí (UFPI), Campus Universitário Ministro Petrônio Portella
Ininga —Teresina (PI) — Brasil
CEP 64049-550
Tel. (+55 86) 3215-5513
E-mail: morgannaneves@hotmail.com

Polyphenols for improvement of inflammation and symptoms in rheumatic diseases: systematic review

Hillary Nascimento Coletro[I], Amanda Popolino Diniz[II], Nathália Sernizon Guimarães[III], Júlia Cristina Cardoso Carraro[IV], Raquel de Deus Mendonça[V], Adriana Lúcia Meireles[VI]

Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil

[I]MSc. Doctoral Student, Postgraduate Program on Health and Nutrition, School of Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil; Doctoral Student, Grupo de Pesquisa e Ensino em Nutrição e Saúde Coletiva (GPENSC), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0002-9142-6079

[II]MSc. Doctoral Student, Postgraduate Program on Health and Nutrition, School of Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil; Doctoral Student, Grupo de Pesquisa e Ensino em Nutrição e Saúde Coletiva (GPENSC), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0002-3300-0440

[III]PhD. Former Postdoctoral Fellow in the Postgraduate Program on Health and Nutrition, School of Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0002-0487-0500

[IV]PhD. Adjunct Professor, Department of Clinical and Social Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil; Adjunct Professor, Grupo de Pesquisa e Ensino em Nutrição e Saúde Coletiva (GPENSC), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0003-0027-2690

[V]PhD. Adjunct Professor, Department of Clinical and Social Nutrition, School of Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil; Adjunct Professor, Grupo de Pesquisa e Ensino em Nutrição e Saúde Coletiva (GPENSC), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0001-7599-8715

[VI]PhD. Adjunct Professor, Department of Clinical and Social Nutrition, School of Nutrition, Universidade Federal de Ouro Preto (UFOP), Ouro Preto (MG), Brazil; Adjunct Professor, Grupo de Pesquisa e Ensino em Nutrição e Saúde Coletiva (GPENSC), Ouro Preto (MG), Brazil.
https://orcid.org/0000-0002-1447-953X

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ABSTRACT

BACKGROUND: Rheumatic diseases (RDs) are a group of pathological conditions characterized by inflammation and functional disability. There is evidence suggesting that regular consumption of polyphenols has therapeutic effects capable of relieving RD symptoms.

OBJECTIVE: To synthesize data from randomized controlled trials on administration of polyphenols and their effects on RD activity.

DESIGN AND SETTING: Systematic review conducted at Universidade Federal de Ouro Preto, Minas Gerais, Brazil.

METHODS: A systematic search was conducted in the databases PubMed (Medline), LILACS (BVS), IBECS (BVS), CUMED (BVS), BINACIS (BVS), EMBASE, Web of Science and Cochrane Library and in the grey literature. The present study followed a PRISMA-P checklist.

RESULTS: In total, 646 articles were considered potentially eligible, of which 33 were then subjected to complete reading. Out of these, 17 randomized controlled trials articles were selected to form the final sample. Among these 17 articles, 64.71% assessed osteoarthritis (n = 11), 23.53% rheumatoid arthritis (n = 4), 5.88% rheumatoid arthritis and fibromyalgia (n = 1) and 5.88% osteoarthritis and rheumatoid (n = 1). Intake of polyphenol showed positive effects in most of the studies assessed (94.12%): it improved pain (64.70%) and inflammation (58.82%).

CONCLUSION: Polyphenols are potential allies for treating RD activity. However, the range of polyphenol sources administered was a limitation of this review, as also was the lack of information about the methodological characteristics of the studies evaluated. Thus, further primary studies are needed in order to evaluate the effects of polyphenol consumption for reducing RD activity.

SYSTEMATIC REVIEW REGISTER: PROSPERO - CRD42020145349.

INTRODUCTION

Rheumatic diseases (RDs) belong to a group of chronic musculoskeletal pathological conditions characterized by joint damage, inflammation, pain, functional disability and impact on individuals' quality of life.[1-4] Rheumatic diseases include chronic clinical conditions of multicausal etiopathogenesis characterized by disruption of immunological tolerance, production of autoantibodies, production of a number of substances accounting for lesions in many body structures,[4] mechanical stress in the joints and changes to the alignment of bones, cartilage and other structures necessary for joint stability.[5]

They give rise to a heterogeneous group of clinical conditions, such as rheumatoid arthritis, osteoarthritis, scleroderma, systemic sclerosis, ankylosing spondylitis, fibromyalgia, osteoporosis, tendinitis, gout and lupus, among others. Osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common RDs.[3] OA is the first chronic, inflammatory and degenerative disease that arises through joint cartilage wear or loss.[2] RA is an inflammatory disease that mainly affects joints without being degenerative. Instead, it causes structural damage and joint inflammation, which result in progressive structural and functional losses.[4]

RDs are more common in developed countries and in women. In Europe and North America, their prevalence is 0.5%-1.0%.[6] OA is the most common form of arthritis, affecting approximately 14 million people in the United States.[7] Moreover, RA affects about five in every 1,000 adults and the number of individuals affected is expected to rise to approximately 67 million by 2030.[8]

Many treatments for diminishing RD activity are available. These include tumor necrosis factor-alpha inhibitors and the disease-modifying anti-rheumatic drugs (DMARDs) infliximab,

etanercept, certolizumab pegol, golimumab, adalimumab, tocilizumab, abatacept, rituximab, tofacitinib, baricitinib, upadacitinib, secukinumab, ustekinumab, ixekizumab, guselkumab and belimumab. However, these can be costly and can have side effects like abdominal pain, back pain, chest pain and nausea.[8]

Diet therapy can be used to assist RD therapies, since it helps to reduce pain and inflammation effects.[9] The Nurses' Health Study cohort showed lower RA incidence among individuals who followed healthy dietary patterns (as assessed using the Healthy Eating Index, HEI-2010) than among individuals who followed inadequate dietary patterns.[10] Regular consumption of fresh fruits, vegetables and spices rich in phytochemicals can mitigate oxidative stress and inflammation, and relieve symptoms.[11]

The therapeutic effects of phytochemicals, especially polyphenols, on RDs have been studied, given their antioxidant, anti-inflammatory and immunomodulatory properties.[3] Polyphenols are metabolites found in plants that are produced in metabolic pathways triggered by plant interactions with environmental factors. They are involved in plant reproduction and in communication between plants, as well as in their defense against pathogens. Polyphenols are found in vegetables, fruits, cocoa and nuts, and also in their derivatives, such as juices and teas.[12]

Epidemiological studies have presented associations between polyphenol intake and RDs,[13-15] and experimental studies on animal models and in vitro investigations about the role played by polyphenols in RDs have been conducted. Diets rich in bioactive compounds are associated with improvement of disease activity, since these substances act as protective factors against inflammatory processes and against endothelial dysfunction linked to development of worsening of clinical signs and symptoms.[3]

A systematic review of the literature showed that total flavonoids and specific subclasses of flavonoids such as flavanols, flavanones, flavones, isoflavones and anthocyanins (but without addressing total polyphenols in diets) are associated with low risk of developing diabetes, cardiovascular events and mortality.[16] However, to the best of our knowledge, no systematic review has been conducted with the aim of evaluating the association between administration of polyphenols and RD symptoms.

OBJECTIVE

The aim of the present article was to review the effects of polyphenols on RD activity, based on information available in the literature (randomized clinical trials).

METHODS

Protocol and registration

The present systematic review was conducted in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" guidelines (PRISMA-P). To define the research question, the PICOS (Patient-Intervention-Comparison-Outcome) strategy was used, as shown in **Supplementary Material Table 1** (available from https://drive.google.com/file/d/106nzdLxTUbI7rRQt9s0kAsA_V8rOvxe6/view?usp=sharing). The analytic methods and inclusion criteria for the present review were documented in a systematic review protocol recorded on the PROSPERO platform of the University of York, United Kingdom (CRD42020145349).

Information sources

A search was conducted in the PubMed (via Medline), LILACS, IBECS, CUMED, BINACIS, EMBASE, Cochrane Library and Web of Science databases and in the grey literature to find studies in which the aim had been to investigate associations between polyphenol administration and rheumatic diseases. This search was conducted between July 22, 2019, and September 10, 2020.

The descriptors used were previously defined in the MeSH, DECS and Emtree databases. These related to "Rheumatic Diseases" or "Disease, Rheumatic" or "Rheumatic Disease" or "Rheumatism" and "Polyphenols" or "Provinols". Detailed search strategies are presented in **Supplementary Material** that is available from https://drive.google.com/file/d/106nzdLxTUbI7rRQt9s0kAsA_V8rOvxe6/view?usp=sharing.

Inclusion and exclusion criteria

Only double-blind randomized controlled trials (RCTs) analyzing outcomes from interventions consisting of polyphenol administration to improve disease activity were included in this study. No restrictions on the date of publication or language used were imposed in relation to article selection.

The exclusion criteria encompassed duplicates, in vitro studies, reviews, cross-sectional or observational studies, case reports, case series, ecological studies, studies about other morbidities or studies on pregnant women, children or teenagers.

Data collection process

The references retrieved through the search strategies were exported to an Endnote file (Clarivate Analytics, Philadelphia, United States), and duplicates were removed. Two independent researchers (HNC and APD) selected titles and abstracts; potential texts were evaluated to check their eligibility based on the criteria described above. A third researcher (NSG) resolved any discrepancies resulting from disagreements between HNC and APD. In addition, the grey literature, such as monographs, dissertations, theses and conference proceedings, was assessed based on references in the articles selected.

Data extraction

Two independent researchers (HNC and APD) extracted data on features such as study design, name of the first author, publication year, participants, participants' age and sex, intervention features, placebo groups (sample, age, sex), intervention types (polyphenol use), sample size and outcomes (rheumatic disease activity: pain, functional capacity, inflammatory markers, laboratory markers, antioxidant activity and quality of life).

Evaluation of the methodological quality of the studies included

The quality of the RCT methodology was assessed through the Cochrane tool for risk of bias in Cochrane randomized studies (RoB 2.0, London, England), which classifies studies as having high or low risk of bias. The methodological quality was assessed by two independent researchers (HNC and APD), and a third researcher (NSG) resolved any score divergences.

RESULTS

The search in the databases and in the grey literature resulted in 646 studies. In total, 641 publications were evaluated after duplicate removal (n = 5). From among these, 542 articles were excluded from the sample because of the title and 66 through reading the abstract. The remaining 33 studies were then read in full (**Figure 1**). Sixteen articles were excluded during this text analysis stage due to their methodologies (pilot studies or experimental studies). Thus, 17 articles composed the final sample of the present review (**Figure 1**).

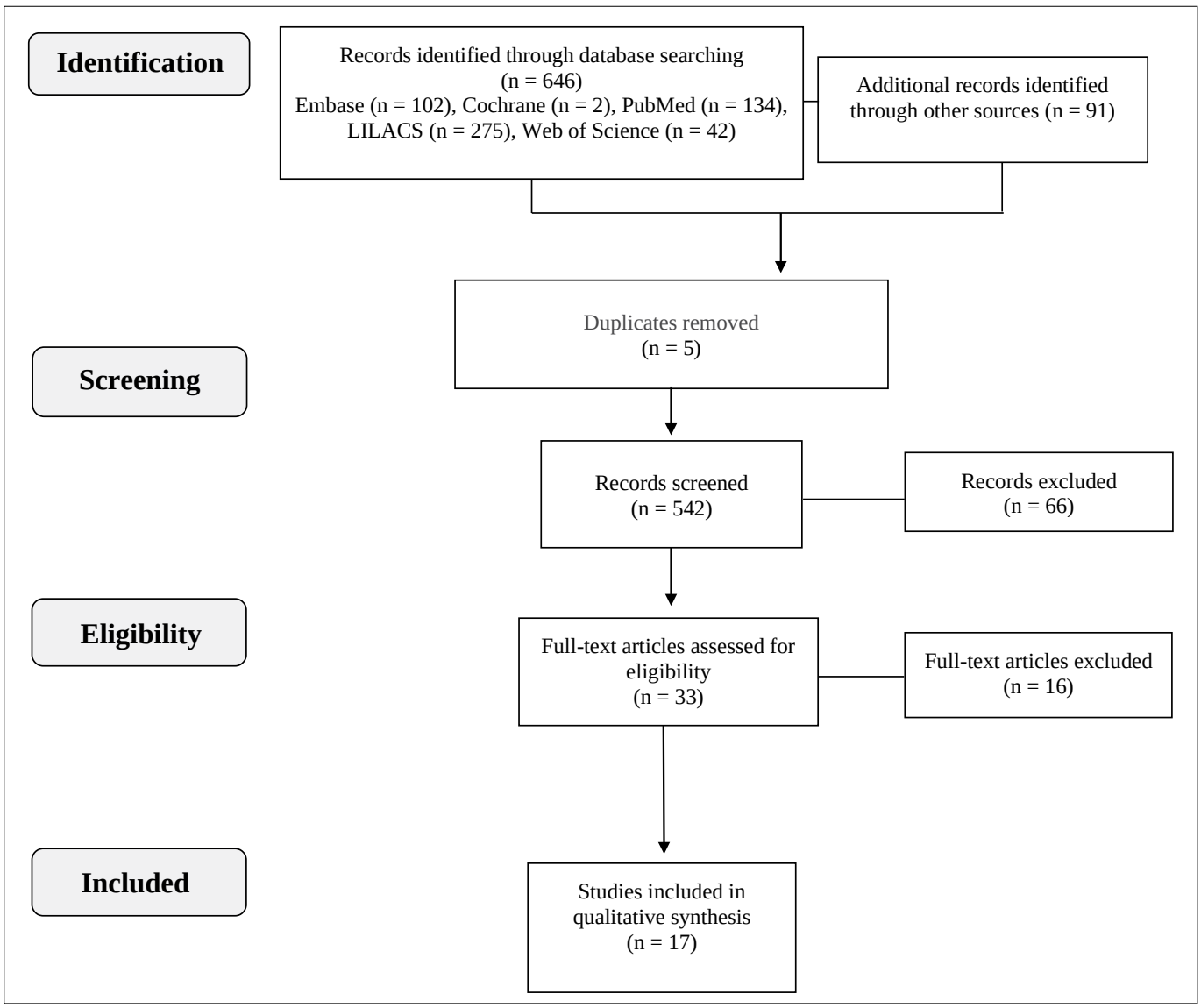

Figure 1. PRISMA flow of studies included in the review.

Among these 17 clinical trials, 52.94% (n = 9) were published in the last five years (2015-2019); 23.53% were conducted in the United States (n = 4), 17.65% in Iran (n = 3), 11.65% in India (n = 2), 5.89% in Iraq (n = 1), 5.89% in Armenia (n = 1), 5.89% in Australia (n = 1), 5.89% in Japan (n = 1), 5.89% in Egypt (n = 1), 5.89% in Belgium (n = 1), 5.89% in Brazil (n = 1) and 5.89% in Finland (n = 1). The number of individuals evaluated reached 1,244 (the minimum and maximum sample groups encompassed 17 and 201 subjects, respectively). Studies reporting the sample characteristics (n = 14) showed that 55.55% of the participants were women (n = 691). In all the studies, the total of 1,244 participants were in the age group 45-85 years.

The analysis on the studies included in this review was demonstrated through three tables that were organized according to the pathological conditions found. **Table 1** presents the results found for studies that assessed OA; **Table 2**, RA; and **Table 3**, the studies that assessed both of these diseases plus fibromyalgia (rheumatoid arthritis and fibromyalgia; osteoarthritis and rheumatoid arthritis).

Among RDs, 64.71% of the studies assessed osteoarthritis (n = 11) (**Table 1**); 23.53%, rheumatoid arthritis (n = 4) (**Table 2**); 5.88%, rheumatoid arthritis and fibromyalgia; and 5.88%, osteoarthritis and rheumatoid (**Table 3**).

Polyphenols were administered in the form of either capsules of a specific polyphenol or concentrates of food sources of polyphenols (**Online Supplementary Material**, available from: https://drive.google.com/file/d/106nzdLxTUbI7rRQt9s0kAsA_V8rOvxe6/view?usp=sharing). The polyphenol doses administered ranged from 42 mg/day[17] to 1,585 mg/day.[18] **Table 2** in **Online Supplementary Material** (available from https://drive.google.com/file/d/106nzdLxTUbI7rRQt9s0kAsA_V8rOvxe6/view?usp=sharing) describes the doses administered, their source and the polyphenol composition.

The intervention with polyphenols to mitigate/rule out disease activity (pain, functional capacity, inflammatory markers, laboratory markers, antioxidant activity and quality of life) of rheumatic diseases (outcome variable) led to positive results in 94.12% of the studies selected. Pain improved in 64.70% of the cases (n = 11), based on assessment using a visual analogue scale, and inflammation improved in 58.82% of the cases (n = 10). The only study that recorded negative results for RD mitigation only assessed participants' antioxidant capacity based on biochemical markers.[19]

The lack of information about the methodological characteristics of the studies evaluated in the present review made it difficult to classify the quality of evidence, as shown in **Figure 2**. Eight studies did not mention any method of randomization.[19-26] Among all the articles, five did not mention the allocation method.[18,19,22,23,27] Nine studies had a high risk of bias because the study participants were not blinded to either the intervention or the placebo groups.[20,21,24,25,29,30] In six studies, an imbalance in either the number of or the reasons for missing data, between the experimental and control groups, was observed.[18,20,25,26,28,30] Lastly, just four authors described all the outcomes targeted and measured.[20,26,28,30]

DISCUSSION

We found out that polyphenols are capable of helping to treat RDs, with reductions of inflammation and pain. Therefore, their use in treatments for RDs can impact the quality of life of the individuals affected.

To the best of our knowledge, the present systematic review was a pioneer in assessing the association between polyphenol administration and mitigation/improvement of rheumatic disease activity in humans.

Positive effects from polyphenol intake on the improvement/mitigation of rheumatic disease activity were observed in most of the studies selected (94.12% of the articles).[17,18,20-33] Based on the information in these articles, pain and inflammation in patients with osteoarthritis or rheumatoid arthritis were the main symptoms mitigated/relieved in the populations assessed.[17,18,20,21,22,28,32]

The studies showed positive results in terms of reduction of RD activity, due to pain relief;[18,20,21,22,28,30,31,32] reductions of the levels of cytokines and pro-inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukins 6 (IL-6) and 1β (IL-1β) and tumor necrosis factor α (TNF-α);[18,23,27,29,30] reductions of disease activity as assessed through reductions of the levels of undercarboxylated osteocalcin (ucOc), matrix metalloproteinases (MMP-3), anti-cyclic citrullinated peptide (anti-CCP) and Coll2-1 markers;[17,18,23,26] increased levels of anti-inflammatory cytokines, such as IL-13;[28] and improvements in oxidative stress caused by increasing the levels of antioxidant enzymes such as superoxide dismutase (SOD) and reducing malondialdehyde (MDA).[33]

RD improvement was mostly identified by means of biochemical markers that indicate normal or pathological functioning.[34] Inflammatory biomarker levels are increased in RDs, and are associated with the pain and other symptoms of the disease.[6] They can be divided into the following categories: pro-inflammatory cytokines, anti-inflammatory cytokines, adipokines and chemokines. Pro-inflammatory cytokines are mainly produced by adipocytes: the main ones are IL-6, IL-8, IL-1β and TNF-α.[34] Specific biomarkers of RD, such as MMP, stand out among them. These biomarkers belong to a family of enzymes that account for the extracellular degradation of cartilage matrix components, including collagen type II and aggrecan; they change bone metabolism, cartilage and the synovial membrane, which leads to joint destruction.[35]

There is a specific treatment for each clinical condition in RDs. These treatments can range from medication to secondary therapies such as individualized diet therapy.[6,36] Overall, drug therapy involves use of non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and meloxicam, but these substances lead to

Table 1. Features of randomized controlled trials evaluating the effect of polyphenol administration on osteoarthritis

Author	Country, year	Sample features	Intervention	Control group	Outcome	Results after intervention
Du et al.[28]	United States, 2019	n = 49; ♀ = 71.4%; mean age = 55.6 years	40 g/day of blueberry concentrate	Yes	Pain, inflammation and daily performance	↓ stiffness, pain and difficulty performing daily activities (P < 0.05) ↑ IL-13 in the intervention group (P < 0.05) ↓ MCP-1 in the intervention group (P < 0.05)
Hussain et al.[21]	Iraq, 2018	n = 92; age group: 45 - 75 years	500 mg/day of resveratrol + 15 mg/day of meloxicam	Yes	Pain and functional disability	↓ stiffness, pain and difficulty performing daily activities (P < 0.05)
Schell et al.[18]	United States, 2017	n = 17; ♀ = 76.5%; mean age = 57 ± 7 years	50 g/day of strawberry concentrate	Yes	Pain, inflammation and quality of life	↓ IL-6, IL-1β and MMP-3 (P < 0.05) ↓ intermittent pain and constant pain
Wong et al.[20]	Australia, 2017	n = 72; ♀ = 100%; mean age = 61.5 ± 0.9 years	75 mg/day of trans-resveratrol	Yes	Pain, sleep disorders, symptoms of menopause, symptoms of depression, quality of life and mood	Pain improvement/mitigation (P = 0.004)
Panahi et al.[33]	Iran, 2015	n = 40; ♂ = 100%; age < 80 years	1500 mg/day of curcuminoid + 15 mg/day of biopterin	Yes	Antioxidant activity and GSH and MDA concentrations	↑ SOD (P < 0.001) ↓ MDA concentration (P < 0.04)
Shep et al.[22]	India, 2019	n = 139; ♂ = 66.9%	500 mg/day of curcumin	No	Pain	↓ VAS scoring for pain (P < 0.01) KOOS score improvement (P < 0.01)
Haroyan et al.[25]	Armenia, 2018	n = 201; ♀ = 93.03%; mean age = 56.2 years	500 mg/day of Curamin and/or 500 mg/day of Curamed	Yes	Pain, inflammation and physical performance	↓ pain parameters (P < 0.01) Improved physical and functional performance (P < 0.05)
Nakagawa et al.[32]	Japan, 2014	n = 41; ♀ = 78%; mean age = 68.7 years	6 capsules of Theracurmin/day	Yes	Pain and stiffness, daily performance and health conditions	↓ VAS score for pain (P = 0.023)
Henrotin et al.[17]	Belgium, 2014	n = 22; ♀ = 68.2%; mean age = 64.3 ± 8.4 years	6 capsules of Flexofytol/day	No	Pain and disease activity	↓ biomarker Coll2-1 (P = 0.002) ↓ disease activity (P = 0.0047)
Naderi et al.[27]	Iran, 2012	n = 100; ♀ = 90% Age group: 50 - 70 years	1 g/day of ginger	Yes	Inflammation	↓ CRP and nitric oxide (P < 0.001)
Shumacher et al.[30]	United States, 2013	n = 58; ♂= 75.86%; mean age = 57 ± 11 years	500 ml of tart cherry juice/day	Yes	Pain, stiffness and functional capacity	↑ WOMAC Score (P = 0.002) Pain improvement (P = 0.042) Functional capacity improvement (P < 0.001) ↓ hsCRP (P = 0.006)

VAS = visual analogue scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; MDA = malondialdehyde; IL = interleukin; MCP-1 = monocyte chemoattractant protein-1; CRP = C-reactive protein; MMP-3 = matrix metalloproteinase-3; M1 = δ-(3,4-dihydroxy-phenyl) – γ- valerolactone; SOD = superoxide dismutase; Coll2-1 = cartilage biomarker; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; hsCRP = high-sensitivity C-reactive protein.

Table 2. Features of randomized controlled trials evaluating the effect of polyphenol administration on rheumatoid arthritis

Author	Country, year	Sample features	Intervention	Control group	Outcome	Results after intervention
Khojah et al.[23]	Egypt, 2018	n = 100; ♀ = 68%	1 g/day of resveratrol + antirheumatic drugs	Yes	Biochemical and inflammatory markers	↓ CRP (P < 0.05) ↓ESR, ucOC, MMP-3, TNF-α and IL-6 (P < 0.001)
Chandran and Goel[24]	India, 2012	n = 45; ♀ = 84.4%; mean age = 47.8 years	500 mg/day of curcumin + 50 mg/day of sodium diclofenac	Yes	Disease activity	Mitigating disease activity (P < 0.05) ↓ CRP (P < 0.05)
Javadi et al.[19]	Iran, 2014	n = 40; ♀ = 100%; mean age = 47.3 years	500 mg/day of quercetin	Yes	Antioxidant capacity	There was no statistically significant difference after intervention with quercetin
Thimotéo et al.[26]	Brazil, 2018	n = 41; ♀ = 100%; mean age = 52.75 years	500 ml of reduced-energy cranberry juice/day	Yes	Biochemical markers and disease activity	Mitigating disease activity (P = 0.048) ↓ anti-CCP (P = 0.034)

ESR = erythrocyte sedimentation rate; ucOC = undercarboxylated osteocalcin; CRP = C-reactive protein; MMP-3 = matrix metalloproteinase-3; IL = interleukin; TNF = tumor necrosis factor; Anti-CCP = anti-cyclic citrullinated peptide.

Table 3. Features of randomized controlled trials evaluating the effect of polyphenol administration on rheumatic diseases

Author	Country, year	Sample features	Intervention	Control group	Rheumatic disease	Outcome	Results after intervention
Hänninen, et al.[31]	Finland, 2000	115	Diet of living food*	Yes	Rheumatoid arthritis and fibromyalgia	Symptoms of rheumatoid arthritis and fibromyalgia	↓ rheumatoid arthritis activity (P = 0.03) Joint stiffness mitigation (P = 0.001) Pain mitigation (P = 0.003)
Bitler, et al.[29]	United States, 2007	90	400 mg/day of olive pulp	Yes	Osteoarthritis and rheumatoid arthritis	Ability to perform daily activities, disease activity and inflammation	↓ CRP (P < 0.01)

*Diet of living food consisted of vegan diet without cooking; CRP = C-reactive protein.

several side effects like peptic ulcers. Accordingly, anti-inflammatory compounds can come from food. Thus, it is essential to define the compounds capable of mitigating pain and inflammation.

Polyphenols have been described in the literature as potent anti-inflammatory drugs that can be used to minimize the effects of diseases on different health conditions.[36] Polyphenols link to aromatic rings that reduce free radicals, inhibit formation of reactive species during metabolism, perform anti-inflammatory immunomodulatory actions[3] and have an anabolic effect on cartilage cells.[37] Experimental studies have already shown the beneficial action of flavonoids with regard to increasing cartilage anabolic activity and improving the levels of insulin-like growth factor-1 (IGF-1), osteocalcin and physical morphogenetic protein.[38] Reproduced clinical trials have shown that blueberries are a source of polyphenols that have anti-inflammatory effects and can improve gait capacity parameters among older adults.[39,40]

The magnitude of the results recorded can change depending on polyphenol type, dose (extract, fruit concentrate or others), delivery route (oral or injection into the synovial fluid), association with other compounds (such as drug therapy) and the types of markers analyzed.[17]

Polyphenols from different sources were administered in the studies reviewed here. This made it difficult to interpret the results,

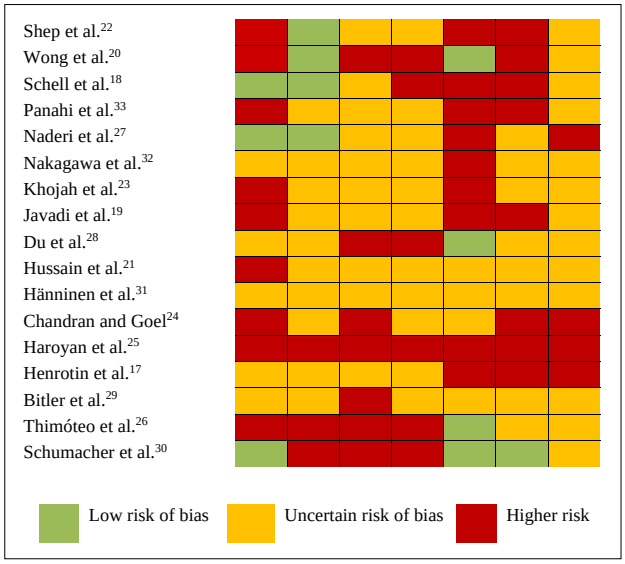

Figure 2. Assessment of the quality of randomized clinical trials selected to form part of the present review, 2020.

since there may have different mechanisms of action[41] and even different degrees of bioavailability.[42-45] However, studies that have reviewed the effects of polyphenols for prevention or treatment of several diseases used a wide variety of sources and different quantities of polyphenols,[46-48] given the heterogeneity of sources of polyphenols and the scarcity of existing literature on this subject from primary studies. Lack of information about the medications or dietary supplements used by participants in the 17 studies evaluated may have been another form of bias. Some studies did not mention the type or dosage of medication administered to control the diseases assessed. Therefore, doubts regarding the effects of polyphenols in isolation are raised.

Lack of clarity about several aspects of the studies evaluated in the present review made it difficult to classify the quality of evidence found in these studies. According to Gordis et al.,[49] randomized controlled clinical trials presenting good methodological quality are characterized by clear planning, execution and reporting, and should guarantee adequate confidentiality of allocation, degree of blinding and randomization. Thus, when these studies are meticulously designed, executed and reported, they can be considered to represent the gold standard for assessing the effectiveness of healthcare interventions. However, despite the large numbers of studies included in the search and analysis processes of the present review, it was not possible to perform a meta-analysis. This was because the studies selected assessed different evaluation parameters for disease activity in RDs, and also used different doses and types of polyphenols.

Given the lack of consensus on the best doses and types of polyphenols in the studies assessed in this review, the results should be interpreted with caution and attention. There is a need to conduct primary studies that focus on the minimum dose necessary to achieve the protective effects of polyphenols on the health of patients with RDs. Accordingly, for better guidance for healthcare professionals and patients, future research must focus on, and align with, daily recommendations for foods that are known to be source of polyphenols that are capable of preventing and protecting health and helping in treating RDs, due to the importance of consuming such bioactive compounds.

Despite the bias in the primary data sources that is reported here, this review produced promising results, considering that, overall, the dietary intake from polyphenol-rich sources had positive effects with regard to reducing both inflammation and the symptoms of RDs.

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Address for correspondence:
Adriana Lúcia Meireles
Universidade Federal de Ouro Preto (UFOP)
Campus Morro do Cruzeiro, s/nº
Bauxita — Ouro Preto (MG) — Brasil
CEP 35400-000
Tel. (+55 31) 3559-1838
E-mail: adriana.meireles@ufop.edu.br

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Analysis on mental-insanity and cessation-of-dangerousness examinations in three Brazilian custodial institutions: a retrospective cross-sectional study

Tania Maria Nava Marchewka[I], Alvaro Nagib Atallah[II], Nathalia Marchewka Valente[III], Tamara Melnik[IV]

Department of Evidence-Based Health, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]PhD. Full Professor, Department of Evidence-Based Health, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Researcher and Public Attorney, Public Attorney's Office of the Federal District and Territories, Brasília (DF), Brazil.
https://orcid.org/0000-0002-9627-9135

[II]MD, PhD. Full Professor and Head, Discipline of Emergency Medicine and Evidence-Based Medicine, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Director, Cochrane Brazil, São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0890-594X

[III]LLB. Research Assistant and Lawyer, Pontifícia Universidade Católica do Rio de Janeiro (PUC-Rio), Rio de Janeiro (RJ), Brazil.
https://orcid.org/0000-0003-0056-0991

[IV]PsyD, PhD, Professor, Internal Medicine and Evidence-Based Medicine, Universidade Federal de Sao Paulo (UNIFESP), São Paulo (SP), Brazil; and Researcher, Cochrane Brazil, São Paulo (SP), Brazil.
https://orcid.org/0000-0002-8477-3662

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ABSTRACT

BACKGROUND: In Brazil, the right to healthcare and the incorporation of best scientific evidence in public health are universally guaranteed by law. However, the treatment offered to patients with mental disorders in custodial hospitals in this country has not been rigorously evaluated.

OBJECTIVES: To analyze the psychiatric diagnoses and treatments implemented in three Brazilian custodial institutions.

DESIGN AND SETTING: This was a retrospective, cross-sectional and descriptive study on patients held in custody in three Brazilian institutions, as judicially-determined safety measures due to their mental disorders, and the tools used in diagnoses and treatments. These institutions are in Rio de Janeiro and the Federal District.

METHODS: The data from medical and judicial records that were made available were assessed regarding the diagnoses that were made and the instruments that were used.

RESULTS: None of these inpatients were evaluated using validated tools, and only a few medical records presented clear descriptions of the cases. No patient with substance involvement had undergone laboratory toxicological assays. It was not possible to verify the adequacy of treatments because the procedures were inadequately described in the records.

CONCLUSIONS: No standardized protocols or instruments for diagnosing mental health disorders or assessing use of psychoactive substances had been applied among the inpatients at these custodial institutions in Rio de Janeiro and the Federal District. The treatments that were prescribed to these inpatients consisted mainly of drugs.

INTRODUCTION

The Brazilian constitution has established that healthcare is a right for all citizens and a duty of the state. Moreover, Brazilian law no. 12,401 (2011) and law no. 10,216 (2001) both give legal support for the use of the best scientific evidence in public healthcare as the basis for diagnosing and treating diseases in this country.[1-3]

In the Brazilian penal system, individuals who cannot be criminally responsible due to mental disorders cannot be penalized. Instead, security measures should be taken, and treatment should be provided. Thus, individuals with mental disorders who are considered dangerous and have committed a crime are not sent to prison in Brazil: they must comply with security measures in a custodial hospital, where patients like these should receive treatment. However, a large proportion of the inpatients at custodial hospitals for psychiatric treatment in Brazil do not receive proper medical-psychological care.[4-6] In most cases, custodial hospitals are not integrated with the Brazilian National Health System.[5]

To the best of our knowledge, no studies have verified whether the diagnoses reported in the medical records of inpatients at these Brazilian custodial hospitals, and the treatment that these patients received, were in accordance with the recommendations and/or best scientific evidence from well-conducted clinical trials.

OBJECTIVES

To analyze the psychiatric diagnoses and the treatments implemented in three institutions within the Brazilian Criminal Justice System through descriptive and exploratory mapping of

the available reports and medical records on mental-insanity and cessation-of-dangerousness examinations.

METHODS

Study design and setting

This was a cross-sectional descriptive study on the diagnoses made and treatments used for inpatients, both men and women, at custodial and psychiatric treatment hospitals for individuals who had in some way conflicted with the law and required security measures (and not psychiatric patients from general hospitals and clinics). This study was conducted between March 2011 and June 2012 at an institution in Brasília, Federal District (DF), and between 2012 and 2013 at custodial hospitals in the state of Rio de Janeiro (RJ).

The present study was based on legal reports and other data included in the inpatients' medical records. The investigation was conducted at two institutions in RJ and one in DF: the custodial and psychiatric treatment hospitals Heitor Carrilho, in the municipality of Rio de Janeiro, RJ, and Henrique Roxo, in Niterói, RJ; and the psychiatric ward of a women's penitentiary in Brasília, DF (since there are no custodial hospitals in Brasília).

All data collected during the search were obtained through personal visits to the three participating institutions, by the principal investigator and three assistants (who had previously been trained). Copies of all documents required were made. Pre-formulated data collection forms were used in the present study to gather the variables described below. No data were obtained over the phone.

Ethics and funding

This study was approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP), under protocol no. 38313812.2.0000.5505, on December 18, 2014. The privacy of all participants was respected, and their identities were kept confidential. The researchers involved did not contact the participants, and the analysis was limited to assessment of documents in the medical records. Thus, there was no need for a free and informed consent statement.

The present study did not receive any form of funding from either public or private sources. The authors, who are all public employees, did not have any conflict of interest to declare regarding this study.

Participants

All legal medical reports and data available from the medical records of inpatients at the three custodial units within the period studied were included. The participants in the present study were individuals with mental disorders in accordance with the International Classification of Diseases 10th version (ICD-10).[7] They included users of psychoactive substances who had received a diagnosis of chemical dependency and were considered not criminally responsible, in accordance with article 26 of the Brazilian penal code.[8]

Patients diagnosed with sociopathy/psychopathy were excluded because of the differentiated treatment recommended in the penal code (sole paragraph of article 26 and article 98).[8] Such patients are considered semi-responsible for their criminal actions.

Data collection

In the Federal District, the study was started by collecting reports and medical records that were documented in the judicial processes relating to the inpatients in the psychiatric unit.

All inpatients treated at the three institutions were identified and all documents on them that were available were evaluated (reports on mental insanity and cessation of dangerousness, reports on visits and medical consultations and, when available, the medical records containing the prescriptions for treatments).

One of the custodial and psychiatric treatment hospitals in RJ (the Heitor Carrilho Custodial and Psychiatric Treatment Hospital) was going through a process of deinstitutionalization (concluded in 2013). At the time of this study, inpatients for whom a report declaring positive cessation of dangerousness had been issued were being released. The inpatients whose families could not be located by the hospital team remained at the institution as sheltered individuals and no longer as inpatients, but still receiving assistance from the healthcare team. Thus, the Henrique Roxo Hospital became the entrance to the penal system, while the Heitor Carrilho Hospital became the exit. The entire release process is now conducted at the latter hospital, involving examinations to assess cessation of dangerousness for all inpatients who, according to the team, were in a condition that allowed them to be released. All inpatients in Rio who were included in the present study had gone through both institutions and for this reason were analyzed together.

Variables and data analysis

The data gathered from the legal medical reports and medical records were used to define sociodemographic and family profiles, diagnoses, duration of hospitalization and therapeutic measures applied. Therapeutic projects, i.e. descriptions of treatment plans that were drawn up for individual implementation, were also included if they existed. The following data were collected:

- demographic data such as nationality, age, gender or sex of the patient, marital status, educational level, profession, address and place of birth.
- dates in which diagnostic evaluations, medical examinations and hospitalization for psychiatric treatment took place.

- mental insanity examinations that were performed: types, dates and methods (anamnesis or interview), and the instruments used for these evaluations.
- use of mental insanity examinations and structured interviews conducted by means of an instrument such as SCID (Structured Clinical Interview for DSM Disorders; New York: Biometrics Research, New York State Psychiatric Institute);[9]
- diagnoses stated in the mental insanity report and in the examination regarding cessation of dangerousness, and the security measures adopted.
- reports from the psychosocial department and social care teams.
- use of the Historical Clinical Risk Management of Violence (HCR-20) scale[10,11] in examinations regarding cessation of dangerousness, to assess the risk of violence and security measures.
- therapeutic measures adopted: types of medications prescribed (with dosage and period) and psychotherapy.

In cases of divergence between the reports on mental insanity and cessation of dangerousness and the reports from the psychosocial sector or the medical-psychological care teams of the establishments, the findings from the report on mental insanity were given precedence.

The inpatient profile and the diagnoses and treatments received were summarized in order to facilitate comparison with the recommendations that are presented in the scientific literature.

RESULTS

Visits and the general situation of the files and patients

During the study period, several visits to each of the three treatment centers were needed, in order to identify cases and gain access to data. Because of the precarious situation of the infrastructure, personnel (psychiatric and psychological care, occupational therapy and social care teams) and care provided for inpatients at all three locations, many documents were missing from the inpatients' individual files. Most of the files only included the reports from the examination for cessation of dangerousness, without the mental insanity examination. Information regarding the mental disorder that motivated hospitalization was incomplete, insufficient or absent from the reports on custodial patients. Moreover, the code of the International Classification of Diseases (ICD) was missing in many cases.

The deactivation of the Heitor Carrilho Hospital hampered the process of gathering filed data. To overcome this difficulty, hospital personnel (social assistants and part of the team of psychologists) were contacted to search for information on the patients' situation. In 23 out of the 78 cases at Heitor Carrilho, the inpatients had grown old and had been living at the hospital for many years. Although in these cases the patients met the requirements for being released, the social care teams had been unable to contact their families to receive them, and so they remained at the institution.

In the Federal District, due to the singularity of the treatment center, it was possible to obtain mental insanity examinations and those regarding cessation of dangerousness for almost all inpatients in the feminine psychiatric unit of the local penitentiary system. However, there were no individual medical records showing whether the treatments were being properly followed.

During the period studied, 109 inpatients were identified at these three institutions. The characteristics of these individuals are described in **Table 1**.[12]

Both in the Federal District and in Rio de Janeiro, most of the inmates were men; they were either single or widowed and had low educational levels. The data on inpatients at the two hospitals in RJ were combined in the same spreadsheet, since these hospitals are under the same management.

Diagnoses

Information on the mental disorders that led to hospitalization were incomplete, insufficient or absent in the medical records of the custodial inpatients.

Table 1. Characteristics of inpatients in the Federal District and in Rio de Janeiro

Characteristics	Federal District (n = 39)		Rio de Janeiro (n = 70)	
Gender				
Male	36	92.3%	62	88.6%
Female	3	7.7%	8	11.4%
Marital status				
Married	4	10.3%	6	8.6%
In stable relationship	2	5.1%	-	-
Divorced (legally)	3	7.7%	1	1.4%
Separated	-	-	3	4.3%
Single	27	69.2%	47	67.1%
Widower	1	2.6%	1	1.4%
No information	2	5.1%	12	17.1%
Education				
Illiterate	1	2.6%	8	11.4%
Middle school: partially completed*	24	61.5%	39	55.7%
Middle school: fully completed*	3	7.7%	1	1.4%
High school: incomplete*	-	-	2	2.9%
High school: complete*	-	-	4	5.7%
College/university: incomplete	1	2.6%	2	2.9%
College/university: complete	-	-	3	4.3%
No information	10	25.6%	11	15.7%

*Although the Brazilian educational system was modified in 1996,[12] when the name "fundamental" started to be used to describe middle school / elementary education, and also "high school" for junior, sophomore and senior years, many medical records of the inpatients were registered with the old nomenclature (i.e. using "primeiro grau, segundo grau" etc.).

Limitations found due to lack of documentation and adequate medical records are described in numbers in **Table 2**. This also shows in numbers the diagnostic groups affected by this negligence.

The heterogeneity of descriptions of diagnoses in the inpatients' records is shown in **Table 3**. The word "schizophrenia" was noted as a diagnosis in the records of 10 of the 45 inpatients for whom this diagnosis was reported (22%). ICD registration was present for only 7.7% of the patients in DF and for 17.1% in RJ. Moreover, different ICD codes were present in the two examinations on one patient in DF (2.6%) and one patient in RJ (1.4%).

The examinations and diagnoses regarding mental insanity and cessation of dangerousness that were conducted, with or without designation of ICD codes, are compared between Rio de Janeiro and the Federal District in **Table 4**. In this table, "complete diagnosis" means that presents complete information about both the diagnosis and the ICD was presented. The ICD registration was seen to be insufficient in the examinations on both mental insanity and cessation of dangerousness, in both the Federal District and Rio de Janeiro. The analysis on the medical reports and inpatients' records was unsuccessful with regard to providing information about the ICD.

Most diagnoses were based on either anamnesis alone or anamnesis and interviews with a family member, as shown in **Table 5**.

Treatments

Table 6 shows the recommended treatments for these inpatients in the Federal District and Rio de Janeiro, according to their mental disorders. However, several of the reports evaluated did not state the medication that was administered to these individuals.

Table 2. Documents/medical records not found and diagnostic groups affected

Description of medical records / diagnostic groups	Federal District (n = 39)		Rio de Janeiro (n = 70)	
Mental insanity examination not found	16	41.02%	50	71.42%
Cessation of dangerousness examination not found	18	46.15%	11	15.71%
Medical or technical reports not found	13	33.33%	24	34.28%
Disease registered without ICD information	5	12.82%	26	37.14%
Mental illness	16	41%	29	41.4%
Mental illness and drug/alcohol abuse	9	23.1%	5	7.1%
Mental retardation	1	2.6%	4	5.7%
Alcohol abuse	-	-	3	4.3%
Drug abuse	1	2.6%	2	2.9%
Mental illness and mental retardation	-	-	1	1.4%
Mental and neurological illness	1	2.6%	1	1.4%
Others	2	5.1%	6	8.6%
No information	9	23.1%	19	27.1%

ICD = International Classification of Diseases.

Table 3. Diagnoses among inpatients in the Federal District and Rio de Janeiro

Diagnostic	Federal District (n = 16)		Rio de Janeiro (n = 29)	
Unspecified nonorganic psychosis	6	37.50%	-	-
Schizophrenia	3	18.80%	2	6.90%
Persistent delusional disorders; schizophrenia	1	6.30%	-	-
Residual schizophrenia	1	6.30%	6	20.70%
Paranoid schizophrenia	1	6.30%	6	20.70%
Unspecified psychosis not due to a substance or known physiological condition	1	6.30%	-	-
Bipolar affective disorder, manic episode with severe psychotic symptoms	1	6.30%	-	-
Delirious disorder	1	6.30%	-	-
Mental disorder (unspecified)	1	6.30%	-	-
Mental and behavioral disorders due to alcohol use	-	-	1	3.40%
Hebephrenic schizophrenia; severe schizophrenia	-	-	1	3.40%
Paranoid schizophrenia; stabilized paranoid schizophrenia	-	-	1	3.40%
Paranoid schizophrenia; borderline disorder	-	-	1	3.40%
Schizophrenia; residual schizophrenia	-	-	1	3.40%
Nonorganic psychosis	-	-	1	3.40%
Unspecified nonorganic psychosis	-	-	1	3.40%
Unspecified nonorganic psychosis; paranoid schizophrenia	-	-	1	3.40%
Chronic psychosis	-	-	1	3.40%
Residual psychosis	-	-	1	3.40%
Schizophrenic psychosis	-	-	1	3.40%
Dementia syndrome	-	-	1	3.40%
Psychotic outbreak	-	-	1	3.40%
Mood disorder	-	-	1	3.40%
Acute psychotic delusional disorder; delusional acute psychotic disorder	-	-	1	3.40%

Table 4. Examinations and diagnoses regarding mental insanity and cessation of dangerousness, compared between Rio de Janeiro and the Federal District

	Federal District (n = 39)		Rio de Janeiro (n = 70)	
Examinations done				
No examinations	2	5.1%	1	1.4%
Mental insanity examination only	18	46.2%	13	18.6%
Cessation of dangerousness examination only	8	20.5%	47	67.1%
Both examinations	11	28.2%	9	12.9%
Examinations that were diagnostic				
No diagnosis	9	23.1%	19	27.1%
Diagnosis made from one examination	27	69.2%	39	55.7%
Diagnosis made from both examinations	3	7.7%	12	17.1%
Comparison between the ICDs in the examinations				
Same ICDs	2	5.1%	-	-
Different ICDs	1	2.6%	1	1.4%
Insufficient information	19	48.7%	19	27.1%
No information at all	17	43.6%	50	71.4%
Comparison between the diagnostic examinations				
Consistent diagnosis	2	5.1%	6	8.6%
Inconsistent diagnosis	1	2.6%	6	8.6%
Incomplete diagnosis	27	69.2%	39	55.7%
No information	9	23.1%	19	27.1%
Evaluation on the diagnosis from the mental insanity examination				
Complete diagnosis	20	51.3%	14	20.0%
Incomplete diagnosis	5	12.8%	14	20.0%
No information	14	35.9%	42	60.0%
Evaluation on the diagnosis from the cessation of dangerousness examination				
Complete diagnosis	7	17.9%	7	10.0%
Incomplete diagnosis	1	2.6%	28	40.0%
No information	31	79.5%	35	50.0%

ICD = International Classification of Diseases.

Table 5. How the diagnoses were made

Instruments	Federal District (n = 16)		Rio de Janeiro (n = 29)	
Anamnesis and analysis of previous medical records	4	25.0%	-	-
Anamnesis	2	12.50%	-	-
Psychometric examination, anamnesis, interview with mother and wife, analysis of previous medical records and clinical examination	1	6.30%	-	-
Anamnesis, interview with sister and analysis of previous medical and social records	1	6.30%	-	-
Anamnesis and interview with mother	1	6.30%	-	-
Anamnesis, interview with mother and analysis of previous medical records	1	6.30%	-	-
Anamnesis, interview with mother, clinical examination and analysis of previous medical records	1	6.30%	-	-
Anamnesis and interview with police officer	1	6.30%	-	-
Anamnesis, interview with sister, clinical examination, psychodiagnosis evaluation, psychometric examination and analysis of previous medical records	1	6.30%	-	-
Anamnesis, interview with father and analysis of previous medical records	1	6.30%	-	-
Anamnesis and clinical examination	1	6.30%	-	-
Anamnesis, clinical examination and analysis of previous medical records	1	6.30%	-	-
Psychiatric expertise	-	-	12	41.40%
Anamnesis and psychological examination	-	-	5	17.20%

Continue…

Table 5. Continuation

Instruments	Federal District (n = 16)		Rio de Janeiro (n = 29)	
Mental insanity examination	-	-	3	10.30%
Psychiatric medical record	-	-	1	3.40%
Ruling on the cessation of dangerousness	-	-	1	3.40%
No information	-	-	7	24.13%
Instruments	**Federal District (n = 9)**		**Rio de Janeiro (n = 5)**	
Anamnesis, interview with mother and sister and clinical examination	1	6.30%	-	-
Anamnesis	1	6.30%	-	-
Anamnesis, analysis of previous medical records and psychometric examination	1	6.30%	-	-
Psychometric examination, interview with mother, clinical examination and analysis of previous medical records	1	6.30%	-	-
Anamnesis, interview with mother, clinical examination, analysis of previous medical records and psychological record from IML 80/01	1	6.30%	-	-
Anamnesis, interview with brother and clinical examination	1	6.30%	-	-
Anamnesis, interview with stepfather and analysis of previous medical records	1	6.30%	-	-
Anamnesis, clinical examination, interview with mother and analysis of previous medical records	1	6.30%	-	-
Anamnesis and drug test	1	6.30%	-	-
No information	-	-	2	6.68%
Psychiatric expertise	-	-	1	3,40%
Mental insanity examination	-	-	1	3.40%
Anamnesis and psychiatric expertise	-	-	1	3.40%

IML = Medico-Legal Institute.

Table 6. Treatments prescribed

Treatment	Federal District (n = 16)		Rio de Janeiro (n = 29)	
Hospitalization and medication	8	50.0%	-	-
Hospitalization in a place without risk of escape, medication and social service monitoring	2	12.5%	-	-
Hospitalization, medication, activities and outpatient treatment	1	6.3%	-	-
Hospitalization	1	6.3%	-	-
Hospitalization, medication and group and individual activities	1	6.3%	-	-
Hospitalization, /medication, /psychotherapy and low-sodium diet	1	6.3%	-	-
Hospitalization, medication and follow-up through "Life at Home" program	1	6.3%	-	-
Hospitalization, elimination of drugs, psychotherapy and social service monitoring	1	6.3%	-	-
No information	-	-	17	58.6%
Psychiatric treatment	-	-	2	6.9%
Outpatient treatment	-	-	2	6.9%
Interdisciplinary care aimed at building a therapeutic link and providing stability in the psychiatric setting	-	-	1	3.4%
Hospitalization in psychiatric ward and outpatient treatment	-	-	1	3.4%
Hospitalization	-	-	1	3.4%
Medication and multiprofessional treatment	-	-	1	3.4%
Medication and therapeutic treatments; patient without stable attachment to family	-	-	1	3.4%
No need for inpatient psychiatric treatment	-	-	1	3.4%
Shelter with family or in an ordinary hospital for the handicapped and disabled	-	-	1	3.4%
Medication, physical therapy and outpatient social support	-	-	1	3.4%

This table presents information exactly as noted in these inpatients' medical records.

DISCUSSION

Documentation used in the study

The present study was the first exhaustive survey in Brazil on the care received by patients with mental disorders and/or chemical dependency who had been involved with conflicts with the law and who, for this reason, were inpatients at three custodial hospitals between 2011 and 2013. However, despite numerous visits to each center to obtain documentation, and contacts with administrative personnel, no comparison between the current guidelines for diagnoses and treatments and what was being practiced at these institutions was possible, simply because of the huge gaps in the records. This alone is an example of inadequacy in relation to what is recommended in international guidelines: these individuals who had committed crimes were considered to present mental disorders, but the documentation of the diagnostic process was either flawed or absent, thus indicating that there may have been a considerable amount of subjectivity in their evaluations. Judging by what was reported at these institutions, these patients had not been receiving diagnoses in accordance with standardized instruments and, therefore, their treatments could not be reviewed with regard to fulfillment of the recommendations in the literature.

This blatant negligence in the documentation of these three custodial institutions alone demonstrates some of the aspects of the precarious situation within which these patients were being treated in Brazil.[13]

Evidence-based diagnoses

Anamnesis is only one of the elements of a psychiatric examination.[14] A complete psychiatric examination usually includes an interview with the patient; interviews with third parties (such as family members or people who have social relationships with the individual); physical examination, with emphasis on neurological, endocrine and cardiac assessments; complementary examinations, including laboratory tests; functional tests and imaging examinations; and neuropsychological tests.[14]

Evaluators need to use their knowledge of psychopathology and, hopefully, the best scientific evidence available, to make a diagnosis.[17] This demonstrates the importance of using structured interviews, which are objective instruments for measuring mental functions, including the risk of violence.[15-17]

The diagnosis of mental disorders may also be based on clinical data, structural neuroimaging examinations (computed tomography and magnetic resonance, etc.) and functional tests (single photon emission computed tomography, SPECT; positron emission tomography, PET; and electroencephalogram mapping, etc.). Nonetheless, psychological and neuropsychological tests are very helpful, especially for making differential diagnoses between primary psychiatric disorders (schizophrenia or primary depression, etc.) and neurological diseases.[16]

The present study showed that standardized diagnostic instruments or structured questionnaires to assess custodial inpatients were not being used at the institutions investigated. Not even family members had been interviewed, in more than half of the cases in DF and in all cases in Rio. A psychometric examination was performed on only two patients, with no description of the method or instrument applied. This means that diagnoses such as "schizophrenia", "mental retardation", "alcohol addiction" or others in this sample were based exclusively on the analysis of an expert examiner, who only used interviews to reach this conclusion.[16]

According to manuals such as ICD-10 and DSM,[7,18,19] there are objective criteria that should be followed, in order to define a diagnosis of mental disorder.[20] These include the presence of a certain number of symptoms over a defined period, to characterize the psychopathological condition. Psychiatric diagnoses and classifications of mental disorders were a matter of controversy over the course of the 20th century.[16,17]

There are currently two major diagnostic systems: the one proposed by the American Psychiatric Association (APA), called the Diagnostic and Statistical Manual of Mental Disorders (DSM);[18] and the one recommended by the World Health Organization (WHO), the Classification of Mental and Behavioral Disorders of ICD-10 (International Classification of Diseases, 10th Edition). This latter system has two versions: the Clinical Descriptions and Diagnostic Guidelines ("Blue Book") and the Diagnostic Criteria for Research ("Green Book").[7] The system established by the APA was created in 1980 and has been revised over the years. It is now in its fifth version.[18] The DSM is a particularly objective instrument and is the system that best meets clinical needs, although it has not been officially adopted in Brazil. Thus, when performing a forensic analysis, Brazilian doctors must apply the classification proposed by WHO, the ICD-10, using its Chapter V, "Mental and Behavioral Disorders".[7] However, the ICD codes in the medical records analyzed in the present study were mostly either deficient or nonexistent. Thus, many patients may have been hospitalized without a diagnosis.

Dangerousness tests and their accuracy

Over the past 20 years, standardized instruments have been developed to assess either dangerousness or the possibility that patients may commit violent acts under certain circumstances.[21,22] These instruments include the following:

- Psychopathy Checklist-Revised (PCL-R): This instrument was based on the classical concept of psychopathy and contains 20 items that were chosen to assess behaviors and emotional traits that are characteristic of a psychopathic personality.[23,24]
- Barratt Impulsiveness Scale (BIS-II): This was developed to measure the three main components of impulsivity: motor component, cognitive component and absence of planning.[25,26]
- Historical Clinical Risk Management of Violence (HCR-20): This instrument was specially developed to evaluate the risk of future violent behavior in psychiatric and criminal populations. It contains historical, clinical and risk management subscales, and lists risk factors such as previous violence, young age during first violent incident, instability in relationships, work-related problems, problems regarding substance use and others.[9,10]

In the present study, there was no documentation regarding any use of any instrument for assessing levels of dangerousness (or cessation of dangerousness) among the inpatients. The HCR-20 scale,[9,10] for example, offers the option of 10 different levels of risk of violence and could give a more objective and realistic estimate of an inpatient's situation, but it was not used in any of the cases analyzed. HCR-20 was considered to be a good predictor for violent behavior after release, in an analysis on a community of men with psychiatric disorders.[17]

This is yet another phenomenon that contributes towards perpetuation of hospitalization, as opposed to measures for resocialization and social reintegration, which are greatly emphasized in the anti-asylum movement. These individuals committed crimes but were considered not criminally responsible for their actions due to mental disorders, and they remained imprisoned even though they may have a low level of dangerousness.

In Canada, cases of individuals who are not criminally responsible on account of mental disorders (NCRMD) were recently reviewed in a set of studies conducted in three provinces.[14,16] One of these studies[27] also showed that there were significant heterogeneities in applying Canadian law and in the forensic procedures regarding these cases, such that individuals affected by mental disorders can be detained for longer in some provinces than in others.[16]

We consider that evaluating the accuracy of diagnostic instruments is paramount. The sensitivity and specificity of these instruments should be assessed in appropriate studies, through identification of true-positive, false-positive and true-negative cases. In this manner, appropriate conduct at diagnostic, institutional and therapeutic levels can be implemented with greater safety.

Evidence-based treatment

The therapeutic measures recommended and those noted in the inpatient records evaluated differed greatly.[20,28-31] The inpatient records were frequently unclear and occasionally absent. It was unclear whether some medications were being used because of their capacity to prevent psychotic events or because they promote an anxiolytic or sedative effect, thereby controlling patients' behavior, for example. In turn, it was also unclear whether anticonvulsants were used for epileptic conditions or as mood stabilizers.[32,33] However, considering custodial hospitals within the context of healthcare, it needs to be borne in mind that while more advanced technologies can promote better treatment results, physicians still need to be trained to use them.[4]

Implications for practice and research

The findings from the present study indicate that there is a need for legal professionals (lawyers, attorneys and judges) to have knowledge in the field of evidence-based mental health and to be able to perform searches in the available databases.[29] Judges in Brazil operate only on the basis of their trust in the healthcare professionals who advise them: whatever they determine is then practiced for an indeterminate time.

In the field of research, there is a clear need for better training for specialized professionals, for application of instruments that have been validated internationally to assess individuals with mental disorders. In the present study, it was seen that the professionals involved in making diagnoses and administering treatments among the inpatients apparently had not received any training or, if they had, they were not using the instruments available. Partnerships between custodial institutions and universities could assist with this problem, through identifying weaknesses in the system and proposing solutions. Universities can benefit these institutions through providing training and, in return, would find a fertile field for research within psychiatry. This idea needs to be tested through meticulously designed studies, which could include psychiatric reexaminations on patients (which was not possible in the present study).

The flowchart (**Figure 1**) illustrates how it was not possible to verify the scientific credibility of the medical records due to the inadequacy of these records. It was, on the other hand, possible to verify that most of the inpatients had received a schizophrenia diagnosis, both in Rio de Janeiro and in the Federal District, albeit without further details. This was followed, in terms of frequency, by a diagnosis of use of psychoactive substances, but with no supporting drug tests or reports.

This flowchart (**Figure 1**) shows the distribution of information resulting from the examinations on the inpatients regarding mental insanity and cessation of dangerousness in the Federal District and Rio de Janeiro.

Thus, it became more difficult to establish a pathological profile for these inpatients who were subject to security measures. The visits made to the institutions showed, as presented in the Results section, that the lack of human resources determined the lack of individual medical records. There were absences of remedial therapists and there were some reports on cessation of dangerousness without any mental insanity examination. All of this indicates the

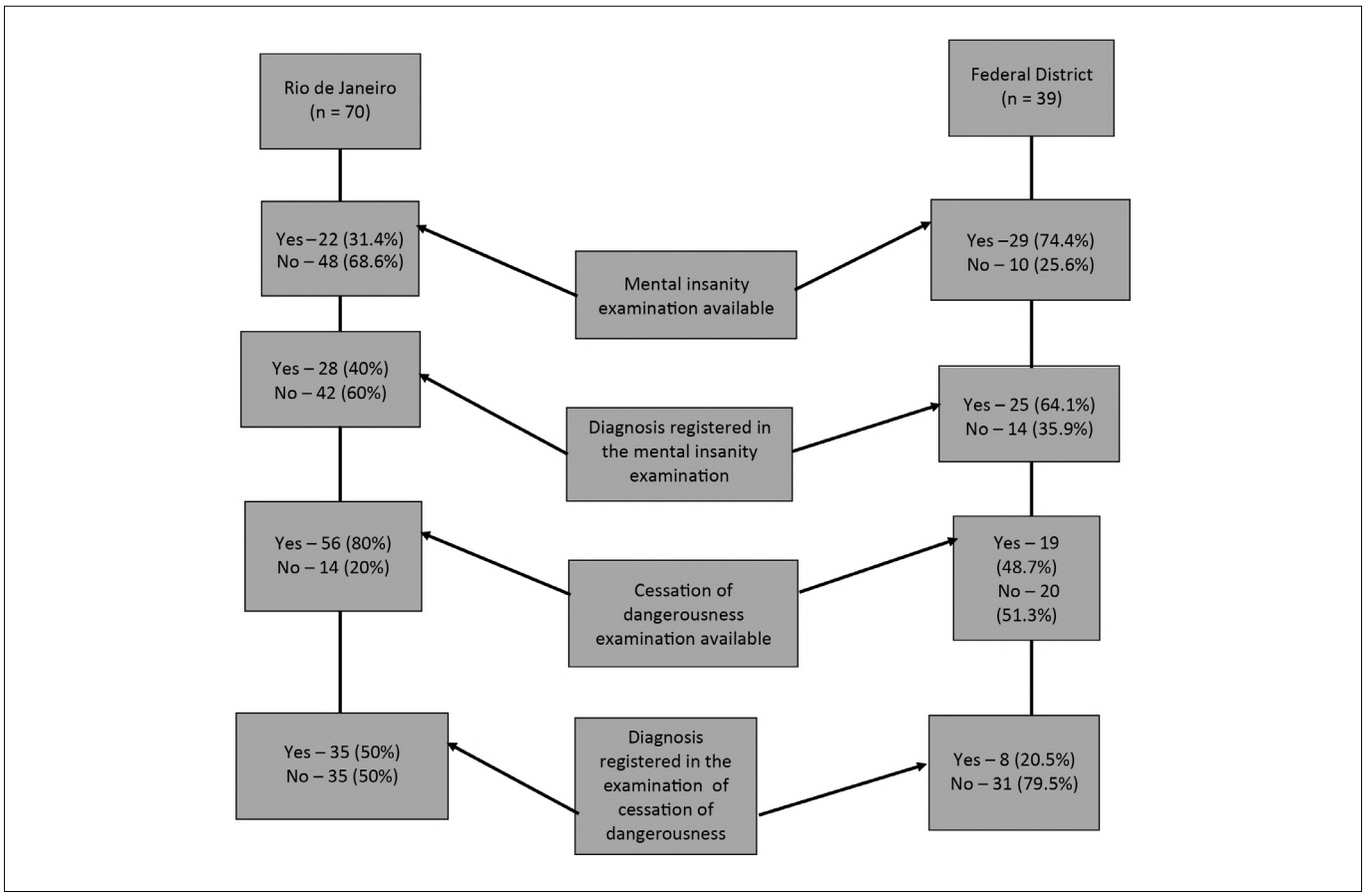

Figure 1. Flowchart for sample.

inadequacy of the situation in relation to what is recommended by the international guidance: for instance, with regard to subjects who are considered to have a mental illness and who are therefore unaccountable before the law.

CONCLUSIONS

This novel analysis corroborates the hypothesis that the treatments applied were not based on the current scientific evidence. Standardized instruments to assess the level of dangerousness of the inpatients at the custodial institutions were not used, either. This lack of evidence-based diagnoses makes adequate treatment impossible. There were also no standardized records regarding the recommended treatments and whether these were pharmacological.

Based on the sparse and incomplete documentation of the diagnoses presented in the medical reports, the largest proportion of the inpatients were diagnosed as having schizophrenia, with no further details, followed by the proportion with a diagnosis of use of psychoactive substances, but with no supporting toxicological screenings. This finding makes it difficult to establish a psychopathological profile for inpatients who are subject to security measures at these institutions, and to ensure quality treatment.

The lack of scientific support for these diagnoses and treatments from the best scientific evidence reveals a flaw in the integration of the fields of medicine and law. This ultimately compromises the human rights of inpatients at custodial hospitals in Brazil. These inpatients are entitled by law to the most effective and safe treatment, but the present study demonstrated that this has not been practiced.

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Address for correspondence:
Álvaro Nagib Atallah
Cochrane Brasil
R. Borges Lagoa, 564
Vila Mariana — São Paulo (SP) — Brasil
CEP 04038-001
Tel. (+55 11) 5571-4721/5575-2389
E-mail: atallahmbe@uol.com.br

Authors' contributions: Marchewka TMN: conceptualization (lead), data curation (lead), formal analysis (lead), funding acquisition (lead), investigation (lead), methodology (lead), project administration (lead), resources (lead), software (lead), supervision (lead), validation (lead), visualization (lead), writing-original draft (lead) and writing-review and editing (lead); Atallah AN: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal) and project administration (equal); Valente NM: formal analysis (equal), investigation (equal), methodology (equal) and project administration (equal); and Melnik T: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal) and project administration (equal). All authors actively contributed to discussion of the results from the study, and reviewed and approved the final version to be released

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Plastic surgery professional misconduct: a cross-sectional study on cases between 2008 and 2017, filed before the São Paulo State Medical Board

Paulo Cézar Mariani[I], Clóvis Francisco Constantino[II], Rui Nunes[III]

Conselho Regional de Medicina de São Paulo (CREMESP), São Paulo (SP), Brazil

[I]MD. Doctoral Student, Faculdade de Medicina da Universidade do Porto, Porto, Portugal.
https://orcid.org/0000-0002-9576-5510

[II]PhD. Physician and Professor, Universidade de Santo Amaro (UNISA), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-7540-2632

[III]PhD. Professor, Faculdade de Medicina da Universidade do Porto, Porto, Portugal.
https://orcid.org/0000-0002-1377-9899

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ABSTRACT

BACKGROUND: In plastic surgery, a lack of ethical and moral behavior by professionals can result in unfortunate circumstances and can justify ethical-disciplinary procedures.

OBJECTIVE: To review 421 plastic surgery professional-misconduct cases filed before the São Paulo State Medical Board (CREMESP) between 2008 and 2017.

DESIGN AND SETTING: Cross-sectional study conducted in a medical council.

METHODS: The cases were categorized according to sex, age, medical specialty (plastic surgery, other field or none), medical ethics code chapter(s) involved, ethics code articles violated and board ruling/outcome.

RESULTS: Most of the defendants were men over 40 years of age who were experienced in their professional practice and who graduated from public and private universities all over Brazil; 47.74% had a specialist title in plastic surgery. Violation of professional responsibility (medical malpractice, recklessness or negligence) was the commonest complaint (28.43%), followed by medical advertising (24.19%) and poor doctor-patient relationship (10.39%), in violation of articles 18, 51, 75 and 1. Among the 233 cases adjudicated over this period, 133 resulted in disciplinary sanction, 80 were ruled in the physician's favor and 20 were dismissed.

CONCLUSION: Classification of plastic surgery professional-misconduct cases creates possibilities for adopting preventive measures for good practice in this specialty, which would consequently reduce the number of complaints to the regional medical boards.

INTRODUCTION

Plastic surgery is a medical procedure that consists of various surgical or non-surgical procedures that reshape human body parts. The purpose is to treat "anatomical, congenital, acquired, post-traumatic, degenerative and oncological deformities to improve patients' biopsychosocial health and subsequently their quality of life".[1]

Borges[1] reported that there had been an explosive increase in lawsuits involving plastic-surgery malpractice, which has led to challenges for physicians and medical associations. Two phenomena explain this considerable increase in lawsuits: on the one hand, patients are increasingly more aware of their rights enshrined in articles 196 and 200 of the Brazilian Constitution, including redress for medical malpractice; and on the other hand, patients are clearly being affected by job instability, especially in the government, and by media influence, deteriorating doctor-patient relationships and inefficient university residency and postgraduate programs. These issues have led to greater legislative protections for patients seeking answers for care or treatment that was deemed unsatisfactory.[2]

Physicians commit ethical violations when they fail to follow medical guidelines.[3-6] Therefore, civil liability for medical malpractice should be examined from two separate angles: a) liability for services directly and personally rendered by physicians as self-employed individuals; b) medical liability for rendering medical services as a business, which includes inpatient and outpatient hospitals, clinics, blood banks and medical laboratories.[7,8]

In medical practice, malpractice is understood as a wrongful act that damages or jeopardizes the health of another person and occasions poor or adverse result(s) owing to a physician's action

or inaction, in violation of medical guidelines.[9-11] Malpractice can be qualified by any of the three types listed in article 1 of the medical ethics code, based on the Brazilian penal code, the Brazilian constitution or the Brazilian civil procedure code, namely negligence, recklessness and professional malpractice.

The article governing professional responsibility is the article most often violated by doctors.[12] The Brazilian Medical Association (BMA) and regional medical boards are tasked with being notified of, investigating and ruling on all complaints filed, as well as for regulating the practice of medicine.[13-15] Once a professional-misconduct case has been instituted, and once it has been established that there has been a violation of the medical ethics code, any of the five disciplinary sanctions listed in article 22 of Brazilian law 3.268/1957 can be handed down to the physician: confidential warning – classified notice (punishment A); confidential reprimand – classified notice (punishment B); public reprimand – notice on public record (punishment C); suspension of license to practice for up to 30 days (punishment D); or revocation of license to practice pending final ruling by the Brazilian Medical Association (punishment E). Either party may appeal against any punishment administered.[16,17]

OBJECTIVE

The objective of this study was to classify cases relating to plastic surgery professional misconduct filed before the São Paulo State Medical Board (CREMESP) between 2008 and 2017, considering the demographic and professional characteristics: sex, age, private or public university education, medical specialty (plastic surgery, other field or none); and the case characteristics: medical ethics code chapter involved in the case, ethics code article(s) violated and ruling/outcome.

METHODS

This was a retrospective cross-sectional database study that included all professional-misconduct cases involving plastic surgery that were filed before CREMESP over a 10-year period from 2008 to 2017. A total of 421 such cases were investigated (and closed) by CREMESP over this period. Notably, among these 421 cases, there were physicians under investigation in more than one case, such that 273 physicians, with or without a specialty qualification in plastic surgery, were involved.

We analyzed complaints involving plastic surgery in the CREMESP database after firstly receiving authorization from CREMESP (through a letter from its board, without reference number, but dated September 12, 2017) and then receiving ethics approval from the research ethics committee of the university where this study was conducted (no. 2.338.983; dated October 19, 2017). The board furnished the research team only with complaints involving plastic surgery, and the parties to the complaints were not identified. This research was conducted in accordance with the ethical and care standards and set forth in the Declaration of Helsinki and Nuremberg Code (Brazilian Medical Association Ruling 1785/2006). Professional-misconduct cases that had been dismissed or that were converted to administrative proceedings were not included.

The following variables were extracted from the database: sex, age, possession of medical specialty title in plastic surgery, case subject matter, medical ethics code article(s) violated and ruling/outcome.

The quantitative research design was descriptive, in accordance with the nature of the variable. The results are presented in tables, as described below.

RESULTS

A total of 7,789 professional-misconduct cases of all natures were filed before CREMESP during the period in question. Of these, 421 cases (5.40%) involved 273 physicians with or without a specialty qualification in plastic surgery. All regional-board cases filed or pending before the CREMESP between 2008 and 2017 were included in the present review.

At the time of this review, among the 421 professional-misconduct cases that met the inclusion criterion, 233 (55.35%) cases had been adjudicated. Of these 233 cases, 133 (57%) resulted in disciplinary sanction, 80 (34.5%) were ruled in the physician's favor and 20 (8.5%) were dismissed. A total of 188 cases (44.65%) were still pending investigation and judgment at the end of the year 2017, when data were collected for this review.

Classification of defendants

Table 1 lists the general characteristics of the defendant physicians: sex, age, type of university education and whether they had a medical specialty title in plastic surgery.

The average age of the physicians accused of misconduct was 49.5 years. The youngest was 30 years old and the oldest, 73 years old. The majority (58.43%) were younger than 50 years at the time when the complaint was filed. Most of the defendants had received their medical degrees from private universities and were not specialists in plastic surgery.

Table 2 shows the breakdown of all the physicians without a specialty title in plastic surgery who were accused of medical misconduct, namely: physicians with a medical specialty other than physical surgery; and physicians bearing no record of any medical specialty.

Among the 421 cases, 201 cases (47.74%) were brought against specialists in plastic surgery, 147 cases (34.91%) were brought against physicians who were not licensed in any specialty and 73 cases (17.34%) were brought against physicians who were licensed as medical specialists in fields other than plastic surgery.

Table 1. Breakdown of the 421 cases according to sex, age, type of university education, and possession of a specialty title in plastic surgery, in numbers and percentages

Physician profile	n	%
Sex		
Male	325	77.19
Female	96	22.81
Total	**421**	**100.00**
Age (years)		
30-39	109	25.89
40-49	137	32.54
50-59	85	20.19
60-69	56	13.30
> 70	34	8.08
Total	**421**	**100.00**
University type		
Public	175	41.57
Private	246	58.43
Total	**421**	**100.00**
Plastic surgery specialty		
Yes	201	47.74
No	220	52.26
Total	**421**	**100.00**

Table 2. Distribution of the numbers of physicians without a specialty title in plastic surgery who were accused of medical misconduct, including physicians with a medical specialty other than plastic surgery and physicians with no record of any medical specialty, in numbers and percentages

Distribution of physicians without a specialty title in plastic surgery		
Other specialties	**n**	**%**
Anesthesiology	17	7.72
Angiology/vascular surgery	1	0.45
Oncology	1	0.45
General surgery	1	0.45
Vascular surgery	1	0.45
Internal medicine	1	0.45
Internal medicine – endocrinology and metabolic health	1	0.45
Dermatology	23	10.45
Endocrinology and metabolic health	1	0.45
Obstetrics and gynecology	5	2.27
Homeopathy – pediatrics	2	0.91
Family medicine and community health	1	0.45
Occupational health	3	1.36
Clinical nutrition	1	0.45
Ophthalmology	2	0.91
Orthopedics	5	2.27
Otorhinolaryngology	6	2.73
Pathology	1	0.45
No record of any specialty	147	66.88
Total	**220**	**100.00**

Classification of complaints

Table 3 lists the medical ethics code chapters (subject/topic) cited in the 421 cases. The most frequent subject/topic cited in these cases brought between 2008 and 2017 was violation of professional responsibility (medical malpractice, recklessness or negligence) (79.10%), followed by doctor-doctor relationships (complaints filed by fellow physicians) (52.49%) and then by professional confidentiality (34.67%).

The medical ethics code articles most often violated were articles 18 (35.82%), 51 (27.45%), 75 (20.22%) and 1 (16.51%). These are all deontological articles referring to professional responsibility, doctor-doctor relationships and professional confidentiality.

Among the cases filed over the study period, 233 cases (55.35%) had been adjudicated by the end of the year 2017, when data were collected for this review. The other 188 cases remained pending, awaiting the board's ruling. Among the 233 adjudicated cases, 133 (57%) resulted in disciplinary sanction and 80 (34.5%) were ruled in the physician's favor.

Table 4 shows the distribution of disciplinary sanctions taken in the 133 cases in which the physician was found guilty, with a breakdown according to sex, age, type of medical university and possession of a specialist title in plastic surgery.

It was observed that male physicians were most often sanctioned with punishment B (35.95%), while female physicians were most often sanctioned with punishment C (43.33%). Regardless of the type of punishment, male physicians in general faced more punishment than female physicians. With regard to age group, physicians aged 30-39 years were most likely to be administered punishment C (77.50%), physicians aged 40-49 were most likely to be administered punishment B (62.96%), physicians aged 60-69 were most likely to be administered punishment A (58.33%) and physicians aged 70 and older were most likely to be administered punishment E (75.00%). Also, punishment C was most applied to doctors aged 30-39 (the youngest cohort), and punishment E was most applied to doctors aged 70 and over (the oldest cohort).

Table 3. Distribution of medical ethics code chapters (subject/topic) cited in the 421 cases, in numbers (occurrences) and percentages

Breakdown of medical ethics code subjects/topics cited		
Ethics code subjects and topics	**Occurrences**	**% (n = 421)**
Professional responsibility	333	79.10
Human rights	95	22.56
Doctor-patient relationship	100	23.75
Doctor-doctor relationship	221	52.49
Professional remuneration	132	31.35
Professional confidentiality	146	34.67
Medical documents	141	33.49
Teaching and medical research	03	0.71
Medical advertising	137	32.54

Table 4. Breakdown of disciplinary sanctions taken in the 133 cases in which physicians were found guilty, with a breakdown by sex, age, type of medical university, and specialty title in plastic surgery status, in numbers and percentages

	Breakdown of disciplinary sanctions in 133 cases in which physicians were found guilty											
	Punishment A		Punishment B		Punishment C		Punishment D		Punishment E		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Sex												
Male	11	10.67	37	35.95	31	30.09	15	14.56	09	8.73	103	77.44
Female	3	10.00	10	33.33	13	43.33	04	13.34	0	0.00	30	22.56
Total	**14**	**10.52**	**47**	**35.33**	**44**	**33.08**	**19**	**14.28**	**09**	**6.79**	**133**	**100.00**
Age												
30-39	0	0.00	6	15.00	31	77.50	3	7.50	0	0.00	40	30.07
40-49	0	0.00	34	62.96	7	12.96	10	18.51	3	5.57	54	40.60
50-59	6	31.57	6	31.57	4	21.08	3	15.78	0	0.00	19	14.28
60-69	7	58.33	1	8.35	2	16.66	2	16.66	0	0.00	12	9.03
> 70	1	12.50	0	0.00	0	0.00	1	12.50	6	75.00	8	6.02
Total	**14**	**10.52**	**47**	**35.33**	**44**	**33.08**	**19**	**14.28**	**9**	**6.79**	**133**	**100.00**
University Type												
Public	3	6.00	17	34.00	17	34.00	6	12.00	07	14.00	50	37.59
Private	11	13.25	30	36.14	27	32.55	13	15.66	02	2.40	83	62.41
Total	**14**	**10.52**	**47**	**35.33**	**44**	**33.08**	**19**	**14.28**	**09**	**6.79**	**133**	**100.00**
Specialty title in plastic surgery												
Yes	7	11.66	26	43.35	23	38.33	4	6.66	0	0.00	60	45.11
No	7	9.58	21	28.76	21	28.76	15	20.54	9	12.36	73	54.89
Total	**14**	**10.52**	**47**	**35.33**	**44**	**33.08**	**19**	**14.28**	**9**	**6.79**	**133**	**100.00**

Regarding university type, physicians who studied at a private institution were more likely to face disciplinary sanction (62.41%) than were those who studied at public institutions (37.59%). Regardless of the type of institution, punishments B and C were administered most frequently.

Physicians without a medical specialty title in plastic surgery were more likely to face disciplinary sanction (54.89%) than were those who were specialists in plastic surgery. However, in looking more closely at the punishments applied to those with a specialty title in plastic surgery, punishments B and C (43.35% and 38.33% respectively) are seen to be most prevalent.

DISCUSSION

Sex

Out of the 273 physicians involved in the 421 cases analyzed here, 77.19% were male, a finding that is consistent with other studies.[16,18] It was noted that complaints were brought against male physicians and that male physicians were found guilty of misconduct three times more often than was observed among female physicians.

Carvalho[19] reported that complaints were filed less frequently against female physicians because they interacted more with patients, spent more time listening to them during examinations, saw fewer patients overall and treated patients with less serious conditions or complaints. In other words, women were perceived to be better at interacting, listening, talking and explaining, and they seemed to be more attentive as well. Despite the physician-physician relationship, this may explain the comparatively low number of complaints filed with regional medical boards against female physicians, compared with male physicians.

Age

The average age of the physicians accused of misconduct was 49.5. The age range in which the greatest number of physicians was found guilty was the 40 to 49-year-old group (40.60%), while the oldest group (70+ years old) was the age group found guilty least often (6.02%).

These numbers referred to physicians who had been licensed for about 10 years and who were, therefore, in their most productive phase. At this time in their careers, they undertake a large volume of medical procedures, with high number of complex surgeries, while experiencing a time of greater financial demand relating to family and personal responsibilities.

The average age range of the physicians accused of misconduct, namely 40-49 years old, was consistent with the findings.[20-22] This symmetry corroborates the results of this study.

Medical specialty title in plastic surgery

This study shows that 220 of the cases in which complaints were filed (52.26%) were against physicians who were not medical specialists in plastic surgery. Brazilian law allows doctors to perform any procedure provided that they possess the requisite technical knowledge.[10] Physicians licensed for other specialties are performing plastic surgeries for which they are not prepared, which increases patient risk. One study conducted by CREMESP in 2008 showed that 97% of the cases of mistakes (or misconducts) in plastic surgeries were filed against physicians who did not possess a specialist title in plastic surgery.[23]

In Brazil, given the shortage of residency places and given the personal need to begin working, it is common for physicians to begin practicing internal medicine and to informally practice plastic surgery. They may occasionally obtain a license in plastic surgery, following a review of their knowledge and experience by the medical association.[24]

It can be noted that a generalist profile is very common among physicians in small towns, while in big cities there is greater demand for specialized professionals.

Standardization of care, through better regulation and standards regarding medical specialization, is needed to ensure patient safety and to provide back-up for patients' options in choosing a licensed plastic surgeon.[25]

Medical ethics code chapters (subject/topic)

Violation of professional responsibility (medical malpractice, recklessness or negligence) was the most common complaint. This result is consistent with published data.[12]

The existence of complaints of negligence, medical malpractice or recklessness makes it clear that most mistakes or misconducts that occur in the practice of plastic surgery are due to physicians' omissions or passiveness in relation to patients who should be receiving more attention and care. This is corroborated by the rate of cases found in physicians' favor on account of a lack of evidence to back up the complaints.[21]

However, the general understanding is that it is legally permitted to practice medicine provided that the physician meets the legal and professional licensing requirements. It is illegal to practice medicine with any degree of recklessness, malpractice or negligence. When recklessness, medical malpractice or negligence occurs, Brazilian law calls for redress and punishment and establishes that damages should be awarded to the patient(s) harmed. In these situations, culpability is generally and usually attributed to the physician. Advances in medical science have led to greater medical responsibility, and, in this light, physicians are now liable for greater risks and for a greater number of possible accidents, which may be grounds for a discussion on culpability lying outside of physicians' purview.[26]

Physicians filing complaints against their colleagues was the second most common plastic-surgery-related complaint filed (doctor-doctor relationship). The medical ethics code explicitly lists medical professionals' rights and duties. Although it may seem unethical to file a complaint against a fellow physician, situations in which colleagues fail, through omission or commission, to honor the medical ethics code give rise to a duty among physicians to report their colleagues' conduct to the regional medical board. The medical ethics code seeks to safeguard professional relationships.[27]

The problems that physicians may face in relation to their colleagues fall into two types: interpersonal matters like a lack of communication, cooperation or harmony; and professional matters like anti-ethical self-promotion or publicizing of "foolproof" methods and innovative and exclusive techniques, etc. Such violations consequently lead to a breakdown of trust among physicians and weaken professional relationships, as stated in the medical ethics code of 2009. It is therefore important that physicians do file complaints before the regional medical board so that it can investigate any violations of the code. Since these complaints are considered to be administrative cases, physicians need not be wary of filing complaints; by bringing cases to the board's attention, they are fulfilling their civic duty.

In relation to professional confidentiality, a distinction is made between ethics and morality. Confidentiality has always been the moral obligation of professionals working in the field of medicine. Morality, like confidentiality, involves principles that guide a given behavior, while ethics consists of philosophical discussions for critical evaluation of morality and professional confidentiality. Therefore, ethics is a treatise within morality, dealing with values on scales from good to bad and from right to wrong. It needs to be noted that, despite the existence of a moral compass in the medical profession that is codified through rules to guide proper behavior, some physicians do not follow this and fail to respect confidentiality between doctors, patients and family information.

Medical ethics code articles most commonly violated

This study showed that the four most commonly violated ethics code articles among those in effect when the complaints were filed were 18, 51, 75 and 1. Article 18 ("Disobeying or disrespecting Brazilian Medical Association (CFM) or regional medical council rulings or appellate decisions") was cited most often in a previous study on complaints and cases against physicians who were found guilty and received punishment; those findings are corroborated by the results from the present study.[28] Article 51 ("Engaging in unfair competition with another physician") primarily relates to self-promotion. Article 75 ("Making reference to identifiable clinical cases or exposing patients or their profiles in medical advertisements, medical publications or the media in

general without patient consent") is most often found in marketing and advertising involving pre and postoperative patient photos. Lastly, article 1 ("Causing harm to the patient, through omission or commission, characterized by medical malpractice, recklessness or negligence") is referred to collectively in the present paper as "professional misconduct".[29]

Although medical advertising was not the subject of the majority of the complaints filed during the period of the present study, all four of the aforementioned articles involve medical advertising to some degree, as explained in a previous study.[30] In plastic surgery, medical advertising strongly influences the mistake or misconduct identified. Profiting from the profession through marketing of medicine is considered to be unethical behavior. In this vein, physicians are not allowed to be party to any commercials or advertisements that in any way promote or profit from the profession. Regardless of the specialty, physicians should not guarantee results or treatment. Physicians must clearly inform patients of the benefits and risks of a given procedure. Advertising in which physicians publicize simple and quick treatment that is 100% effective is an invitation for lawsuits to hold physicians to the purported results. Promising results put the physician in a delicate situation, since complications may arise during treatment. Medical information should include what is scientifically correct and accepted as good medical practice, and medical professionals should base their practice on the laws that are in effect.

Disciplinary sanctions

Our review of the disciplinary sanctions taken showed that punishment B (confidential reprimand – classified notice) was the punishment most often administered. This finding speaks to one of CREMESP's maxims, namely that professional-misconduct cases are meant to serve as a means for educating physicians. There is generally no reason to put the ruling or sanctions imposed into the public record, except in cases in which the situation is grave, or in cases of repeated offense and cases in which there is imminent indisputable risk or harm to others. These findings are similar to previous findings regarding the prevalence of confidential disciplinary sanctions.[16-31]

The data shows that punishment C was applied most to doctors aged 30-39 (the youngest group), and punishment E was applied most to doctors aged 70 and over (the oldest group).

It is not surprising that a punishment of public record was applied most to doctors in the 30-39-year-old cohort. Physician behavior at this age perfectly explains this phenomenon. The heavy workload facing the youngest group means that there is greater likelihood of facing a complaint. Moreover, self-confidence and possible consequent carelessness explain complaints filed against the oldest group. This supports similar findings that negligence was the complaint most often cited, reported in some previous studies.[21,22]

Physicians without a medical specialty title in plastic surgery were more likely to face disciplinary sanction (54.89%) than those who were specialists in plastic surgery. However, looking more closely at the punishments applied to those with a specialty in plastic surgery, punishments B and C (43.35% and 38.33% respectively) were seen to be most prevalent. Greater severity of disciplinary sanctions for certain violations shows the existence of concern regarding where the field of medicine is heading and, primarily, concern regarding safeguarding society from medical malpractice, which is the *raison d'être* of the regional medical boards.

CONCLUSION

The classification of physicians against whom plastic surgery medical misconduct cases were filed before the São Paulo State Medical Board (CREMESP) that was presented in this study was similar to what has been shown elsewhere in the medical literature. Physicians of all medical specialties, including plastic surgeons, are aware that medical practice nowadays is replete with many ethical assumptions and bioethical dilemmas stemming from new technologies and procedures. This demands deeper ethical reflection before making medical decisions. Medical misconduct due to negligence has become more rigorously punished on ethical grounds, both in Brazil and internationally.

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Address for correspondence:
Paulo Cézar Mariani
Rua Hum, 2.366
Jales (SP) — Brasil
CEP 15700-002
Tel. (+55 17) 3632-6410
E-mail: drpaulomariani@hotmail.com

Major risk factors for obstructive sleep apnea monitored in the home. A cross-sectional study

Ricardo Silva[I], Tharcisio Pereira Brito[II], Antônio Cavalcanti Wanderley Neto[III], Renata Botelho Frota[IV], João Cateb Melo[V]

School of Medicine, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil

[I]MD. Full Professor, Department of Cardiology, School of Medicine, Universidade Federal do Ceará (UFCE), Fortaleza (CE), Brazil.
https://orcid.org/0000-0001-6992-9318

[II]MD. Postgraduate Student, Department of Cardiology, School of Medicine, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil.
https://orcid.org/0000-0002-5519-4944

[III]MD. Postgraduate Student, Department of Cardiology, School of Medicine, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil.
https://orcid.org/0000-0002-1300-2617

[IV]MD. Attending Physician, Clínica Cateb Melo, Fortaleza (CE), Brazil.
https://orcid.org/0000-0002-8259-3254

[V]MD. Attending Physician, Clínica Cateb Melo, Fortaleza (CE), Brazil.
https://orcid.org/0000-0003-0829-5133

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Age.
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ABSTRACT

BACKGROUND: Obstructive sleep apnea (OSA) is characterized by recurrent pharyngeal wall collapse during sleep caused by anatomical or functional changes associated with obesity or dislocation of maxillofacial structures.

OBJECTIVE: To determine the major risk factors for obstructive sleep apnea monitored in the home.

DESIGN AND SETTING: Cross-sectional study conducted in a private clinic in Fortaleza (CE), Brazil.

METHODS: Between 2015 and 2018, 427 patients were screened for OSA with home-based monitoring, yielding 374 positives. Information was collected on age, sex, body mass index (BMI), hypertension, diabetes (DM), dyslipidemia, coronary artery disease (CAD), arrhythmia, peripheral artery occlusive disease (PAOD), heart failure (HF) and lung disease. The home sleep apnea test result was then compared with the clinical diagnosis. Lastly, parameters identified as significant in the univariate analysis were subjected to multivariate logistic regression.

RESULTS: Male sex predominated, although not significantly. OSA was associated with hypertension, DM, dyslipidemia, age and BMI. The risk of OSA being associated with these parameters was 2.195 (hypertension), 11.14 (DM), 2.044 (dyslipidemia) and 5.71 (BMI). The association was also significant for BMI categories (normal, overweight or obese). No significant association was observed for CAD, arrhythmia, PAOD, HF or lung disease. After multivariate logistic analysis, only age and BMI (and its categories) remained significant.

CONCLUSION: OSA was associated with hypertension, DM, dyslipidemia, age and BMI in univariate analyses, but only with age and BMI (and its categories) in multivariate logistic analysis.

INTRODUCTION

Obstructive sleep apnea is characterized by recurrent pharyngeal wall collapse during sleep, caused by anatomical or functional changes associated with obesity or dislocation of maxillofacial structures.[1]

This condition is highly prevalent in patients with cardiovascular disease. In fact, the syndrome is accompanied by hypoxia, oxidative stress, sympathetic activation and endothelial dysfunction, all of which are mediators of cardiovascular disease.[2]

Moreover, several authors in the literature have stated that ageing affects the severity of obstructive sleep apnea syndrome and the associated cardiovascular risk.[3] The relationship between obstructive sleep apnea and cardiovascular disease involves the mechanisms of platelet activation and inflammation. Therefore, abnormalities may be observed in laboratory tests based on markers for platelet activation and inflammation, such as mean platelet volume, platelet-lymphocyte ratio, red blood cell distribution width and neutrophil-lymphocyte ratio.[4]

The incidence of obstructive sleep apnea is 14% in men and 5% in women. The condition is diagnosed through a sleep study, and the gold standard for this is polysomnography. Because very few clinics offer this type of examination, the vast majority of cases (80%-90%) will most likely never be formally diagnosed. As a cheaper alternative, home-based monitoring may be performed without the presence of a technician.[5]

There is evidence to suggest the existence of an association between obstructive sleep apnea and metabolic syndrome or diabetes.[6] The pathophysiology is not well understood, but intermittent hypoxia is likely to play an important role.[7] In addition to hypoxia, sleep fragmentation leads to activation of the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis and pro-inflammatory pathways or oxidative stress.[8] Both intermittent hypoxia and sleep fragmentation have been shown to be associated with several inflammatory biomarkers, thus leading to systemic inflammation.[9]

Among cardiovascular disorders, obstructive sleep apnea predisposes to arrhythmia, including atrial fibrillation, which is diagnosed in 6% of obstructive sleep apnea patients (20% if male). Greater prevalence of atrial fibrillation is positively associated with greater severity of obstructive sleep apnea.[10] In association with obstructive sleep apnea, QT prolongation is a risk factor for severe arrhythmia.[11] The fact that obstructive sleep apnea predisposes to coronary disease is supported by data from a systematic review of three trials, which showed that 12% of 5,067 obstructive sleep apnea patients had myocardial infarction or stroke or needed myocardial revascularization, with a fatality rate of 25% for cardiovascular events.[12]

Systemic arterial hypertension is also closely linked with obstructive sleep apnea, especially resistant systemic arterial hypertension. Among the drugs used to treat systemic arterial hypertension, angiotensin receptor blockers combined with continuous positive airway pressure can reduce pressure, while antimineralocorticoids moderately reduce the severity of obstructive sleep apnea.[13] Continuous positive airway pressure is standard therapy in cases of severe obstructive sleep apnea. In a study monitoring 554 obstructive sleep apnea patients for cardiovascular outcomes, 50 cardiovascular events occurred in 44 patients over an average follow-up period of 5.9 years. Events were more frequent in patients with severe obstructive sleep apnea. The risk of cardiovascular events was 2.66 times greater in the group not treated with continuous positive airway pressure.[14]

The association between obstructive sleep apnea and cardiovascular disease has been tested in populations with different ethnic backgrounds. For example, the Australian Longitudinal Study on Male Health followed 13,423 men and found prevalences of 2.2% and 7.8% for men aged 18-25 and 45-55 years, respectively. Obstructive sleep apnea was significantly associated with age, unemployment, asthma, chronic obstructive pulmonary disease/bronchitis, diabetes, hypercholesterolemia, systemic arterial hypertension, heart failure, angina, depression, anxiety and schizophrenia.[15] Obstructive sleep apnea is also highly prevalent among Iranians and, in one study, was associated with cardiovascular disease (26%) and systemic arterial hypertension (74%).[16]

OBJECTIVE

To determine the major risk factors for obstructive sleep apnea monitored in the home.

METHODS

Between April 2015 and April 2018, we screened 427 patients for obstructive sleep apnea through home-based monitoring. The result was positive for 374 and negative for 53 (**Table 1**).

We also collected information on sex, age, body mass index (BMI) and diagnoses of obstructive sleep apnea, diabetes, dyslipidemia, coronary disease, arrhythmia, peripheral artery occlusive disease, heart failure and lung disease. Lastly, we correlated each clinical diagnosis with the result from the respective home sleep apnea test (**Table 1**).

Table 1. Clinical characteristics versus obstructive sleep apnea

		Obstructive sleep apnea			
		No		Yes	
		n	%	n	%
Sex	Female	22	41.5%	143	38.2%
	Male	31	58.5%	231	61.8%
Hypertension	Yes	19	35.8%	206	55.1%
	No	34	64.2%	168	44.9%
Diabetes	Yes	1	1.9%	66	17.6%
	No	52	98.1%	308	82.4%
Dyslipidemia	Yes	15	28.3%	167	44.7%
	No	38	71.7%	207	55.3%
CAD	Yes	4	7.5%	47	12.6%
	No	49	92.5%	327	87.4%
Arrhythmia	Yes	5	9.4%	69	18.4%
	No	48	90.6%	305	81.6%
PAD	Yes	4	7.5%	17	4.5%
	No	49	92.5%	357	95.5%
HF	Yes	2	3.8%	18	4.8%
	No	51	96.2%	356	95.2%
COPD	Yes	3	5.7%	8	2.1%
	No	50	94.3%	366	97.9%

CAD = coronary artery disease; PAD = peripheral arterial disease; HF = heart failure; COPD = chronic obstructive pulmonary disease.

The study protocol was approved on February 7, 2018, by the research ethics committee of the local university hospital and was filed under #2.489.575.

Statistical analysis

Quantitative variables were expressed as mean values ± standard deviation, while categorical variables were expressed as frequencies and prevalence, in order to test for associations between risk factors and the presence of obstructive sleep apnea. Group parameters were compared using the Mann-Whitney U test due to their non-normal distribution. Potential associations between categorical variables were analyzed using Pearson's chi-square test and Fisher's exact test.

All analyses were performed using the SPSS Statistical Package for the Social Sciences (SPSS) software, version 22.0 (Norman H. Nie, C. Hadlai (Tex) Hull and Dale H. Bent, Chicago, United States), and the R 3.3.1 software (Ross Ihaka and Robert Gentleman, Auckland, New Zealand). Parameters identified as significant in univariate analyses were subjected to multivariate logistic analysis. The level of statistical significance was set at 5% ($P < 0.05$).

RESULTS

Male sex was predominant, although not significantly (**Table 2**). Presence of obstructive sleep apnea was associated with systemic arterial hypertension, diabetes, dyslipidemia, age and body mass index. The risk of obstructive sleep apnea being associated with systemic arterial hypertension was estimated as 2.195 (**Table 3**). The corresponding figures for diabetes, dyslipidemia and body mass index were, respectively, 11.14 (**Table 4**), 2.044 (**Table 5**) and 5.71 (**Table 6**). BMI categories (normal, overweight or obese) were also associated with obstructive sleep apnea. On the other hand, obstructive sleep apnea was not associated with coronary artery disease, arrhythmia, peripheral artery occlusive disease, heart failure or lung disease. Nearly all the coronary disease patients (49 out of 53; 92%) had a history of revascularization by means of surgery or stent implantation. When the associations between obstructive sleep apnea and the variables of systemic arterial hypertension, diabetes, dyslipidemia, age and body mass index were subjected to multivariate logistic regression, only age and body mass index (and its categories) remained significant (**Table 7**).

Table 2. Sex versus obstructive sleep apnea

		Obstructive sleep apnea		
		Yes	No	Total
Female	n	143	22	165
	%	38.2%	41.5%	38.6%
Male	n	231	31	262
	%	61.8%	58.5%	61.4%
Total	**n**	**374**	**53**	**427**
	%	**100.0%**	**100.0%**	**100.0%**

P = 0.647.

Table 3. Hypertension versus obstructive sleep apnea

			Obstructive sleep apnea		
			Yes	No	Total
Hypertension	**Yes**	n	206	19	225
		%	55.1%	35.8%	52.7%
	No	n	168	34	202
		%	44.9%	64.2%	47.3%
Total		**n**	**374**	**53**	**427**
		%	**100.0%**	**100.0%**	**100.0%**

P = 0.009; odds ratio = 2.194.

Table 4. Diabetes versus obstructive sleep apnea (OSA)

			Obstructive sleep apnea		
			Yes	No	Total
Diabetes	**Yes**	n	66	1	67
		%	17.6%	1.9%	15.7%
	No	n	308	52	360
		%	82.4%	98.1%	84.3%
Total		**n**	**374**	**53**	**427**
		%	**100.0%**	**100.0%**	**100.0%**

P = 0.003; odds ratio = 11.14.

Table 5. Dyslipidemia versus obstructive sleep apnea

			Obstructive sleep apnea		
			Yes	No	Total
Dyslipidemia	**Yes**	n	167	15	182
		%	44.7%	28.3%	42.6%
	No	n	207	38	245
		%	55.3%	71.7%	57.4%
Total		**n**	**374**	**53**	**427**
		%	**100.0%**	**100.0%**	**100.0%**

Table 6. Body mass index (BMI) range versus obstructive sleep apnea

		Frequency	Percentage
BMI	18-25	66	15.5
	25-30	163	38.2
	30-35	121	28.3
	> 35	65	15.2
	Total	415	97.2
Absent		12	2.8
Total		**427**	**100.0**

P = 0.000; odds ratio = 2.89 for BMI of 25 to 30, 5.71 for BMI from 30 to 35 and 4.85 for BMI > 35.

Table 7. Multivariate logistic regression

Clinical characteristics	OR (95% CI)		P
Hypertension	0.917	(0.451-1.864)	0.81
Diabetes	6.088	(0.8-46.326)	0.081
Dyslipidemia	1.453	(0.718-2.94)	0.299
Age	1.049	(1.026-1.073)	**< 0.001**
Body mass index			
18-25			-
25-30	2.554	(1.167-5.588)	**0.019**
30-35	7.683	(2.906-20.31)	**< 0.001**
> 35	6.652	(2.131-20.76)	**0001**

OR = odds ratio; CI = confidence interval.

DISCUSSION

Obstructive sleep apnea is highly prevalent in patients with cardiovascular disease and occurs predominantly in males (14% versus 5%).[2,5] Our sample consisted of patients with suspected obstructive sleep apnea; thus, unsurprisingly, 87% tested positive (374/427). While polysomnography is the gold standard for diagnosing obstructive sleep apnea, low-cost home-based monitoring yields reliable results and does not require the presence of a technician,[5] which justifies the choice of this type of test for the present study.

Interesting rheological data on patients with obstructive sleep apnea syndrome have been reported. Patients with obstructive sleep apnea have elevated morning fibrinogen levels and higher plasma viscosity, which correlate positively with indices of sleep apnea severity. These changes in blood rheology are independent of cardiovascular risk factors.[17]

We found that occurrences of obstructive sleep apnea were associated with diabetes, like in many other studies.[5,6] However, we did not find any association with arrhythmia, which is a frequently reported association. Furthermore, we did not find any evidence of the otherwise well-documented fact that obstructive sleep apnea predisposes to coronary artery disease,[12] but the latter was unusually severe in our sample (49 out of 53 coronary artery disease patients had previously been revascularized through surgery or stent implantation).

Another frequently reported association, between systemic arterial hypertension and obstructive sleep apnea, was confirmed in the present study.[13] Moreover, the estimated risk of this association was very high (2.195). Like in the Australian Longitudinal Study on Male Health,[15] obstructive sleep apnea was significantly associated with hypercholesterolemia in the present study, with an estimated risk of 2.044. However, despite the significance of the associations between obstructive sleep apnea and the parameters of systemic arterial hypertension, diabetes, dyslipidemia, age and body mass index (and its categories), only the last two variables remained significant after multivariate logistic analysis.

CONCLUSION

Occurrences of obstructive sleep apnea were associated with hypertension, diabetes, dyslipidemia, age and body mass index in univariate analyses, but only with age and body mass index (and its categories) in multivariate logistic analysis.

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Address for correspondence:
Ricardo Silva
Faculdade de Medicina do Ceará (UFC)
R. Prof. Costa Mendes, 1.608 — 4º andar
Fortaleza (CE) — Brasil
CEP 60714-030
Tel. (+55 85) 33366-8052
E-mail: ricardopereirasilva.ufc@gmail.com

Authors' contributions: Silva RP: conceptualization (lead), data curation (equal), formal analysis (lead), funding acquisition (supporting), investigation (lead), methodology (equal), project administration (lead), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (lead) and writing-review and editing (supporting); Brito TP: formal analysis (equal), investigation (equal), methodology (equal) and project administration (supporting); Wanderley Neto AC: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), software (equal), supervision (supporting), validation (supporting), visualization (equal), writing-original draft (supporting) and writing-review and editing (supporting); Frota RB: conceptualization (equal), data curation (equal), formal analysis (lead), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), software (equal), supervision (supporting), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); and Melo JC: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal) project administration (equal), software (equal), supervision (supporting), validation (supporting), visualization (equal), writing-original draft (equal) and writing-review and editing (equal)

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Effects of isometric handgrip training on blood pressure among hypertensive patients seen within public primary healthcare: a randomized controlled trial

Aline Cabral Palmeira[I], Breno Quintella Farah[II], Gustavo Oliveira da Silva[III], Sérgio Rodrigues Moreira[IV], Mauro Virgílio Gomes de Barros[V], Marilia de Almeida Correia[VI], Gabriel Grizzo Cucato[VII], Raphael Mendes Ritti-Dias[VIII]

Primary healthcare units within the Family Health Program, Petrolina (PE), Brazil

[I]MSc. Professor, Physiotherapy and Nursing Departments, Faculdade São Francisco de Juazeiro (FASJ), Juazeiro (BA), Brazil.
https://orcid.org/0000-0002-6515-0523

[II]PhD. Professor, Physical Education Department, Universidade Federal Rural de Pernambuco, Recife (PE), Brazil; Associate Researcher, Postgraduate Program on Physical Education, Universidade Federal do Pernambuco (UFPE), Recife (PE), Brazil.
https://orcid.org/0000-0003-2286-5892

[III]MSc. Doctoral Student, Postgraduate Program on Rehabilitation Sciences, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-6341-345X

[IV]PhD. Professor, Postgraduate Program on Physical Education, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil.
https://orcid.org/0000-0002-3068-5093

[V]PhD. Professor, Postgraduate Program on Physical Education, Universidade de Pernambuco (UPE), Recife (PE), Brazil.
https://orcid.org/0000-0003-3165-0965

[VI]PhD. Professor, Postgraduate Program on Medicine, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-8983-3433

[VII]PhD. Professor, Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle upon Tyne, United Kingdom.
https://orcid.org/0000-0002-2060-8852

[VIII]PhD. Professor, Postgraduate Program on Rehabilitation Sciences, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-7883-6746

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ABSTRACT

BACKGROUND: Meta-analyses have demonstrated that isometric handgrip training (IHT) decreases blood pressure in hypertensive individuals. Nonetheless, most studies were conducted in laboratory settings and its effects in real-world settings remain unclear.

OBJECTIVE: To analyze the effects of IHT on office and ambulatory blood pressure in hypertensive patients attended within primary healthcare.

DESIGN AND SETTING: Randomized controlled trial conducted in primary healthcare units within the Family Health Program, Petrolina, Pernambuco, Brazil.

METHODS: 63 hypertensive patients (30-79 years old; 70% female) were randomly allocated into IHT or control groups. IHT was performed three times per week (4 x 2 minutes at 30% of maximal voluntary contraction, one-minute rest between bouts, alternating the hands). Before and after the 12-week training period, office and ambulatory blood pressure and heart rate variability were obtained. The significance level was set at $P < 0.05$ (two-tailed testing) for all analyses.

RESULTS: IHT significantly decreased office systolic blood pressure (IHT: 129 ± 4 versus 121 ± 3 mmHg, $P < 0.05$; control: 126 ± 4 versus 126 ± 3 mmHg, $P > 0.05$), whereas there was no effect on diastolic blood pressure (IHT: 83 ± 3 versus 79 ± 2 mmHg, $P > 0.05$; control: 81 ± 3 versus 77 ± 3 mmHg, $P > 0.05$). Heart rate variability and ambulatory blood pressure were not altered by the interventions ($P > 0.05$ for all).

CONCLUSION: IHT reduced office systolic blood pressure in hypertensive patients attended within primary care. However, there were effects regarding diastolic blood pressure, ambulatory blood pressure or heart rate variability.

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INTRODUCTION

Hypertension impacts over one billion people worldwide and is the main risk factor for heart and cerebrovascular diseases, accounting for 13% of global deaths.[1-3] The therapeutic approach for hypertensive patients includes drug therapy and lifestyle changes in association with drug therapy, with the aim of reducing blood pressure (BP) to the target normal range (< 130/80 mmHg).[2]

Previous meta-analyses have shown that isometric handgrip training (IHT) decreases office BP in hypertensive patients by more than 5 mmHg after a few weeks.[4-9] The American College of Cardiology and the American Heart Association have recently recommended IHT as a potential alternative strategy for lowering BP, but with a low level of evidence.[10]

From a clinical point of view, reductions in BP are relevant when this impacts on BP levels during a major part of the time. Interestingly, the effects of IHT on ambulatory BP, which is more related to cardiovascular events than office BP, have not been demonstrated. In fact, in three previous studies, despite significant reductions in office BP, no effects on ambulatory BP were shown among hypertensive individuals after IHT, thus suggesting that there was a need for further studies.[11-13]

The benefits of IHT comprise its ease of application and the short time needed for doing the exercise. Therefore, it is ideal for application within primary care, in non-laboratory settings. However, all clinical trials studies analyzing the effects of IHT on BP were conducted either in

laboratory[14] or in home settings.[11,15] The potential effectiveness of this type of training at primary healthcare units is therefore unknown. Primary healthcare is the first point of contact that people have with the healthcare system when they have a health problem. The healthcare services provided within primary care include treatment of health conditions and support for managing long-term healthcare, including chronic conditions such as hypertension, at lower cost than in hospital settings.

OBJECTIVE

In this study, we analyzed the effects of IHT on office and ambulatory BP in hypertensive patients attended at a primary healthcare unit. Our hypothesis was that IHT would reduce BP similarly in non-laboratory settings.

METHODS

Experimental approach to the problem

A randomized controlled trial was used to investigate the effects of IHT on office and ambulatory BP among hypertensive patients attended at a primary healthcare unit. Medicated hypertensive patients were randomly assigned to either the IHT group or the control group. Ambulatory BP, office BP and heart rate variability parameters were measured before and after the 12-week intervention period by researchers blinded to the group allocations.

Trial design

This randomized controlled trial followed the Consolidated Standards of Reporting Trials (CONSORT) and was registered in the www.clinicaltrials.gov database under the registration number NCT03216317 and formed part of the ISOPRESS network.[16,17] The study methods were approved by the Institutional Review Board of Universidade Federal do Vale do São Francisco (protocol number: 61442216.5.0000.5196; approval date: May 16, 2017) in conformity with the national research ethics system guidelines and with the Helsinki Declaration of 1975 (revised in 1983). Before participation, subjects provided written informed consent.[18]

Subjects

We invited medicated hypertensive patients at primary care units within the Family Health Program in the city of Petrolina, state of Pernambuco, northeastern Brazil, to participate in this study. These primary care units form part of the Brazilian public healthcare system, which serves the population in places near patients' homes. The eligibility criteria for the study were that the subjects needed to: i) be using anti-hypertensive medications; ii) be over the age of 18 years old; iii) have no presence of diabetes or cardiovascular disease (other than hypertension); iv) have no limitations on undergoing isometric handgrip training; and v) not be engaged in any systematic exercise programs assessed through the International Physical Activity Questionnaire. The exclusion criteria were any of the following situations: (a) changes to the type or dose of blood pressure control medicine; (b) engaging in another exercise program; or (c) taking part in less than 80% of the isometric handgrip training sessions.

Randomization and allocation

The participants were block-randomized using a random number table (using the website https://www.randomizer.org), with stratification according to sex and baseline office systolic BP (done by a researcher who did not participate in the subject recruitment or data collection), into two groups: IHT group and control group. The allocation information was concealed from the researchers performing the measurements.

Interventions

The patients allocated to the IHT group trained three times per week, for a total of 12 weeks, in healthcare units that form part of the Family Health Program. Each session was composed of four sets of two-minute isometric contractions (alternating the hands), done through a handgrip dynamometer (Zona Health, Boise, Idaho, United States) at 30% of each patient's maximal voluntary contraction, which was established at the start of each session via the handgrip dynamometer. The Zona Plus dynamometer was developed specifically for isometric handgrip training. The screen in the device provides instantaneous feedback of the amount of force and indicates whether the amount of force applied is sufficient for the intensity selected. In addition, the device has a timer that provides information regarding the duration of the exercise and the rest intervals. Patients allocated to the control group were encouraged to increase their level of physical activity, but with no particular guidance on physical activity.

Measurements

Cardiovascular variables were measured at the baseline and at a follow-up (12 weeks later). The participants received the following instructions for what they should do before the cardiovascular evaluations: (a) have a light meal prior to arrival at the laboratory; (b) refrain from moderate-to-vigorous physical activity for at least 24 h before to the visit; and (c) refrain from smoking or alcohol or caffeine consumption for at least 12 h. Researchers who were blinded to the group allocations collected the data. The post-intervention evaluation was performed at least 72 hours after the last exercise session.

Office BP: The office BP was measured through the Omron HEM 742 device (Omron Healthcare, Kyoto, Japan). After 10 minutes of supine rest, at least three consecutive measurements with

one-minute intervals between them were assessed. The measurements were made on the right arm, with an appropriate cuff size for the arm circumference.[19] The intraclass correlation coefficient for systolic BP was 0.85, and for diastolic BP it was 0.92.[20]

Ambulatory BP: The ambulatory BP was obtained through an oscillometric device (Dyna-MAPA, Cardios, Brazil) that had previously been set up for performing BP assessments every 15 minutes during the daytime period and every 30 minutes during the nighttime, based on previously reported procedures.[21] Also, patients were counseled to report crucial everyday activities, such as meals, movement from one place to another and medications.

Heart rate variability: The heart rate variability was evaluated from the RR intervals, measured through a heart rate monitor (Polar V800, Polar Electro, Kempele, Finland) in the supine position for 10 minutes. At least five minutes of stationary R-R interval data were analyzed. All analyses were carried out by a single experienced evaluator who was blind to the group allocations. The intraclass correlation coefficient for this evaluator spanned from 0.990 to 0.993.[22] All heart rate variability analysis procedures followed previously described guidelines.[23] The Kubios HRV software (Biosignal Analysis and Medical Imaging Group, Joensuu, Finland) was used for the analysis. The time (standard deviation of all RR intervals [SDNN], root mean square of the squared differences between adjacent normal RR intervals [RMSSD] and percentage of adjacent intervals over 50 ms [PNN50]) and frequency (low frequency component, high frequency component and sympathovagal balance) domain variables were obtained.

Statistical analyses

To determine the sample size, we used previously demonstrated data on the mean reduction and standard deviation (SD) of office systolic BP following IHT.[24] Given an expected reduction of 6.0 ± 4.6 mmHg and α of 0.05 and β of 0.20, an estimated sample size of 28 participants (14 per group) was deemed sufficient.

Normality and homogeneity of variances were verified by means of the Shapiro-Wilk test and the Levene test, respectively. Clinical characteristics were compared between the groups using the t test, chi-square test and Fisher test. To analyze the effects of isometric handgrip training on BP, generalized estimating equations were used, along with post-hoc pairwise comparison using the Bonferroni correction for multiple comparisons. Effect size (ES) was used to stipulate the magnitude of differences in the same group. Intention-to-treat analysis was used to estimate overall effects, among all the randomized patients while ignoring noncompliance and dropouts, and the data were imputed with linear regression weighted according to group. The significance level was set at $P < 0.05$ (two-tailed testing) for all analyses. The data were presented as means and standard errors or as 95% confidence intervals. Categorical variables were summarized as relative frequencies.

RESULTS

The recruitment and intervention periods encompassed July 2017 July to July 2018. The study flowchart is shown in **Figure 1**. The groups were similar at the baseline (**Table 1**).

The dropout rates were 51.6% in the isometric handgrip training group and 53.1% in the control group. Through comparing the characteristics of the patients who were included and the dropouts in the isometric handgrip training group (**Table 2**), only a difference in calcium channel blocker use could be seen ($P < 0.05$). One 61-year-old woman in the isometric handgrip training dropped out due to joint pain. Adherence in the IHT group was 84.6% (95% confidence interval, CI: 82.2% to 87.1%).

Figure 2 and **Table 3** present the effects of IHT on office BP and heart rate variability parameters, respectively. A group-time (GxT) interaction was observed for office systolic BP (power = 0.83), which indicated that only the group that performed isometric handgrip training presented reductions in office systolic BP (IHT: 129 ± 4 versus 121 ± 3 mmHg; and control: 126 ± 4 versus 126 ± 3 mmHg; $P < 0.05$). No GxT interaction was observed in relation to office diastolic BP (IHT: 83 ± 3 versus 79 ± 2 mmHg; and control: 81 ± 3 versus 77 ± 3 mmHg; $P > 0.05$) (power = 0.52) and heart rate variability parameters ($P > 0.05$ for all).

Figure 3 presents the effects of IHT on ambulatory BP. No group-time interaction ($P > 0.05$ for all) was observed for BP, overall over a 24-hour period (systolic BP: IHT 119.2 ± 3.3 versus 119.2 ± 3.0 mmHg, ES = 0.01; control 116.9 ± 2.2 versus 118.6 ± 2.4 mmHg, ES = 0.18, power = 0.54; diastolic BP: IHT 80.5 ± 3.0 versus 78.1 ± 2.4 mmHg, ES = 0.27; control 77.5 ± 2.3 versus 77.7 ± 2.2 mmHg, ES = 0.02, power = 0.69); or while the subjects were awake (systolic BP: IHT 120.7 ± 3.3 versus 120.3 ± 2.9 mmHg, ES = 0.03; control 118.4 ± 2.2 versus. 120.1 ± 2.3 mmHg, ES = 0.18; diastolic BP: IHT 82.0 ± 2.9 versus 79.3 ± 2.5 mmHg, ES = 0.27; control 79.0 ± 2.4 versus 79.5 ± 2.3 mmHg, ES = 0.05) or asleep (systolic BP: IHT 113.1 ± 3.7 versus 113.8 ± 2.8 mmHg, ES = 0.06; control 110.0 ± 2.1 versus 111.7 ± 2.7 mmHg, ES=0.17; diastolic BP: IHT 73.3 ± 3.6 versus 72.5 ± 2.4 mmHg, ES = 0.07; control 69.0 ± 2.1 versus 70.8 ± 2.3 mmHg, ES = 0.20) (**Figure 3**).

The intent-to-treat analysis did not reveal any significant effect from the IHT program on any of the outcome variables measured (data not shown).

DISCUSSION

The main results of this study in a primary healthcare unit were the following: (i) IHT reduced office systolic BP among medicated hypertensive individuals; (ii) no effects were observed in relation to office diastolic BP, heart rate variability or ambulatory BP in medicated hypertensive patients.

The main novelty of this study was that the IHT program was conducted in a primary healthcare unit, which is a real-world setting

for supervised training. We demonstrated that there was a reduction in office systolic BP in medicated hypertensive individuals, which corroborates previous studies conducted in laboratory or home settings.[11,14,15] The magnitude of the reduction in office systolic BP was approximately 8 mmHg, which was similar to findings from previous clinical trial studies conducted in laboratory or home settings.[8,25] Moreover, the analysis on individual responses indicated that 63% of the patients showed reductions in systolic BP of more than 5 mmHg, which may represent a reduction of at least 7% in the risks of stroke, coronary disease and death.[26] Thus, IHT may be incorporated as alternative strategy for controlling office systolic BP in medicated hypertensive individuals who are treated in a primary care unit.

On the other hand, 12 weeks of IHT performed in a primary healthcare unit did not change office diastolic BP in these medicated hypertensive individuals. Although this result contrasts with the findings from some studies, there are other studies that also reported that there was no reduction in diastolic BP after IHT, among hypertensive patients.[4-7] After six weeks of IHT in a laboratory setting, Peters et al. did not observe any reduction in office diastolic BP, although they observed a reduction in office systolic BP.[27] Similarly, Taylor et al. demonstrated that there was a decrease in office systolic BP, but not in diastolic BP, after 10 weeks in a laboratory setting.[28] Lastly, after 12 weeks of IHT in a laboratory or home setting, Gordon et al. did not find any reduction in diastolic BP.[15]

It is not clear why office systolic BP, but not diastolic BP, was found to have decreased after the 12-week training period. One possible explanation is that the patients included in the present study presented well-controlled values for diastolic BP in the pre-intervention period (all < 90 mmHg) and, as such, may have had a lower capacity for BP reduction through IHT. In fact, a previous study reported that individuals with higher pre-training resting BP had a greater post-training hypotensive response.[29]

In the present study, 12 weeks of IHT in hypertensive individuals did not have the capacity to promote improvement in cardiac autonomic modulation to the heart. Farah et al. did not find any improvements after 12 weeks of supervised or home-based isometric handgrip training in hypertensive individuals who were using medications. Similarly, Stiller-Moldovan et al. did not find any changes in cardiac autonomic modulation after 8 weeks of isometric handgrip training in hypertensive patients.[11,13] In contrast, Taylor et al. found improvements in high-frequency spectral power among uncontrolled hypertensive individuals after supervised isometric handgrip training. Interestingly, in Taylor's study, the baseline BP values were higher than those of the present study (156 versus 129 mmHg). This indicates that isometric handgrip training might lead to improvements in autonomic cardiac modulation in individuals with uncontrolled BP.[28] Therefore, it

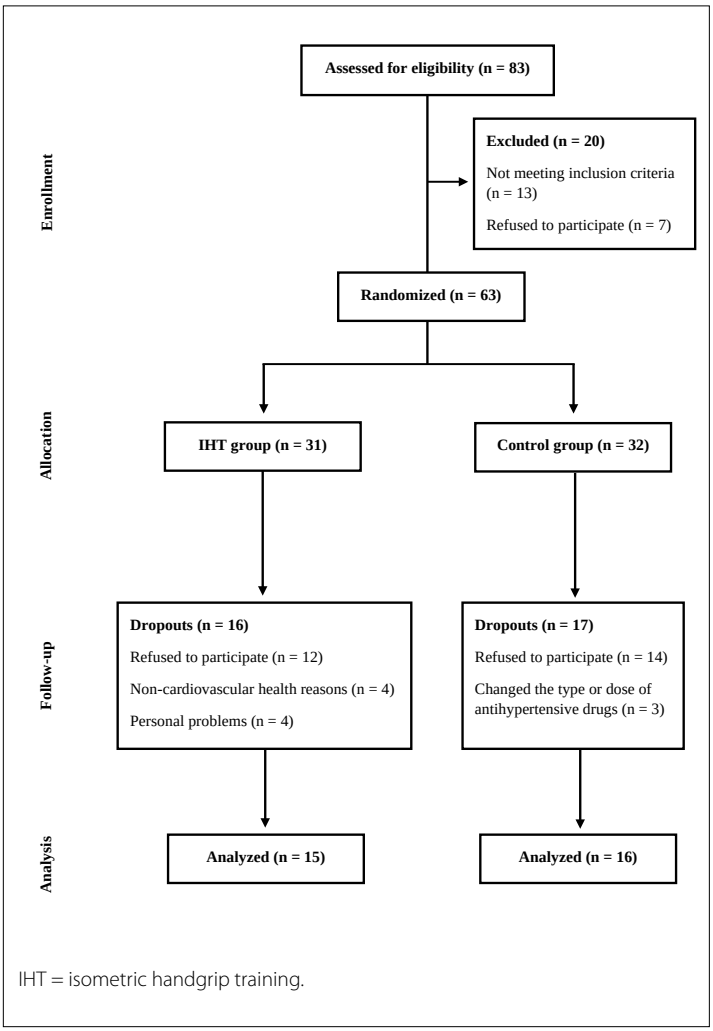

Figure 1. Flowchart of study.

is possible that other mechanisms are involved in the reduction of BP after IHT.[30]

Recently, our group demonstrated[31] that a reduction in arterial stiffness occurs in hypertensive individuals who are responsive to isometric handgrip training. In addition, Peters et al. showed that there was enhancement of oxidative stress after six weeks of training and McGowan et al. observed improvement in endothelial function after eight weeks of IHT.[27,31,32]

Ambulatory BP has been considered more important than office BP, in terms of clinical perspective, since it presents better prediction of target organ damage and cardiovascular mortality.[33] Our results indicated that there was no reduction in any of the ambulatory BP measurements after 12 weeks of IHT performed in a primary healthcare unit and are in agreement with previous studies.[11-13] A study conducted by Stiller-Moldovan et al. did not observe any reduction in ambulatory BP after eight weeks of isometric exercise training performed at 30% of maximal voluntary

Table 1. General characteristics of experimental groups at baseline

Variables	IHT	Control group	P
Age (years)	54.3 ± 3.7	52.7 ± 2.6	0.743
Weight (kg)	74.1 ± 3.2	80.1 ± 4.9	0.319
Body mass index (kg/m²)	29.4 ± 1.1	31.6 ± 1.5	0.247
Office systolic BP (mmHg)	129 ± 4	126 ± 4	0.241
Office diastolic BP (mmHg)	83 ± 3	82 ± 3	0.632
Walking (minutes/week)	122 ± 25	73 ± 17	0.123
Moderate physical activity (minutes/week)	135 ± 35	64 ± 26	0.116
Sex (% men)	27	31	0.909
Current smoker (%)	18.8	0	0.103
Calcium channel blocker (%)	7	6	0.898
Diuretic (%)	73	56	0.290
ß-blocker (%)	20	11	0.478
ACE inhibitor (%)	20	17	0.805
Angiotensin receptor blockers (%)	67	78	0.475

Values that are not percentages are presented as mean ± standard error. IHT = isometric handgrip training; BP = blood pressure.

Table 2. Comparison of the characteristics of the patients who were included and who were dropouts in this study

Variables	Included n = 31	Dropout n = 33	P
Intervention group (%)	45.7	53.3	0.540
Age (years)	53.6 ± 2.2	55.6 ± 1.8	0.417
Weight (kg)	75.6 ± 2.6	75.1 ± 2.8	0.890
Body mass index (kg/m²)	30.1 ± 0.9	29.1 ± 0.9	0.431
Office systolic BP (mmHg)	126 ± 3	128 ± 2	0.518
Office diastolic BP (mmHg)	81 ± 2	79 ± 2	0.401
Walking (minutes/week)	97 ± 15	157 ± 66	0.366
Moderate physical activity (minutes/week)	99 ± 22	99 ± 22	0.165
Sex (% men)	27	50	0.183
Calcium channel blocker (%)	3	33	0.002
Diuretic (%)	64	40	0.079
ß-blocker (%)	15	27	0.259
ACE inhibitor (%)	18	20	0.854
Angiotensin receptor blockers (%)	73	60	0.285

Values that are not percentages are presented as mean ± standard error. IHT = isometric handgrip training; BP = blood pressure.

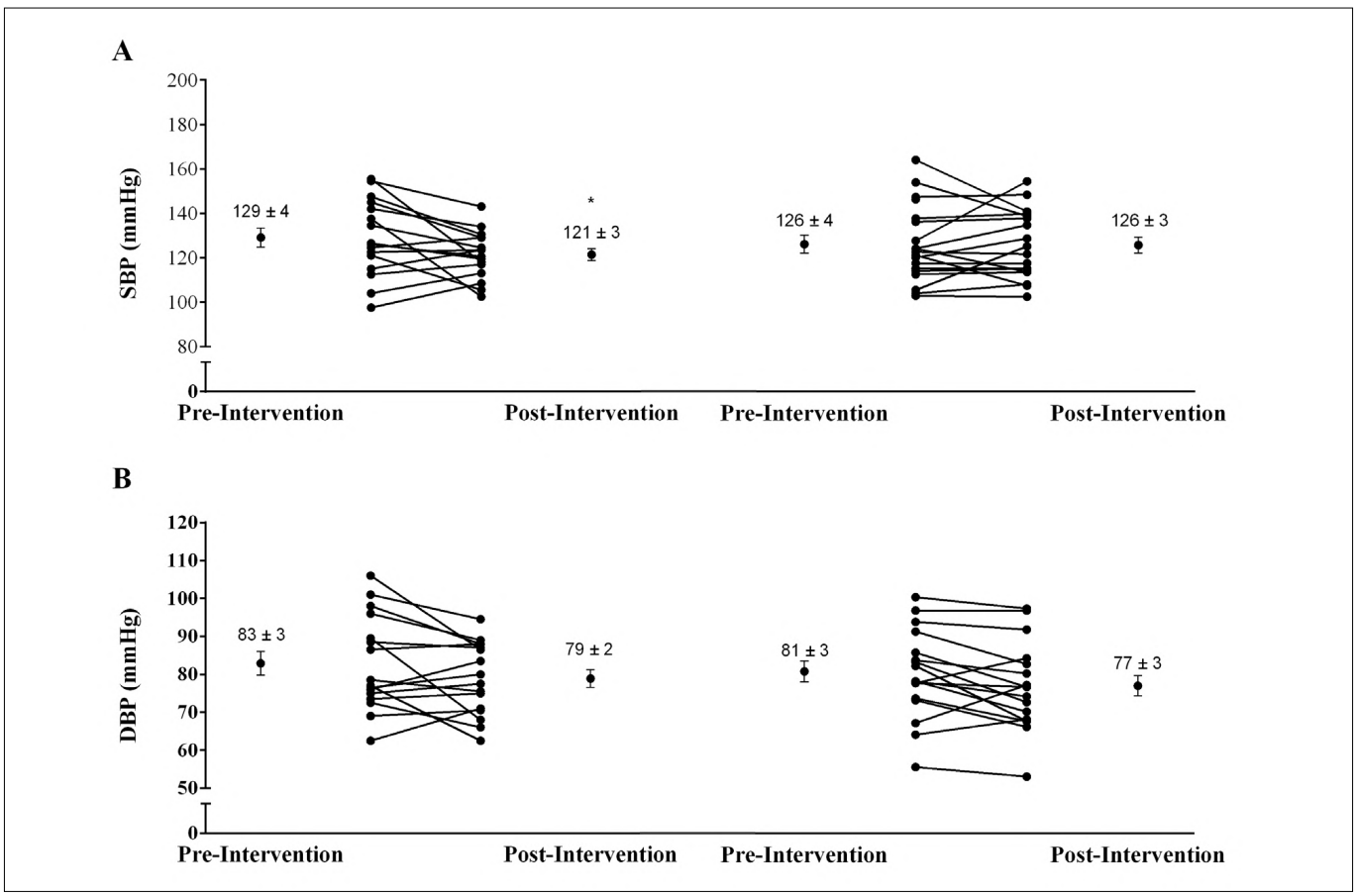

Figure 2. Effects of isometric handgrip training on office blood pressure. A – Systolic blood pressure (SBP) (P-values: group = 0.900; time = 0.088; GxT = 0.049); B – Diastolic blood pressure (DBP) (P-values: group = 0.531; time = 0.003; GxT = 0.933). *Significant difference from Pre (P < 0.05). IHT, isometric handgrip training; CG, control group; GxT, group-time interaction.

Table 3. Effects of isometric handgrip training on heart rate variability parameters in hypertensive individuals

Variables	IHT		Control		P
	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention	
RR interval (ms)	819 ± 32	854 ± 23	831 ± 22	829 ± 25	0.166
SDNN (ms)	31.6 ± 4.5	32.4 ± 5.6	34.3 ± 2.9	34.7 ± 3.3	0.928
RMSSD (ms)	29.1 ± 7.5	32.3 ± 8.8	25.1 ± 2.9	27.0 ± 3.4	0.923
PNN50 (%)	9.2 ± 4.6	11.8 ± 4.7	7.4 ± 2.3	8.5 ± 2.7	0.837
LF (nu)	47.9 ± 4.7	50.0 ± 5.6	57.3 ± 5.1	56.5 ± 4.9	0.595
HF (nu)	51.5 ± 4.7	49.8 ± 5.6	42.5 ± 5.1	43.3 ± 4.9	0.664
LF/HF	1.17 ± 0.18	1.44 ± 0.311	2.07 ± 0.39	2.32 ± 0.76	0.785

Values are presented as mean ± standard error. IHT = isometric handgrip training; HF = High frequency; LF = Low frequency; SDNN = standard deviation of all RR intervals; RMSSD = root mean square of the squared differences between adjacent normal RR intervals; PNN50 = percentage of adjacent intervals over 50 ms; LF/HF = sympathovagal balance; nu = normalized units.

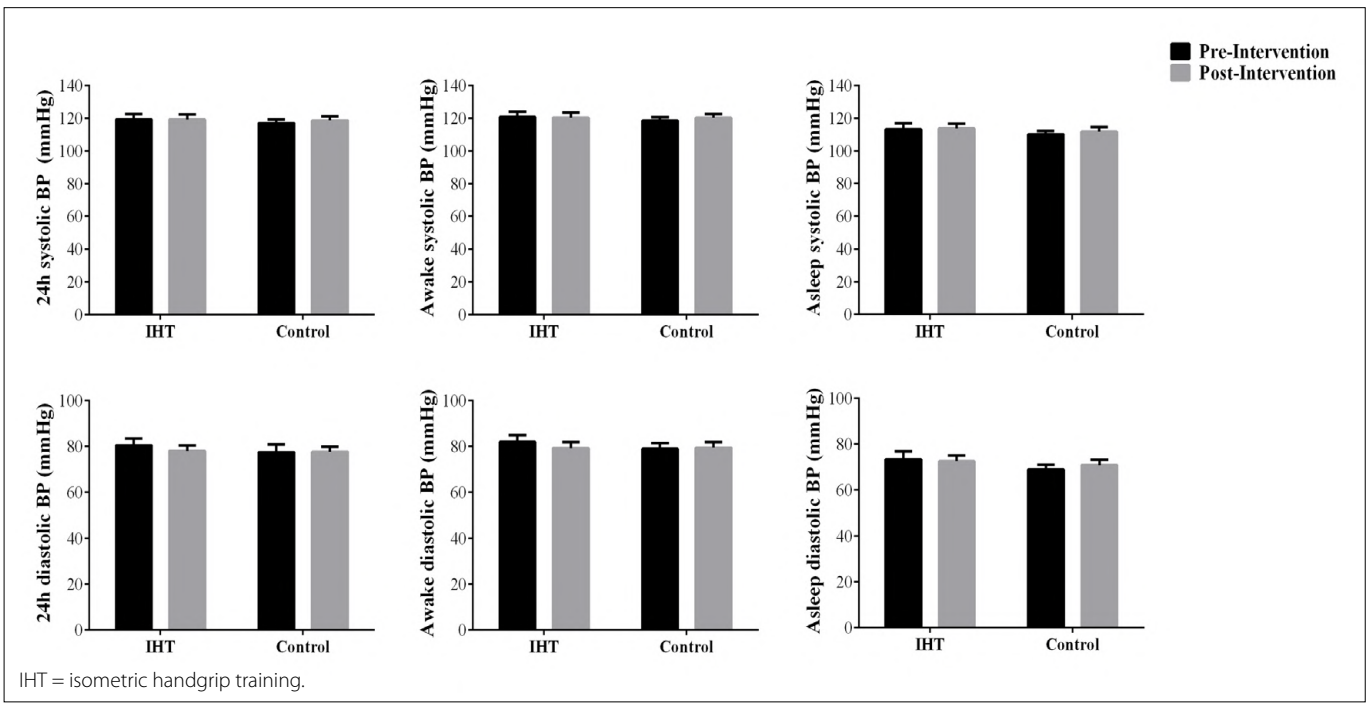

Figure 3. Effects of isometric handgrip training on ambulatory blood pressure.

contraction.[13] Moreover, Pagonas et al. also showed that there was no reduction in ambulatory BP after 12 weeks of handgrip exercise training performed five times per week at 30% of maximal voluntary contraction, in a hypertensive population.[12] Therefore, these results indicate that isometric handgrip training presents only a transient effect on BP that is only observed in office BP and is not prolonged during ambulatory activities.

The American Heart Association and American College of Cardiology have recommended isometric handgrip training as a potential alternative strategy for lowering BP in the hypertensive population.[10] The benefits of this type of training comprise its ease of application and the short time that needs to be dedicated to implementing the exercise, such that it is ideal for application in primary care and in non-laboratory settings. In fact, three sessions per week and 12 minutes per session (i.e. 36 minutes per week) is less time than the current recommendations[34,35] for physical exercise (150 minutes per week), which therefore enables avoidance of important barriers to physical activity practice among patients with cardiovascular diseases.[36,37]

In the present study, we demonstrated that isometric handgrip training reduces office systolic BP in medicated hypertensive patients who were attended in primary healthcare settings. However, we failed to show that this has any efficacy with regard to office diastolic BP, ambulatory BP or heart rate variability parameters. In addition, our dropout rate was higher than in previous studies conducted in laboratory or home settings, which suggests

that caution is required in implementing isometric handgrip training in primary care settings.

The present study presents limitations that should be considered. The sample size did not allow for stratified analysis according to the medication used. This might have enabled comprehension of the mechanism(s) of BP lowering after isometric handgrip training. Generalizations of these findings to other populations (either those with advanced hypertension or other populations) must be made with care. The dropout rate in this study was higher than that we would have liked. It is not possible to assume that similar results would be observed among patients who dropped out of the program, and these data should be considered with caution. In addition, we did not do intention-to-treat analyses. Although without any statistically significant difference, the control group was heavier than the IHT group, and this needs to be taken into account. Lack of control regarding physical activity in both groups was also a limitation, although none of the patients engaged in any exercise programs. Lastly, other mechanisms for BP lowering after isometric handgrip training, such as baroreflex sensitivity, vascular measures or use of biomarkers, were not assessed.[27,32,38]

CONCLUSION

Isometric handgrip training performed in a primary care setting reduced office systolic BP in hypertensive patients, whereas no effects were observed in relation to office diastolic BP, ambulatory BP or heart rate variability.

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Authors' contributions: Palmeira AC: Conception and design, data collection and writing; Farah BQ: conception and design, statistical analysis and writing; Silva GO: statistical analysis and writing; Moreira SR: conception and design, data collection and writing; Barros MVG: conception and design, obtaining funding and critical review; Correia MA: conception and design, data collection and critical review; Cucato GG: conception and design and critical review; and Ritti-Dias RM: conception and design, obtaining funding and critical review. All authors approved the final version to be published and have agreed to be accountable for all aspects of the work and for ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Address for correspondence:
Raphael Mendes Ritti-Dias
Programa de Pós-graduação em Ciência da Reabilitação, Universidade Nove de Julho
R. Vergueiro, 235
São Paulo (SP) — Brasil
CEP 01504-000
Tel. (+55 19) 99940-6878
E-mail: raphaelritti@gmail.com

Dexamethasone for treating SARS-CoV-2 infection: a systematic review and meta-analysis

Lirane Elize Defante Ferreto[I], Durcelina Schiavoni Bortoloti[II], Paulo Cezar Nunes Fortes[III], Franciele Follador[IV], Gisele Arruda[V], João Paulo Ximenez[VI], Guilherme Welter Wendt[VII]

Centro de Ciências da Saúde (CCS), Universidade Estadual do Oeste do Paraná (UNIOESTE), Francisco Beltrão (PR), Brazil; and Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil

[I]PhD. Pharmacist and Associate Professor, Centro de Ciências da Saúde (CCS), Universidade Estadual do Oeste do Paraná (UNIOESTE), Francisco Beltrão (PR), Brazil.
https://orcid.org/0000-0002-0757-3659

[II]PhD. Physical Education Professional and Adjunct Professor of Research Methods, Department of Biological Sciences, Medical and Health, Universidade Paranaense (UNIPAR), Umuarama (PR), Brazil.
https://orcid.org/0000-0001-6976-3661

[III]MD, PhD. Intensive Care Unit Physician and Adjunct Professor, Centro de Ciências da Saúde (CCS), Universidade Estadual do Oeste do Paraná (UNIOESTE), Francisco Beltrão (PR), Brazil.
https://orcid.org/0000-0001-8331-2410

[IV]PhD. Chemist and Associate Professor, Centro de Ciências da Saúde (CCS), Universidade Estadual do Oeste do Paraná (UNIOESTE), Francisco Beltrão (PR), Brazil.
https://orcid.org/0000-0002-9210-1540

[V]PhD. Biologist and Adjunct Professor, Centro de Ciências da Saúde (CCS), Universidade Estadual do Oeste do Paraná (UNIOESTE), Francisco Beltrão (PR), Brazil.
https://orcid.org/0000-0002-5690-2527

[VI]PhD. Pharmacist and Postdoctoral Researcher, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil.
https://orcid.org/0000-0002-6414-5220

[VII]PhD. Psychologist and Adjunct Professor of Quantitative Research Methods, Centro de Ciências da Saúde (CCS), Universidade Estadual do Oeste do Paraná (UNIOESTE), Francisco Beltrão (PR), Brazil.
https://orcid.org/0000-0002-9014-6120

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ABSTRACT

BACKGROUND: Considering the disruptions imposed by lockdowns and social distancing recommendations, coupled with overwhelmed healthcare systems, researchers worldwide have been exploring drug repositioning strategies for treating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

OBJECTIVE: To compile results from randomized clinical trials on the effect of dexamethasone, compared with standard treatment for management of SARS-CoV-2.

DESIGN AND SETTING: We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in a Brazilian public university.

METHODS: We sought to compile data from 6724 hospitalized patients with confirmed or suspected SARS-CoV-2 infection.

RESULTS: Treatment with dexamethasone significantly reduced mortality within 28 days (risk ratio, RR: 0.89; 95% confidence interval, CI: 0.82-0.97). Dexamethasone use was linked with being discharged alive within 28 days (odds ratio, OR: 1.20; 95% CI: 1.07-1.33).

CONCLUSIONS: This study suggests that dexamethasone may significantly improve the outcome among hospitalized patients with SARS-CoV-2 infection and associated severe respiratory complications. Further studies need to consider both dose-dependent administration and outcomes in early and later stages of the disease.

PROSPERO PLATFORM: CRD42021229825.

INTRODUCTION

By June 23, 2021, the coronavirus pandemic had reached 192 countries and regions with > 179 million and > 3.8 million confirmed cases and deaths, respectively.[1] The Coronaviridae Study Group classified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within the family Coronaviridae, suborder Cornidovirineae, order Nidovirales.[2]

Given the disruption caused by lockdowns and social distancing, as well as overburdened healthcare systems, researchers are investigating different strategies for treating SARS-CoV-2 infections and are exploring drug repurposing.[3] The World Health Organization Solidarity Trial report showed that treatments with drugs such as remdesivir, hydroxychloroquine, lopinavir and interferon had either little or no impact on mortality, need for intubation or overall hospital stay.[4] On the other hand, corticosteroids (especially dexamethasone) might be beneficial for treating the SARS-CoV-2-induced cytokine storm.[5] Data from the Recovery Trial noted that dexamethasone significantly reduced SARS-CoV-2-related deaths (by around 30% among patients receiving mechanical ventilation and by around 20% among those receiving oxygen alone).[6] Therefore, several randomized controlled trials (RCTs) are underway to assess the effect of dexamethasone with regard to treatment of SARS-CoV-2 infection.

OBJECTIVE

We sought to synthesize the evidence from randomized controlled trials (RCTs) on the clinical relevance of dexamethasone, compared with standard treatment, among hospitalized SARS-CoV-2 patients.

METHODS

This study followed the guidelines for obtaining up-to-date and qualified biomedical literature.[7] The review was registered on the PROSPERO platform (CRD42021229825).

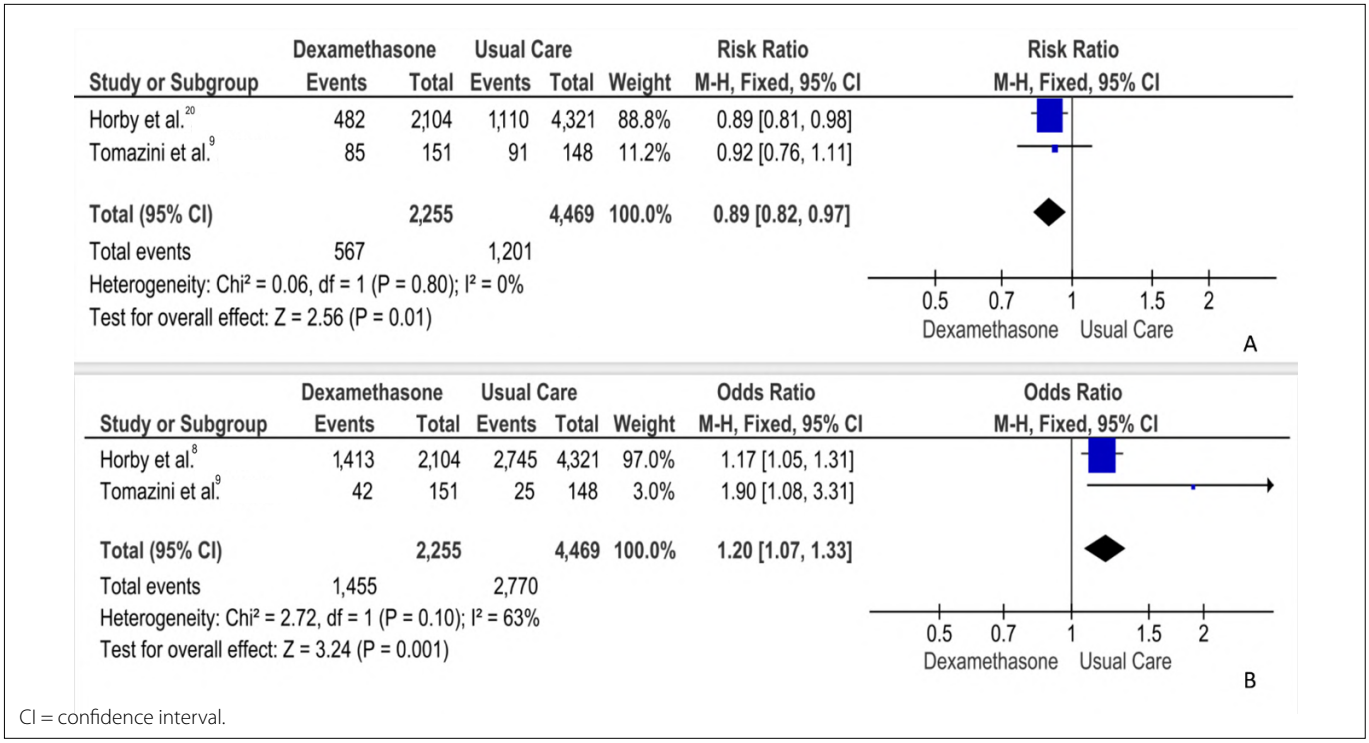
The inclusion criteria were that the studies needed to be RCTs that addressed hospitalized patients with confirmed or suspected SARS-CoV-2 infection, as reported in each study, either published or accepted for publication after the peer review. Other types of research designs, such as cross-sectional studies, as well as editorials, letters, reviews and study protocols, constituted exclusion criteria.

We independently searched the PubMed and Embase databases for RCTs. Publications were retrieved up to a cutoff date of February 14, 2021. The following MeSH terms were used: "coronavirus" OR "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2" OR "severe acute respiratory syndrome" OR "SARS" AND "dexamethasone" AND "randomized controlled trial" or "randomized clinical trial". Three experienced researchers (G.A., L.E.F. and J.P.X.) performed the searches and reviewed the abstracts. Each investigator independently selected studies for further inclusion, based on inclusion and exclusion criteria. The initial search returned 32 results from Embase and 193 from PubMed. After removing editorials, letters, reviews, protocols, duplicates and observational studies, two RCTs were found to fully satisfy our inclusion criteria (**Appendix 1**). These were found in Embase[8,9] and PubMed.[9] There were no disagreements between the review authors regarding the inclusion criteria. For each RCT, sample details, covariates analyzed, dosage and duration of dexamethasone treatment were extracted. The primary outcome measured was the risk ratio (RR) for death at 28 days and the secondary outcome was the odds ratio (OR) of being discharged alive within 28 days. In addition, these trials were assessed for potential risk of bias.[10]

RESULTS

Data were extracted by D.S. and G.W. and were analyzed using RevMan 5.4.[11] Through using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, these two authors concluded that both of the RCTs included had low risk of bias, with the exception of the item "blinding of participants and staff".[10] To test the effect of dexamethasone on mortality, we obtained the RR from these two RCTs, which included 6724 patients. The results indicated that treatment with dexamethasone significantly reduced mortality within 28 days (RR = 0.89; 95% CI: 0.82, 0.97; I^2 = 0%; **Figure 1A**). The effect of dexamethasone on the odds of being discharged alive within 28 days was significant (OR = 1.20; 95% CI: 1.07, 1.33; I^2 = 63%; **Figure 1B**).[8,9]

Horby et al.[8] published results from 6425 hospitalized patients (mean age = 66.1 ± 15.7 years; 36% female) who were admitted between March and June 2020 at 176 healthcare institutions in the United Kingdom with confirmed (~88%) or suspected SARS-CoV-2 infection (~10-12%). Most of the sample (56%) had preexisting diseases, among which at least one in five had diabetes, heart disease or chronic lung disease. Both the healthcare workers and the patients were aware of the treatment status. A 2:1 ratio with regard to receiving standard care (n = 4321) or standard care plus



CI = confidence interval.

Figure 1. Risk ratio for dexamethasone with regard to mortality (A) and odds ratio for being discharged alive (B), among individuals with SARS-CoV-2 infection.

dexamethasone was adopted (n = 2104). Dexamethasone (6 mg) was administered orally or intravenously once daily for up to ten days. Mortality at 28 days was significantly lower in the intervention group (22.9%) than in the usual care group (25.7%). Deaths were lower in the interventions among patients receiving invasive mechanical ventilation (29.3% versus 41.4%) and among those receiving oxygen only (23.3% versus 26.2%). The effect of dexamethasone on mortality was not statistically significant among patients who did not receive any respiratory support at randomization. Hospitalization was shorter in the intervention group (median = 12 days) than in the usual care group (median = 13 days). The intervention group had a risk ratio of 1.10 with regard to being discharged alive within 28 days, and the largest effect in this regard was reported among patients who were receiving invasive mechanical ventilation at the time of randomization.[8]

Tomazini et al.[9] reported results from 299 hospitalized patients with confirmed (> 95%) or suspected SARS-CoV-2 infection (mean age = 61 ± 14.0 years; 37% female). The most frequent underlying health condition was hypertension, in both groups (over 60%), followed by diabetes (over 37%). Recruitment take place between April and June 2020 at 41 intensive care units (ICUs) in Brazil. Both the healthcare workers and the patients were aware of the treatment status. A 1:1 ratio for receiving standard care (n = 148) or standard care plus dexamethasone was adopted. Dexamethasone was administered intravenously at a dosage of 20 mg daily for five days, and then 10 mg once daily for an additional five days or until discharge from the intensive care unit. In contrast to Horby et al.,[8] the primary outcome was ventilator-free days within the first 28 days. The covariates included demographic and physiological data, history of corticosteroid use and time elapsed since symptom onset, among other related data. A higher number of ventilator-free days in the intervention group (6.6 days), in comparison with the standard treatment (4.0 days) within the first 28 days of treatment, was reported as the primary outcome. Mortality at 28 days was lower in the dexamethasone group (56.3%), compared with standard treatment (61.5%), although the differences were not statistically significant. In terms of length of hospital stay, the intervention group had an odds ratio (OR) of 1.90 of being discharged alive within 28 days (27.8% [dexamethasone] versus 16.9% [standard care]).[9]

DISCUSSION

The results from this investigation showed that treatment with dexamethasone had a positive impact on mortality and length of hospitalization among SARS-CoV-2 hospitalized patients. However, the two RCTs assessed used different doses of the drug and both primary and secondary outcomes varied between the studies.[8,9] Consequently, these data must be interpreted as preliminary at this stage and further RCTs are needed in order to obtain an accurate perspective regarding the role and regimen of dexamethasone for treating patients with mild, moderate and severe SARS-CoV-2 infection.

Currently, there are 64 clinical studies registered at ClinicalTrials.gov, which are at different phases and are being conducted in many regions of the world. Hopefully, these results could help immensely in clarifying the protocols that should be adopted for use of dexamethasone for treating SARS-CoV-2 infection.[15]

Although the safety of this drug has been demonstrated in relation to other infectious diseases, such as viral pneumonia,[16,17] the risks from using corticosteroids among patients with mild to severe symptoms, including acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 infection,[18,19] remain unclear.

In severe SARS-CoV-2 infection, the immunopathological responses appear to partially determine the outcome, which would explain why Horby et al.[8] found specific effects in these cases. Early administration of glucocorticoids may impair antiviral activity. Another mechanism possibly related to shorter hospital stays and higher survival rates is the potential of dexamethasone for preventing pulmonary fibrosis in COVID-19 patients and in patients with ARDS that was not caused by SARS-CoV-2 (i.e. sepsis, trauma-induced shock and other viral infections).[13-14]

Importantly, the intervention group of Tomazini et al.[9] was receiving concomitant treatment with other drugs such as hydroxychloroquine (23.8%) and azithromycin (69.9%), while Horby et al.[8] adopted a 2:1 randomization methodology, thus raising some concerns regarding statistical power.[20] Future studies will need to address these limitations through examining dose-dependent administration of dexamethasone in early and later stages of COVID-19 disease, taking into account the confounding effects of other medications and comorbidities.

CONCLUSION

Through combining the evidence, healthcare professionals dealing with the current pandemic can be provided with relevant information, especially in countries where waves of SARS-CoV-2 infection are recurrent. This study suggests that use of dexamethasone could significantly improve the outcomes among critically ill patients with SARS-CoV-2 infection and associated severe respiratory complications.

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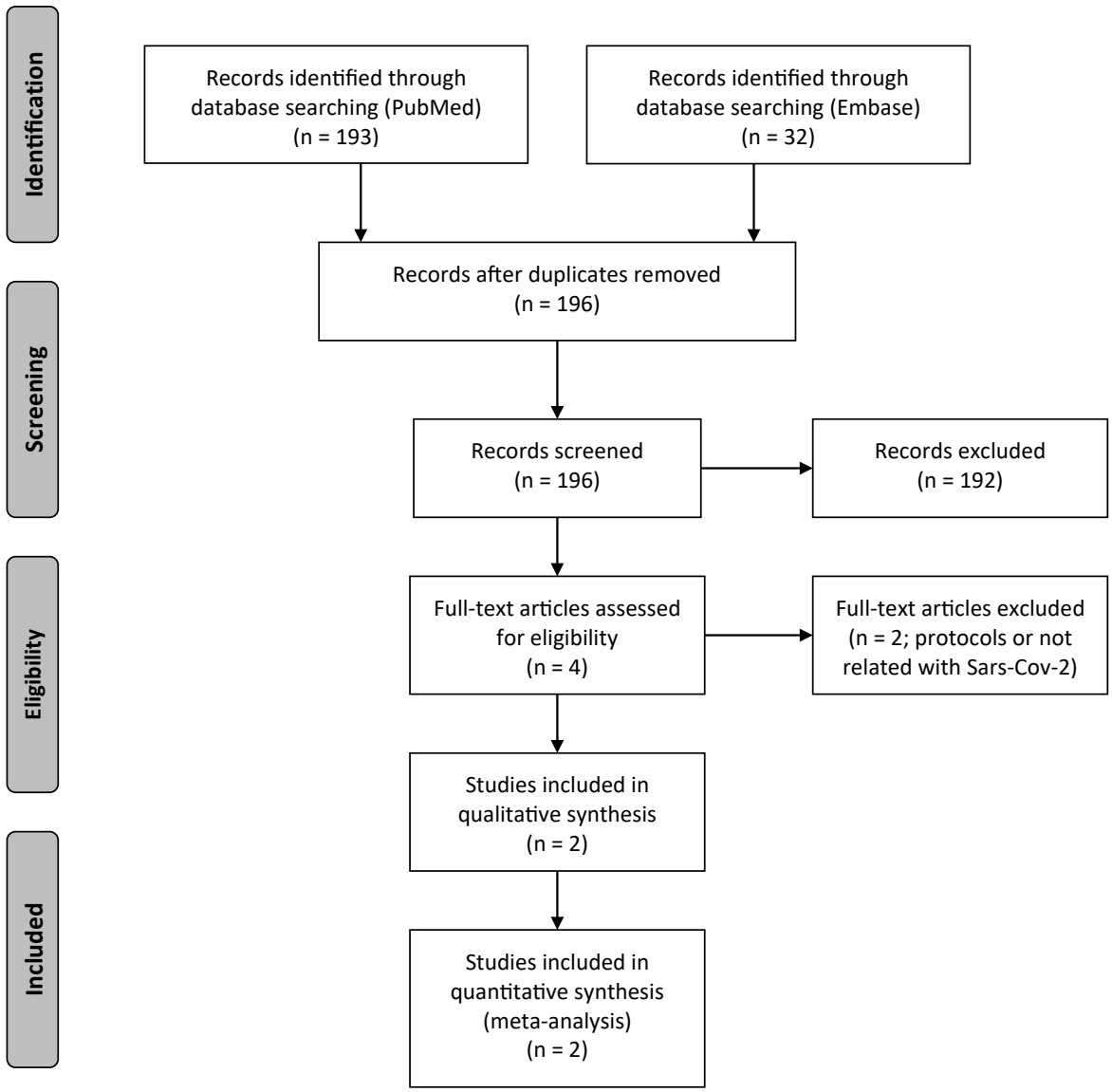
Address for correspondence:
Guilherme Welter Wendt
Centro de Ciências da Saúde (CCS), Universidade Estadual do Oeste do Paraná (UNIOESTE)
Rod. Vitório Traiano, Km 2, Bairro Água Branca
Francisco Beltrão (PR) — Brasil
CEP 85601-970
Tel. (+55 46) 3520-0715
E-mail: guilherme.wendt@unioeste.br

Appendix 1. Prisma Flow Diagram.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
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Mapping changes in women's visual functions during the menstrual cycle: narrative review

Bruna Gabrielli Damascena de Figueiredo[I], Maria Thalita Cardoso Rezende[II], Natanael Antonio dos Santos[III], Michael Jackson Oliveira de Andrade[IV]

Laboratory of Neuroscience, Chronobiology and Sleep Psychology, Universidade Estadual de Minas Gerais (UEMG), Divinópolis (MG), Brazil

[I]Psychology Student, Neurosciences and Behavior Laboratory, Department of Psychology Perception, Universidade Federal da Paraiba (UFPB), João Pessoa (PB), Brazil.
https://orcid.org/0000-0003-4580-9199

[II]Psychology Student, Neurosciences and Behavior Laboratory, Department of Psychology Perception, Universidade Federal da Paraiba (UFPB), João Pessoa (PB), Brazil.
https://orcid.org/0000-0002-9406-7833

[III]PhD. Full Professor, Neurosciences and Behavior Laboratory, Department of Psychology Perception, Universidade Federal da Paraiba (UFPB), João Pessoa (PB), Brazil.
https://orcid.org/0000-0001-7708-9929

[IV]PhD. Associate Professor, Laboratory of Neuroscience, Chronobiology and Sleep Psychology, Department of Psychology, Universidade do Estado de Minas Gerais (UEMG), Divinópolis (MG), Brazil.
https://orcid.org/0000-0002-2650-451X

KEY WORDS (MeSH terms):
Vision disorders.
Menstrual cycle.
Progesterone.
Narrative review [publication type].

AUTHORS' KEY WORDS:
Healthy women.
Estrogen.
Basic visual functions.
Visual contrast.

ABSTRACT

BACKGROUND: This article systematically updates the literature on changes in visual functions during the phases of the normal menstrual cycle in women.

OBJECTIVES: To update Guttridge's 1994 review of visual structures and functions associated with the menstrual cycle and broaden the search through psychophysical, neuroimaging and neurobehavioral measurements covering 1994-2020.

DESIGN AND SETTING: Narrative review conducted in a neurosciences and behavior laboratory in Brazil.

METHODS: The PubMed, Cochrane Clinical Answers and Google Scholar databases were searched. After screening and applying the eligibility criteria, 32 articles were examined. Through this analysis, the following information was extracted: (1) geographical distribution of the study; (2) sample size (according to age and phase of the menstrual cycle); (3) type of measurements according to psychophysical, neuroimaging and neurobehavioral instruments; (4) vision testing model; (5) visual subcategory evaluated; (6) categories of processed visual stimuli; and (7) main findings.

RESULTS: The menstrual phases give rise to significant changes in visual functions, including in relation to orientation and spatial attention, visual campimetry and visual sensitivity. These relate specifically to the follicular and luteal phases.

CONCLUSIONS: These findings theoretically expand the effects of menstrual cycles on visual functions found by Guttridge (1994). Despite some inconsistencies in the studies analyzed, it was found that visual processing during the follicular and luteal phases of the normal menstrual cycle of healthy women can explain physiological, cognitive, behavioral and social modulations.

INTRODUCTION

The menstrual cycle of women is tightly controlled by endocrine, autocrine and paracrine factors that regulate ovarian follicular development, ovulation, luteinization, luteolysis and endometrial remodeling.[1] The female human reproductive cycle is characterized by a cycle duration ranging from 26 to 35 days and can be described in terms of ovarian and uterine or menstrual cycles that are controlled by the hypothalamic-pituitary-ovary system.[2]

The ovarian cycle and its hormonal regulation consist of three phases: follicular (days 1 to 10), ovulatory (days 11-14) and luteal (days 15-28). Didactically, the menstrual cycle is considered to be the interval between the first day of menstruation and the beginning of the next. Thus, 24 hours before the end of the menstrual cycle, the levels of estrogen and progesterone decrease, which results in menstrual bleeding and starts a new cycle.[3] The follicular phase, also known as the early or menstrual follicular phase, is characterized by low levels of estrogen and progesterone. The ovulatory phase is characterized by high levels of estrogen and low levels of progesterone. In the luteal phase, also known as late luteal or premenstrual phase, high levels of estrogen and progesterone occur.

It is important to note that estrogen levels can alter the functioning of the central nervous system. Hormonal changes in the premenstrual phase can compromise the control of homeostasis and labyrinthine fluids, thus generating changes to balance and hearing. Moreover, the sensory thresholds of taste, hearing, pain, smell and vision vary in their functional performance.[4]

The variability of inhibitory neurotransmitters that bind to visual receptors during cyclical hormonal variations can alter visual sensitivity.[5] Guttridge reviewed the literature on the ophthalmological and functional changes that occur in the eye system during the normal human

menstrual cycle.[6] The main findings from that review pointed to variations in thickness, curvature, corneal sensitivity, intraocular pressure, maturation of the connective membrane and production and secretion of vicarious hemorrhagic tears in the eye. Among the functional measurements, changes to flashlight thresholds, detection and discrimination of visual stimuli, visual acuity and color vision can be highlighted.[7] Most of the studies discussed had an ophthalmological or clinical focus and did not explore the psychophysical, neurobehavioral and electrophysiological functioning of vision.[6,8]

Although several conclusions about ophthalmic function performance during the phases of the normal menstrual cycle were reached in previous studies, these data presented some conflicting features, such as with regard to increased visual sensitivity in the premenstrual period.[6] Thus, there is a need to update the data sources on visual function performance during the menstrual cycle.

OBJECTIVES

The phases of the menstrual cycle may be clinically significant in relation to the mechanisms of visual processing, as this may facilitate understanding of the mechanisms underlying visual functions. To this end, the aim of this study was to investigate the methodological practices involved in studies on the normal menstrual cycle, regarding processing of the visual system of healthy women and the underlying visual mechanisms.

METHODS

We carried out an up-to-date search for studies that describe the use of psychophysical, neuroimaging and neurobehavioral tools for analyzing the visual functions of women during the normal menstrual cycle. Our search covered the period from the Guttridge study conducted in 1994, up to 2020. The following databases were used: PubMed, Cochrane Clinical Answers and Google Scholar. The following terms were used: "*visual functions*" OR "*visual system*" OR "*visual perception*" OR "*vision*" AND "*menstrual cycle*" OR "*estrous cycle*" OR "*menstrual period*" OR "*ovarian cycle*". The reference lists of the studies found were also reviewed to identify any additional studies. This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The keywords were chosen even in the absence of the specific Medical Subject Heading (MeSH) term, in order to prioritize sensitivity over specificity.

Research strategy

During the first screening, two reviewers (BG and MT) evaluated the titles and abstracts of each study and excluded those that did not meet the eligibility criteria highlighted below. For each study selected, the full article was read and evaluated to verify whether it met the criteria that had been established. If any disagreements arose, a third evaluator (MA) was contacted. At the screening stage, all titles were analyzed, and studies that were considered important for the topic addressed were selected. Then, the abstracts corresponding to the titles that had been selected were read. Studies that were considered irrelevant to the objective of the present study were excluded. Lastly, the articles thus selected were read in full and further exclusions were made in accordance with the eligibility criteria.

Eligibility criteria

The inclusion criteria were that the studies need to have the following characteristics: (1) randomized clinical trials, quasi-randomized clinical trials, case-control or cohort studies; (2) studies that referred to the normal menstrual cycle; (3) adult and/or healthy women were the participants; (4) visual functions were evaluated; (5) psychophysical, neuroimaging and neurobehavioral instruments were used; (6) full article written in English; and (7) published between 1994 and 2020. The exclusion criteria were the following situations: (1) studies that referred to abnormal menstrual cycles; (2) only visual structures were evaluated; (3) review studies; (4) studies that were carried out during pregnancy or menopause; (5) studies exclusively on use of contraceptives; and (6) letters, editorials, systematic reviews and bibliographic reviews. Studies that showed insufficient information, such as in the statistical analysis, or that showed incomplete procedures, were also excluded.

Quality assessment

The articles were evaluated based on internal validity (e.g. selection bias, performance bias, friction measurement bias and reports) and the validity construct (e.g. suitability of the operational criteria used). In general, the quality of the evidence from the studies was assessed using three main measurements: (1) limitations (poor design, for example); (2) consistency of results; and (3) accuracy (ability to generalize findings and provide sufficient data). Studies that failed with regard to these points were not added or selected.

Data extraction

After assessing the articles in accordance with the pre-established criteria, the following information was extracted for analysis purposes: (1) geographical distribution of the study; (2) sample size (according to age and phase of the menstrual cycle); (3) type of measurements according to the psychophysical, neuroimaging and neurobehavioral instruments; (4) vision testing model; (5) visual subcategory evaluated; (6) categories of processed visual stimuli; and (7) main findings. "NS" (not specified) was used in the tables to denote situations of insufficient information from the studies to determine the data, according to the category.

RESULTS

Figure 1 shows a detailed flow chart of the study selection process. The tabulation showed that a total of 320 potentially eligible articles were found. Many articles were found to be incompatible with the purpose of the present study and/or featured women with irregular menstrual cycles, women using contraceptives, pregnant and lactating women, or women entering menopause. In addition, some studies did not directly assess measurements of visual function during the different phases of the normal menstrual cycle. Thus, after screening and applying the eligibility criteria, a total of 32 articles were examined.

Table 1 summarizes the articles according to the psychophysical methodological criteria. A total of 12 articles were found to fit within the criteria that had been established.

Table 2 summarizes the articles according to the neuroimaging methodological criteria (studies with spatial and temporal paradigms). A total of six articles were found to fit within the criteria that had been established.

Table 3 summarizes the articles according to the neurobehavioral methodological criteria (studies with cognitive and behavioral paradigms). A total of 14 articles were found to fit within the criteria that had been established.

The planning of comparisons, synthesis and interpretation of results were grouped thematically in the discussion, as described below.

DISCUSSION

Perceptual measurements involve basic and cognitive visual functions that describe how the visual system recognizes and interprets elementary sensory stimuli and/or complex visual scenes.[9] In this way, visual tests make it possible to investigate how vision detects, processes and recognizes the presence of light and the shape, size and color of visual stimuli, and enable investigation of visual acuity, visual field, evidence of monocular and binocular vision and even image quality.[9] For visual neuroscience, it is important to describe and understand how these measurements fluctuate with the normal menstrual cycle, i.e. how the peaks and endogenous levels of estradiol and progesterone are related to functional and perceptual changes in vision.[10] A study of this nature is important even considering that parts of this research are usually conducted with samples of men and women together, which makes it difficult to interpret the results.

Sample parameters

Most studies have had randomized blinded repeated-measurement research designs with small numbers of samples.

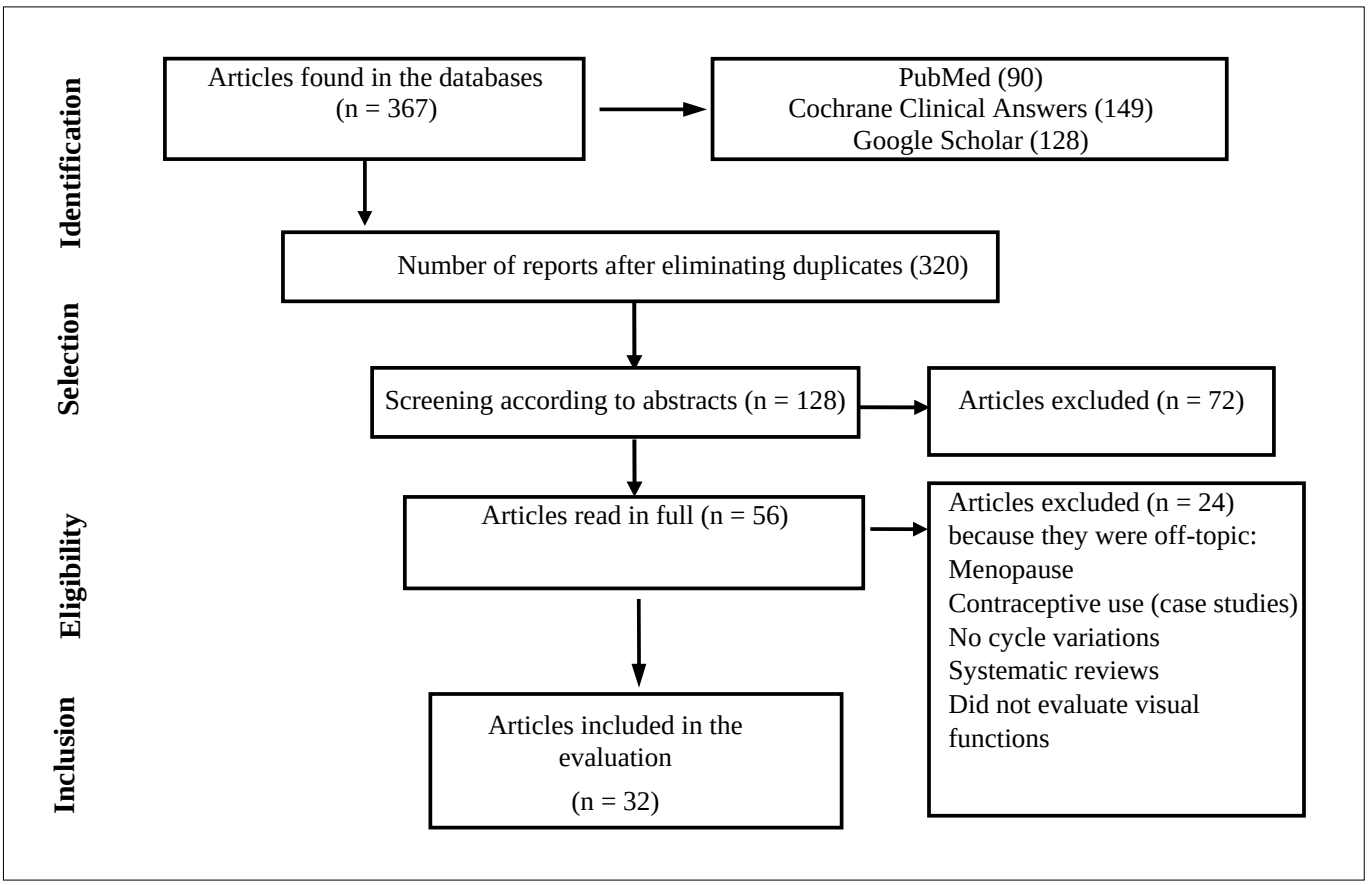

Figure 1. Results from database searches and selection process.

Table 1. Description of the results according to the psychophysical method

Authors (year)	Country	Sample (phases of the cycle)	Method	Testing	Visual task	Stimuli	Results
Darlington, Ross, King & Smith (2001)[24]	New Zealand	12 women aged 21.9 ± 4.0 years (menstrual, follicular, half-cycle and luteal phases)	P	NS	Eye movement	Oculogram and optokinetic (OKR)	There was no difference in eye movement speed
Apaydin, Akar, Akar, Zorlu & Ozer (2004)[34]	Turkey	93 eyes of women in the follicular and luteal phases: 45 eyes of women with diabetes mellitus (34.9 ± 4.7 years) and 48 healthy controls (36.2 ± 5.2 years)	P	M (left eye recording)	Visual field	Humphrey Field Analyzer II (upper temporal, lower temporal, upper nasal and lower nasal)	There were no differences between women with and without diabetes. Women with diabetes had lower sensitivity in the visual field in the luteal phase
Eisner, Burke & Toomey (2004)[28]	United States	4 women aged 21–29 years (menstrual, follicular and luteal phases)	P	M	Visual sensitivity	Temporal stimulus of 1.5 Hz square wave (wavelengths: 440, 460, 490, 510, 540, 580 and 640 nm)	No variation in visual sensitivity
Hausmann (2005)[23]	New Zealand	24 women aged 33.93 ± 10.1 years (menstrual, follicular and luteal phases); 14 men aged 26.96 ± 6.19 years	P	NS	Spatial orientation	Line bisection task (17 horizontal lines)	Greater activation of spatial hemispheric asymmetry in the luteal phase
Giuffrè, Rosa & Fiorino (2007)[31]	Italy	15 women aged 25 ± 4.0 years (3 evaluation phases: menstrual, ovulatory and luteal)	P	M (left-eye and right-eye recording)	Visual acuity, luminance contrast and color view	Vertical sine grids; Farnsworth-Munsell 100-hue test	There were no differences in visual acuity or luminance contrast; greater color vision in the ovulatory phase
Akara et al. (2013)[18]	Turkey	59 eyes of women (follicular and luteal phases) 54 eyes of men	P	Monocular	Visual field	Humphrey Field Analyzer II (upper temporal, lower temporal, upper nasal and lower nasal); Ishiara's color test	Smaller auto-tinted perimeter in visual field sensitivity in the luteal phase
Kumar, Mufti & Kisan (2013)[21]	India	30 women aged 21.33 ± 2.3 years (menstrual, follicular and luteal phases)	P	NS	Visual (TRV) and auditory (TRA) reaction time	Reaction time after the presentation of stimuli (green light; 4,000 Hz)	TRV and TRA were higher during the luteal phase and lower during the follicular phase
Danilenko & Sergeeva (2015)[43]	Russia	16 women aged 27.5 ± 1.9 years (follicular and mid-cycle phases)	P	NS	Visual sensitivity	Lumie SADlight with LEDs; light flashes of wavelengths: blue (480 nm) and red (651 nm)	Greater visual sensitivity at 480 nm during the follicular phase
Abdul et al. (2015)[19]	United Kingdom	30 women in the follicular phase (19.72 ± 1.20 years); 24 women in the luteal phase; 30 men (20.16 ± 1.02 years)	P	Binocular	Spatial orientation	CRFT system (previous mechanical rod and frame test); line stimuli	Largest error in the spatial orientation of verticality for women in the luteal phase
Sudheer, Jagadeesan & Kammar (2016)[33]	India	50 women aged 20-25 years (3 phases of evaluation: menstrual, ovulatory, and luteal)	P	NS	Visual (TRV) and auditory (TRA) reaction time	Reaction time after presentation of stimuli (flash/sound)	TRV and TRA were higher during the menstrual phase and lower during the luteal phase
Sy et al. (2016)[11]	United States	16 women; mean age 22 years (follicular and luteal phases)	P	M (left/right eye recording)	Binocularity	Psychophysics toolbox; circular sinusoidal grid stimuli (4.5 and 30%; 1.48 in diameter)	There was no significant difference in binocularity or temporal dynamics
Webb, Hibbard & O'Gorman (2018)[20]	United Kingdom	21 women aged 21.6 ± 3.8 years (menstrual, ovulatory and luteal phases); 14 women who used contraceptives; 14 men	P	NS	Luminance contrast	Stimuli were Gabor's sinusoidal grids with spatial frequencies of 1, 4 and 16 cpd	There was no difference in luminance contrast according to hormonal shifts

P = psychophysical; NS = not specified; M = monocular; cpd = cycles per degree.

However, the research has varied according to the theoretical paradigms and methodological procedure used. For example, studies with psychophysical methods had at least 8 and a maximum of 32 participants, studies with electrophysiology and neuroimaging (for example, visual evoked potential (VEP) and functional magnetic resonance imaging (fMRI)) had samples with a minimum of 11 and a maximum of 30 participants.[11-14] In studies with neurobehavioral paradigms, the sample size was found to be a minimum of 8 and a maximum number of 202 women.[15] Even if the sensory threshold is a probabilistic value, its momentary values are normally distributed, except for the sample errors. However, it is important to highlight that an approach based on sampling principles can underestimate hypothesis errors and cross-validation of studies. Therefore, solutions for increasing the sample size should be investigated, so as to address the possibility of increasing the data homogeneity.[16]

Table 2. Description of the results according to the neuroimaging method

Authors (year)	Country	Sample (phases of the cycle)	Method	Testing	Visual task	Test and stimuli	Results
Yılmaz, Erkin, Mavioglu & Sungurtekin (1998)[14]	Turkey	30 women aged 29.6 ± 6.4 years (4 evaluation phases: menstrual, follicular, ovulatory and luteal)	N (VEP)	M (left/ right eye recording)	Visual electrophysiology	Visual evoked potential (reverse pattern); P100 latency and visual range (Oz)	Higher mean P100 amplitude during the ovulatory phase
Krug et al. (2007)[13]	Germany	11 women (in the menstrual, ovulatory and luteal phases); mean age 25.3 years	N (VEP)	NS	Visual electrophysiology	Social stimuli (sexy man, baby, people, woman); N1, P2, P3, LPC, SW (700-900 ms), LPC	Greater LPC amplitude to stimulate sexy men in the ovulatory phase
Derntl et al. (2008)[35]	Austria	22 women aged 24.45 ± 3 years (11 in the follicular phase and 11 in the luteal phase)	N (fMRI)	NS	Emotion recognition	3T scanner for amygdala activation (T2 protocol); emotional discrimination task (Vienna Emotion Recognition Tasks (VERT-K)	Greater neural activation for all follicular phase emotions. In particular, negative facial expressions caused greater activation of the amygdala
Zhang, Zhou & Ye (2013)[41]	China	29 women (premenstrual, post-menstrual and ovulation phases); aged 20.6 ± 1.5 years	N (VEP)	NS	Visual electrophysiology	Visual evoked potential; visual latency and amplitude components N1, P2, N2 in Fz, Cz, Pz; P3, LPP in Pz, Oz	Late positive potential (LPP) evokes changes in the premenstrual phase for facial expressions: fear (110-130 ms, 150-190 ms and 300-500 ms), sadness (230-300 ms), and anger (750- 1,000 ms.); lower LPP amplitude in the premenstrual phase
Mareckova et al. (2014)[25]	United Kingdom	20 women (10 in the regular cycle and 10 who used oral contraceptives (menstrual, follicular, mid-cycle and luteal phases); aged 20.44 ± 2.69 years	N (fMRI)	NS	Recognition of emotions	T1-weighted images (T1W), magnetic transfer rate (MTR) and diffusion tensor image (DTI)	Higher level of blood oxygenation (BOLD) in the fusiform area during the mid-cycle phase
Lusk et al. (2015)[37]	Australia	28 women in the follicular phase (23.54 ± 6.6 years); 29 women in the luteal phase (24.41 ± 7.1 years); 27 men	N (VEP)	B	Visual electrophysiology	Visual evoked potential; latency and visual range of P100, P300, N200, N300 and LPP	Early latency in the luteal phase (P1, N1). Early latency for unpleasant images in the menstrual phase in P3 and LPP

N = neuroimaging; NS = not specified; VEP = visual evoked potential; fMRI = functional magnetic resonance imaging; M = monocular; B = neurobehavioral; LPC = late positive complex; LPP = late positive potential.

Table 3. Description of the results according to the neurobehavior method

Authors (year)	Country	Sample (phases of the cycle)	Method	Testing	Visual task	Test / Stimuli	Results
Penton-Voak & Perrett (1999)[30]	United Kingdom	139 women; mean age 20 years (menstrual, follicular and luteal phases)	B	NS	Facial attractiveness	Emotional attractiveness task (female and male face stimuli)	Women showed greater facial attractiveness as facial stimuli in the follicular phase
Penton-Voak et al. (1999)[30]	United Kingdom and Japan	20 women; mean age 21 years (follicular phase and luteal phase)	B	NS	Facial attractiveness	Visual stimuli consisting of male faces	Greater attractiveness to male faces of Caucasians in the follicular phase
Roberts et al. (2004)[47]	United Kingdom and Czech Republic	130 men; 131 women; mean age 25 years	B	NS	Facial attractiveness	Emotional attractiveness task (female face stimuli in the follicular and luteal phases)	Women showed greater facial attractiveness in the menstrual cycle, and higher in the periovulatory than in the luteal phase
Pearson & Lewis (2005)[26]	United Kingdom	50 women of mean age 20 years (12 in the menstrual phase; 13 in the preovulatory phase; 11 in the ovulatory phase; and 14 in the luteal phase)	B	NS	Emotion recognition	Emotion recognition task (Face Bank; Paul Ekman)	Greater accuracy of the fear face in the menstrual phase
Little, Jones, Burt & Perrett (2007)[36]	United Kingdom	31 women aged 20-25 years (in the follicular and luteal phases)	B	NS	Facial attractiveness	Male and female facial stimuli in 2D symmetry	Greater facial attractiveness of symmetrical faces in the follicular phase
Roney & Simmons (2008)[27]	United States	43 women aged 18.36 ± 0.10 years (menstrual phases: follicular, mid-cycle and luteal phases)	B	NS	Facial attractiveness	Visual stimuli consisting of male faces	Greater facial attractiveness of more masculine features in the late follicular phase
Rubinow et al. (2007)[17]	United States	28 women with PMDD (37.9 ± 5.0 years); 27 women without PMDD (33.5 ± 7.0); evaluated in both the follicular and the luteal phases	B	NS	Emotion recognition	Emotional discrimination task	Better discrimination of sad face in the luteal phase for PMDD. Women with PMDD differed significantly from women without PMDD in the luteal phase regarding sad faces
Derntl et al. (2008)[35]	Austria	32 women aged 23.84 ± 3 years (15 in the follicular phase and 17 in the luteal phase)	B	NS	Emotion recognition	Emotional discrimination task (Vienna Emotion Recognition Tasks, VERT-K)	Better performance in the follicular phase; greater confusion in discrimination of negative emotions (anger and disgust) in the luteal phase
Guapo et al. (2009)[32]	Brazil	30 women aged 22.1 ± 2.9 years (11 women in the follicular phase; 9 women in the ovulatory phase; and 10 women in the luteal phase); 10 healthy men	B	NS	Emotion recognition	Prototypes of emotional facial stimuli	Recognition of negative emotions, such as sadness, anger and fear in the follicular phase
Konishi et al. (2009)[29]	Japan	12 women in the menstrual, follicular and luteal phases; aged 22.4 ± 1.1 years	B	NS	Visuospatial memory	Visual memory task using the Baddely model	Higher mental load performance in the luteal phase.
Oberzaucher et al. (2012)[40]	Austria, Czech Republic and Slovakia	10 women and 15 men; aged 23.35 ± 3.1 years)	B	NS	Facial attractiveness	Female facial stimuli in the ovulatory and luteal phases	Greater facial attractiveness of female stimuli in the ovulatory phase. There was no difference regarding the other phases of the menstrual cycle

Continue...

Table 3. Continuation.

Authors (year)	Country	Sample (phases of the cycle)	Method	Testing	Visual task	Test / Stimuli	Results
Puts et al. (2013)[15]	United States	202 women aged 19.6 ± 1.6 years (late follicular and middle luteal phases)	B	NS	Facial attractiveness	Visual stimuli consisting of male faces	Greater facial attractiveness of more masculine features in the late follicular phase (increased estradiol)
Lobmaier, Bobst & Probst (2016)[38]	Switzerland	60 women aged 25.16 ± 5.1 years (2 evaluation phases: ovulatory and luteal)	B	NS	Facial attractiveness	Facial stimuli prototypes	Higher rate of facial recognition during the ovulatory phase
Marcinkowska & Holzleitner (2020)[39]	Poland	102 women aged 28.8 ± 4.6 years	B	NS	Facial attractiveness	Female facial stimuli in the ovulatory and luteal phases	Greater facial attractiveness of female stimuli in the ovulatory phase. There was no difference regarding facial symmetry and sexual dimorphism during the phases of the cycle

B = neurobehavioral; NS = not specified; PMDD = premenstrual dysphoric disorder.

The normal menstrual cycle

The menstrual cycle shows cyclical variations in the levels of various sex hormones. The effects of these hormones are not limited just to the reproductive system but affect other systems too, including the nervous system. All the participants included in the studies had a normal menstrual cycle, but comparative studies between women with a normal menstrual cycle and women who had premenstrual syndrome were also found, along with comparisons with men over periods of time similar to the menstrual cycle.[17-20]

As mentioned earlier, the menstrual cycle can be divided into the follicular, ovulatory and luteal phases.[21] However, studies have pointed to distinct average phases of the cycle in order to describe behavior during all the phases. For example, the following phases have been described: days 1 to 5 days as the menstrual phase (low levels of progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol); day 7 as the middle follicular phase (gradual increase in estradiol); days 8 to 11 as the follicular phase (peak estradiol and gradual increases in progesterone, LH and FSH); days 12 to 15 as the ovulatory phase (peak LH and FSH, a gradual increase in progesterone and low levels of estradiol); days 16 to 20 as the luteal phase (increases in progesterone and estradiol and low levels of LH and FSH); day 21 as the middle luteal phase (peak of progesterone and estradiol and low levels of LH and FSH); and days 22 to 28 as the premenstrual phase (decreased levels of progesterone and estradiol and low levels of LH and FSH).[22,23]

These minute divisions suggest that the length of the menstrual cycle may be a relevant indicator for hormonal secretion. Thus, the studies reviewed here were organized as follows: groups of women in the menstrual, follicular, ovular and luteal phases; groups of women in the menstrual, follicular and luteal phases; groups of women in the menstrual, ovulatory and luteal phases; groups of women in the discrete follicular and luteal phases; groups of women in the ovulatory and luteal phases; groups of women in the follicular and middle luteal phases; groups of women in the premenstrual, follicular and ovulatory phases; and a group of women in the follicular phase.[11-15,17-21,23-43]

In addition, hormonal changes that occur during the menstrual cycle influence the body's homeostasis.[31] Most physiological changes in women occur in the luteal phase: these changes include fluid retention, weight gain, increased energy demand, changes in glucose uptake, lipid profiles, emotional hypersensitivity, generalized pain and changes in dietary habits.[23]

The psychophysical method

Psychophysical measurements are associated with the sample characteristics and dynamics of the experimental protocols, such as clinical and functional evaluations of the visual system and the methodological characteristics of the research apparatus. In the psychophysical method, the threshold values are usually measured using characteristics of the psychometric function underlying the perceptual performance. In this way, the experimental procedure is adaptable to the physical characteristics of the participants and their responses to sequential attempts to present stimuli.[44]

The results from simulations and experiments involving women were reviewed to assess the usefulness of these adaptive procedures and the special circumstances in which one might be superior to another.[45] Different articles measured visual tasks that assessed eye movement, visuospatial attention and visual reaction time.[21,23,24,33] Lastly, there were tests that used the psychophysics toolbox to generate stimuli from circular sinusoidal grids and from Gabor, with the aim of assessing visual sensitivity at different stages of the menstrual cycle.[11,19,20,28,31] The methodological route that psychophysics offers for carrying out empirical studies, such as noninvasive measurements, has become a perceptual sensory tool of high precision for evaluating thresholds in the phases of the menstrual

cycle. Also, from a physiological perspective, this means that these changes have anatomical-physiological connections, with visual pathways integrated with endogenous hormones.

The neuroimaging method

Functional neuroimaging studies involve experimental baseline conditions that reveal time-space models of visual function. A 3T scanner was used in one study to assess the nature of amygdala activation using a T2 relaxation protocol and the Vienna Emotion Recognition Tasks (VERT-K) was used in another study to verify recognition of facial emotions. In both of these studies, the aim was to understand cognitive functions relating to perception of visual stimuli of emotions, in the follicular and luteal phase.[35] The recognition of facial emotions was also analyzed by means of T1e-weighted images and diffusion (DTI).[25] Other models of visual temporal processing were used to measure the latency and amplitude of electroencephalographic components in occipital areas.[14,37,41] VEP and fMRI are techniques that can be used to understand visual neural events during the normal menstrual cycle.[46] Together, all these research studies provide temporal and spatial mapping of brain function. On the other hand, all of the studies that evaluated visual functions had the problem of analyzing results that corresponded to measurement of the response to a stimulus after it had been processed by the central nervous system. The response was therefore the sum of the structural visual function and the constructive mental information.

The neurobehavioral method

This basic and applied research practice uses tests, instruments and behavioral assessment protocols to describe brain functional behavior. Articles in which visual recognition behavior was measured with regard to facial attractiveness of facial stimuli and emotional expressions were found.[15,17,26,27,30,32,35,36,38-40,47] These studies used a variety of stimuli: for example, prototypes of male and female facial stimuli of different ethnicities at different stages of the menstrual cycle.[39] In addition to these models, neurocognitive studies were found that evaluated visuospatial memory and visual working memory.[29]

Visual measurements during the normal menstrual cycle

Spatial vision: monocular and binocular measurement

It is important to highlight that some studies used the participants for recording binocular and monocular measurements.[11,18,31,34] Binocular rivalry occurs when markedly different entries for the two eyes initiate alternations in the perceptual domain between the views of the two eyes.[11] In psychophysical studies to detect and measure visual thresholds, it has been argued that there are no differences between binocular and monocular measurements.[45] This hypothesis was confirmed by Giuffrè et al. who found no differences between the left and right eye regarding visual acuity and luminance contrast.[31] However, Apaydin et al. evaluated 93 eyes of women and highlighted that the lower and upper nasal field of the left eye had greater visual sensitivity in the luteal phase of the menstrual cycle.[34] These findings were confirmed by Akara et al. in an analysis on lower visual sensitivity of 59 eyes of women also in the luteal phase.[18] Yılmaz et al. also showed that the mean P100 latency and amplitude were recorded differently binocularly during the menstrual phase.[14]

In another study on binocularity, fluctuations in the gamma-aminobutyric acid (GABA) concentrations during the menstrual cycle of 16 women in the follicular and luteal phase were measured using psychophysical methods, with stimuli of circular sinusoidal grids.[11] However, no significant changes or trends in menstrual phases were found with regard to the temporal dynamics of ocular dominance. This study pointed to the need for new research perspectives that would investigate GABAergic systems in relation to the dynamics between hormonal steroids and binocular rivalry.

Visual acuity

The ability to visually detect something depends on the arrangement and number of photoreceptors per unit area on the retina. In one study, data from the left and right eyes of 15 women in the menstrual, ovulatory, and luteal phases were recorded separately to check their visual acuity performance on the logarithmic minimum angle of resolution (logMAR) scale. No significant differences in acuity values were found in any of the phases.[31]

Visual sensitivity

From studies measuring visual sensitivity, it has been suggested that light may be a major factor for the hormonal secretory system. However, these studies have not ascertained any central mechanism for its action. For example, in one study, it was investigated whether hormonal alterations might affect the adaptation to light of four women in the menstrual, follicular and luteal phases.[28] Variability in visual sensitivity was found at all stages, but there were no specific individual differences. In another study, the effect of light on reproductive hormones was evaluated and the role of photoreception based on melanopsin sensitive to blue (480 nanometers), for mediating the non-visual effects of light, was addressed. That study was carried out among healthy women with measurements in the menstrual, follicular and luteal phases.[43] The results showed that bright blue light gives rise to secretion of follicle-stimulating hormone in women in the middle follicular phase until the end of the menstrual cycle during the morning, which suggested that a direct functional link between light and the reproductive system existed. The data were seen to be sensitive to the capacity for visual adaptation.

Luminance contrast

Luminance contrast sensitivity to stimuli of vertical sinusoidal grids of frequencies 0.5, 1, 2, 4, 8 and 16 cycles per degree of visual angle (cpd) in the menstrual, ovular, and luteal phases was assessed in one study.[31] No significant differences were found in relation to any of the spatial frequencies tested. Similarly, the luminance contrast of Gabor sinusoidal stimuli was also measured at spatial frequencies of 1, 4 and 16 cpd, in 21 women in the menstrual, ovulatory and luteal phases and in 14 men. It was shown that the sensitivity to visual contrast did not differ according to sex or use of oral contraception. Nor did it vary due to hormonal changes over the course of the menstrual cycle.[20] It was suggested that changes to the phases of the menstrual cycle did not produce any changes in sensitivity to visual luminance contrast.

Visual color

Color discrimination was assessed using the Farnsworth-Munsell 100 test in one study.[31] The results showed that although all the women in that study could be defined as normal from an ophthalmological point of view, they showed variation in their scores, with better performance in the ovulatory phase and greater numbers of errors of disposition of the records in the menstrual and luteal phases. In addition, there were no significant differences in measurements between the left eye and the right eye. The authors argued that the differences found might be associated with cyclical physiological functions or with the women's psychological state, even if imperfectly expressed. It was concluded that variations in color perception might occur during the menstrual cycle, although the differences were subtle.

Visual field

The area of the visual field was measured monocularly in one study, using automated perimetry with a short wavelength, among 48 eyes of healthy women and 45 eyes of women with diabetes mellitus, who were in the follicular and luteal phases of the menstrual cycle.[34] To highlight the results, the authors pointed out that the achromatic visual field tests were not statistically different between diabetic women and the control group. However, the mean values of the temporal retinal region were significantly lower in the luteal phase than in the follicular phase in the diabetic women. In another study, standard achromatic perimetric analysis was performed using automated short-wavelength perimeters of monocular shape, among 59 healthy women in the follicular and luteal phases, and the results were compared with those from 54 men. Unlike in the previous study, a reduction in the average value in the automated perimeter field was found for short wavelength in the luteal phase.[18]

In the above two studies,[18,34] the authors were of the opinion that the hormonal behavior that occurs in the luteal phase correlates with a reduction of loss of sensation in the visual field. However, further clinical trials relating to synchronization and visual campimetry should be conducted in order to provide more accurate information.

Spatial orientation

The perception of verticality was evaluated in one study through the binocular visual acuity of 30 women in the follicular phase and 24 women in the luteal phase, and their results were compared with those of 30 men over the same time periods. The subjects had been matched previously with regard to the menstrual cycle using a mechanical rod and frame test system.[19] A higher proportion of vertical positioning errors was found among the women in the middle luteal phase than among the men or among the women in the follicular phase, which suggested that the phase was associated with the perception of verticality. Similarly, the spatial orientation of 24 women in the menstrual and luteal phases and 14 men was assessed in another study using a visual line bisection task to investigate functional brain asymmetry.[23] It was shown that high levels of estradiol during the luteal phase were related to decreased hemispheric asymmetry of spatial attention, with greater bias towards the left hemisphere.[19] These findings contribute to the idea that the luteal phase can present strong evidence of fluctuations in orientation and spatial attention.

Eye movement

The optokinetic function of 12 women in the menstrual, follicular, half-cycle and luteal phases was measured in one study. The authors suggested that there was no difference in the pattern of eye movement. The results from that study demonstrated that hormonal changes that occur throughout the menstrual cycle had no significant effect on the speed of fixation movements.[24]

Visual electrophysiology

Several studies have investigated the electrophysiological changes in visual functions that occur during the menstrual cycle of women. For example, pattern-reversal visual evoked potentials (PRVEPs) were investigated among 30 healthy women in the menstrual, follicular, ovulatory and luteal phases.[14] Although the results were not statistically significant, there was greater mean amplitude of the P100 during the ovulatory phase in relation to all other phases. Thus, the P180 latency was statistically lower in the follicular phase than in the luteal phase. In another similar study, changes to the potential relating to social stimulus events were investigated among women in the menstrual, ovulatory and luteal phases.[13] Those results also showed an increase in the ovulatory phase in comparison with the luteal phase, for late positive complex (LPC) stimulus processing indicators (500-700 millisecond). According to those authors, the reason for those variations in amplitude and latency was the increase in estrogen in the

follicular phase. They reported that estrogen caused a decrease in the time taken for visual transmission, thereby increasing the sensitivity of receptors in the dopamine optical pathways.

Visual amplitude and latency in the processing of recognition of modulated facial expression during the phases of the menstrual cycle was measured in one study.[41] Visual evoked potentials (VEPs) were evaluated among 29 healthy women in the premenstrual, post-menstrual and ovulation phases, in relation to recognition of different emotional expressions. The authors of that study pointed out that the late positive potential (LPP) (750 to 1,000 milliseconds) was affected in the central parietal area (Pz) and central occipital area (Oz) by the menstrual cycle, for all facial expressions. Thus, the amplitude in the ovulation phase was greater than in the premenstrual phase, which meant that there was a positive correlation between the amplitude of the LPP and performance in facial expression recognition during the ovulation phase. In addition, the amplitude of P3 (300-500 milliseconds) in Oz in the ovulation phase was marginally significant, in comparison with the premenstrual phase and the post-menstrual phase. These greater amplitudes occurred for fear-based stimuli, in comparison with stimuli consisting of neutral and happy faces.

Similarly, in another study, VEPs were investigated by means of visual stimuli among 28 women in the follicular phase and 29 women in the luteal phase. The authors used pleasant and unpleasant image stimuli with low and high intensities and found greater amplitude of P3 and LPP in the luteal phase for unpleasant images, in relation to all other stimulus conditions.[37]

These studies pointed towards cortical processing of visual stimuli and found significant evidence showing that VEPs have a role in improvement of the automatic visual process of emotional stimuli associated with the luteal menstrual phase, especially in relation to unpleasant stimuli and those with a negative emotional charge.

Emotion recognition

Recently, some studies have evaluated neural modulation in relation to recognition of facial emotion according to the phase of the menstrual cycle and sex hormones. For example, the mediating role of the menstrual cycle stage was evaluated with regard to recognition of emotional expressions among 50 women in the menstrual, preovulatory, ovulatory and luteal phases.[26] The authors of that study found that there was greater accuracy regarding fearful faces during the menstrual phase and suggested a hypothesis regarding estrogen levels in the coding of facial stimuli. The fact that fear recognition is affected differently according to the phase of the cycle suggested that there was neural processing distinct from fear.

A comparative study on healthy women and women with premenstrual dysphoric disorder (PMDD) also investigated emotional recognition in order to determine emotional processing errors in the follicular and luteal phases of the menstrual cycle.[17] In that study, there were no differences in emotional recognition among healthy women but it was noted that women with PMDD showed better recognition of negative faces during the luteal phase. According to the authors of that study, this negative bias might contribute to generation of negative mood states during the luteal phase and might suggest the presence of dysfunction in brain regions whose activity mediates recognition of emotion in facial expression. Those findings corroborated the results from electrophysiological investigations.[13,41]

The accuracy of facial emotion recognition was evaluated among 40 healthy volunteers.[32] The results showed that women in the follicular phase had greater accuracy in recognizing emotions of sadness and fear than did women in the luteal phase. Similar results were found using fMRI techniques. fMRI measurements with T1 relaxation were made among 20 women at different stages of the cycle and higher levels of blood oxygenation (BOLD) were found in the right spindle area among women taking oral contraceptives than among women who did not use contraceptives during the follicular phase.[25] In addition, the accuracy of emotional recognition was investigated among 22 women (11 in the follicular phase and 11 in the luteal phase) using fMRI T2 relaxation measurements in relation to amygdala activation, and greater neural activation was found for negative emotions such as fear and disgust in the follicular phase.[35] Similar results were found through a neurobehavioral analysis among 35 women during the follicular and luteal phases.[35] Thus, these authors suggested that there was a significant negative correlation between progesterone levels and performance in emotion recognition, such that there was greater accuracy of socioemotional influence with lower levels of progesterone.

Visual attractiveness

Facial features can serve as a clue to social judgments of multiple human features. In one study, female facial stimuli were used in the ovulatory and luteal phases to ascertain the symmetry of facial attractiveness. It was suggested that the greatest facial attractiveness of women was found in the most fertile phase of the menstrual cycle.[39] In another study, an emotional attractiveness task regarding stimuli consisting of female faces, conducted during the follicular and luteal phases, showed that the attractiveness perceived in the women's faces varied over the course of the menstrual cycle and was greater in the ovulatory phase than in the luteal phase.[47]

Facial attractiveness was evaluated among 60 women who were presented with stimuli consisting of female faces.[38] They did not find particular attractiveness in faces in the late follicular or luteal phase, but found higher attractiveness during the ovulatory phase. It is important to note that women with high levels of estradiol are more likely to choose the faces of women who are also in the ovulatory phase. In another study, the preferences of men and women for female faces during the ovulatory and luteal periods

were investigated and it was shown that there was greater preference for faces in the ovulatory phase. According to the authors of that study, the preference for facial attractiveness in the ovulatory phase correlated with the hormonal fertility state.[40]

Stimuli of male and female faces were used in a study aimed at measuring the facial attractiveness of women in the follicular and luteal phases. It was found that there was a higher attractiveness rate in the follicular phase of the menstrual cycle than in the menstrual and luteal phases.[30] Twenty women in the follicular phase and luteal phase were asked to rate the attractiveness of male faces of Caucasian and Japanese ethnicity.[30] There was greater preference for the faces of Caucasian men during the follicular phase than during the luteal phase. Likewise, the facial attractiveness of 31 women in the follicular and luteal phases was measured through the symmetry of male faces. It was shown that women preferred more symmetrical faces during their peak fertility.[36] In line with previous studies, 43 women in the menstrual, follicular, mid-cycle and luteal phases were evaluated and greater attractiveness towards male faces was found during the late follicular phase.[27] In another study, women were more attracted to faces with a greater trait of masculinity when they were in the late follicular phase, due to the gradual increase in estradiol.[15]

The converging evidence suggests that the menstrual cycle, and, therefore, hormone levels, can affect emotional behavior, in particular recognition of facial emotions. While universal preferences may exist for particular characteristics in populations, it appears that there are several individual differences in facial preferences that are dependent on the individual's situation, individual characteristics and hormone levels.[27,38,39]

Visual reaction time

Reaction time is defined as the time interval between application of a stimulus and an appropriate voluntary response from the individual. The influence of the menstrual cycle on the visual (TRV) and auditory (TRA) reaction times of 30 women was investigated and it was shown that TRV and TRA were more prolonged in the luteal phase than in the follicular phase.[21] These results could be attributed to the fluctuating levels of female sex hormones. In another study, the TRV and TRA of 50 women in the menstrual, ovulatory and luteal phases were measured using presentation of stimuli such as flashes of light and sound.[33] It was concluded that TRV and TRA were longer during the menstrual phase and shorter during the luteal phase of the menstrual cycle. The data were contradictory, but the authors of that study pointed out that the prolonged reaction times during the menstrual phase were attributable to the decrease in driven reaction times, due to increases in the levels of fluids and electrolytes, and that faster reaction times were due to progesterone, which negates the ability of estrogen to cause a delay in driven reaction time.

Visuospatial cognitive function

Working memory is a faculty of the mind that enables multiple tasks to be performed simultaneously, in parallel. It involves controlling the distribution of concentration, with individual differences in attention span. A study examined visuospatial cognitive functions in the follicular, luteal and menstrual phases of 12 healthy women, with regard to visual working memory.[29] The authors showed that the greatest mental workload and stress was perceived in the luteal phase.

CONCLUSIONS

The results from the studies presented were inconclusive, but these inconsistencies may have been related to lack of experimental control and failure to assess the perimetry of the phases of the menstrual cycle. These findings continue those of Guttridge (1994), although it is difficult to draw specific conclusions about the performance of visual functions during the phases of the normal menstrual cycle. Therefore, further research is needed in order to clarify the sensory and perceptual mechanisms involved in the menstrual cycle, especially with regard to facial recognition and attractiveness processes. It is noteworthy that while the study by Guttridge (1994) was aimed more towards optical measurements, our study sought to understand neurological and behavioral perceptual processes. However, the role of hormones and the phases of the menstrual cycle in the psychophysical, neurobiological and behavioral traits of visual functions could be observed, and specifically in relation to the follicular and luteal phases.

Visual detection fluctuates significantly during the menstrual cycle. Observations relating to visual processing during the menstrual cycle may explain the physiological, cognitive, behavioral and social modulations of healthy women. In addition, a good proportion of visual measurements (with some exceptions, such as visual acuity) are dynamic and can naturally fluctuate between one measurement and another. Perhaps for this reason, it is common to use repeated measurements. In addition, yet other variables (for example, circadian rhythms) that can affect visual measurements generally do not appear in studies.

However, correlation of physiological and clinical psychological data with visual data from the phases of the menstrual cycle can provide a contribution, as important biological and behavioral markers of human vision. In addition, this can facilitate knowledge of the sensory and perceptual biological rhythms of vision during the physiological changes of the menstrual cycle.

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Address for correspondence:
Michael Jackson Oliveira de Andrade
Departamento de Psicologia, Universidade Estadual de Minas Gerais, Laboratório de Neurociências, Cronobiologia e Psicologia do Sono
Divinópolis — Minas Gerais — Brasil
CEP 35501-170
Tel. (+55 37) 3229-3590
E-mail: andrademjackson@gmail.com

Evidence from Cochrane systematic reviews for effects of antithrombotic drugs for lower-limb revascularization. A narrative review

Silfayner Victor Mathias Dias[I], Ronald Luiz Gomes Flumignan[II], Wagner Iared[III]

Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]MD. Researcher, Postgraduate Program on Evidence-Based Health, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-9794-6446

[II]MD, PhD. Adjunct Professor, Division of Vascular and Endovascular Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-6440-8011

[III]MD, PhD. Advisory Professor, Postgraduate Program on Evidence-Based Health, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-6426-5636

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ABSTRACT

BACKGROUND: Peripheral arterial disease (PAD) is characterized by progressive narrowing of the arterial lumen, resulting from atherosclerotic plaques. Treatment for PAD aims to control atherosclerosis and improve blood flow. Use of antiplatelet agents and anticoagulants has played important roles in helping to prevent occlusions and stenosis.

OBJECTIVE: To evaluate the evidence from Cochrane systematic reviews regarding the accuracy, effectiveness and safety of use of anticoagulants and antiplatelets in lower-limb revascularization, in patients with peripheral arterial disease.

METHODS: Systematic reviews found through searches in the Cochrane Library were included. Two authors evaluated whether the reviews found were in line with the inclusion criteria for this investigation. A qualitative synthesis of their findings was presented.

RESULTS: Three systematic Cochrane reviews were included. Patients who underwent prosthetic bypass surgery probably presented greater benefit from use of antiplatelets, and patients who underwent vein revascularization probably presented greater benefit from use of anticoagulants. Patients who received endovascular treatment benefited from both antiplatelet and anticoagulant treatment. However, the reliability of the results found was impaired because at the time when these reviews were published, there was no mandatory assessment using the GRADE criteria.

CONCLUSION: Despite the evidence found, it is necessary for these reviews to be updated in order to evaluate the degree of certainty of the results found.

INTRODUCTION

Peripheral arterial disease (PAD) is characterized by progressive narrowing of the arterial lumen resulting from atherosclerotic plaques on the artery walls. The disease has a prevalence of 18% in 50-year-old patients, and this reaches 29% in patients over 70 years of age.[1] Its incidence has been increasing over recent decades due to population growth, aging of the population and increased incidence of diabetes mellitus and smoking.[2]

These patients are at higher risk of mortality due to acute myocardial infarction (AMI) and stroke. Thus, treatment of PAD offers additional prevention for cardiovascular events.[3]

PAD commonly leads to intermittent claudication of the lower limbs, characterized by muscle pain during muscle activity, caused by restricted blood flow to the muscles recruited. This condition improves after a brief rest. As blood flow restriction increases, pain at rest and gangrene arise. In addition, these patients have significantly reduced quality of life due to restricted mobility.[4]

The aim in treating PAD is to control the risk factors for atherosclerosis and bring symptomatic relief through improving blood flow. In more advanced cases of the disease, revascularization of the lower limbs is required through surgery or percutaneous transluminal angioplasty.

Anticoagulant and antiplatelet agents play an important role in helping to prevent occlusions and stenosis, both for patients who have started treatment and for those undergoing revascularization, thus sustaining the clinical improvement.[5,6] Platelets participate in the process of hemostasis and pathogenesis of atherosclerotic disease. The presence of endothelial injuries exposes the subendothelial extracellular matrix to contact with platelets.[7] This mechanism promotes platelet recruitment, adhesion, activation and aggregation, to form a prothrombotic surface that promotes formation of clots and fibrous plaques and the ensuing thromboembolic complications. The latter can lead to acute myocardial infarction, stroke and peripheral vascular occlusions.[7]

OBJECTIVES

The objective of this study was to summarize the evidence from Cochrane systematic reviews on the safety and effectiveness of use of antiplatelet agents and anticoagulants in lower limb revascularization in PAD.

METHODS

Study design and location

This was a narrative review of Cochrane systematic reviews developed within the Evidence-Based Health postgraduate program at Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP).

Inclusion criteria

Types of study

Only Cochrane systematic reviews were included, and only the latest version of the review was considered. Reviews that had been excluded from the Cochrane Library and systematic review protocols (reviews in progress) were not included.

Types of participants

We included reviews in which the participants presented the diagnosis of chronic PAD of the lower limbs and who had undergone revascularization of the lower limbs by means of venous or prosthetic bypasses or through angioplasty.

Types of interventions

We included studies in which patients underwent any treatment with antiplatelet agents or anticoagulants, and relevant outcomes were assessed in relation to the evolution of the disease.

Types of outcomes

Outcomes relating to the evolution of the disease and to morbidity, mortality and safety of treatments were considered.

Search for studies

We performed a systematic search in the Cochrane Database of Systematic Reviews (via Wiley) on July 11, 2020. The search strategy is detailed in Table 1.

Selection of studies

Two authors (SVMD and RLGF) evaluated and selected the titles and abstracts of systematic reviews regarding their agreement with the eligibility criteria of this study. Any occurrences of disagreements were resolved by a third researcher (WI).

Presentation of results

The findings of the systematic reviews were summarized and presented narratively.

RESULTS

The initial search resulted in retrieval of 370 systematic Cochrane reviews, of which three met the inclusion criteria for this review.[8-10] We present, in summary, the main methodological characteristics and the most relevant results of the reviews included. In **Table 2**, we present a summary of the main findings. Reviews involving medications that are no longer available worldwide for clinical use were excluded from this study.

For each of the studies included, the objectives and the outcomes assessed that were relevant to this review are demonstrated. At the end, we presented the authors' opinion in relation to the result.

Table 1. Search strategy used in the Cochrane Library

Lines	Search terms	Numbers of records
#1	MeSH descriptor: [Peripheral Arterial Disease] explode all trees	1,039
#2	MeSH descriptor: [Arterial Occlusive Diseases] explode all trees	12,019
#3	MeSH descriptor: [Peripheral Vascular Diseases] explode all trees	3,211
#4	#1 OR #2 OR #3	13,967
#5	(Peripheral Arterial Disease*) OR (Arterial Occlusive Disease*) OR (Arterial Obstructive Disease*) OR (Vascular Disease*) OR (Peripheral Vascular Disease*) OR (Peripheral Angiopath*)	29,451
#6	MeSH descriptor: [Anticoagulants] explode all trees	4,596
#7	(Anticoagulant Agent*) OR (Anticoagulant Drug*) OR (Anticoagulant) OR (Indirect Thrombin Inhibitor*)	6,517
#8	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees	3,870
#9	(Blood Platelet Antiaggregant*) OR (Platelet Antiaggregant*) OR (Platelet Aggregation Inhibitor*) OR (Blood Platelet Aggregation Inhibitor*) OR (Platelet Inhibitor*) OR (Antiplatelet Agent*) OR (Antiplatelet Drug*) OR (Platelet Antagonist*) OR (Blood Platelet Antagonist*)	11,027
#10	#4 OR #5	38,968
#11	#6 OR #7	9,747
#12	#8 OR #9	11,027
#13	#10 AND (#11 OR #12)	3,231
#14	in Cochrane Reviews	370

Table 2. Characteristics and main results of the systematic reviews on the clinical treatment of peripherical arterial disease of the lower limbs that were included

Review	Interventions	Main results
Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery[6]	ASA 400-990 mg/d or ASA 400-900 mg/d plus DIP 150-450 mg/d versus placebo or nothing	**Benefits with ASA or ASA plus DIP** Primary patency in venous bypass at 12 months Primary patency in prosthetic bypass at 1, 3, 6, 9 and 12 months **No difference among intervention groups** Gastrointestinal side effects; major bleeding; minor bleeding; wound or graft infection; limb amputation; cardiovascular events; mortality; primary patency in venous bypass at 1, 3, 6 and 24 months **Higher risk with ASA or ASA plus DIP** General side effects
	ASA or ASA 1050 mg/d plus DIP 150 mg/d versus pentoxifylline 1200 mg/d; venous or prosthetic bypasses	**Benefit with pentoxifylline** Less gastric intolerance **No difference among intervention groups** Primary patency at 1, 3, 6 and 12 months; gastric bleeding; dizziness; limb amputation; mortality
	ASA 900 mg/d plus DIP 250 mg/d versus indobufen 400 mg/d; venous or prosthetic bypasses	**No difference among intervention groups** Primary patency at 1, 3, 6, 9 and 12 months
	ASA 1000 mg or ASA 1000 mg plus DIP 225 mg/d versus VKA; venous or prosthetic bypasses	**No difference among intervention groups** Graft primary patency at 3, 6, 12 and 24 months; limb amputation; cardiovascular events; mortality
	ASA 900 mg/d plus DIP 300 mg/d versus LMWH 2500 IU/d; venous or prosthetic bypasses	**Benefits with ASA plus DIP** mortality **No difference among intervention groups** Graft primary patency at 6 and 12 months
	Ticlopidine 500 mg/d versus placebo; venous bypass	**Benefits with ticlopidine** Graft primary patency at 6, 12 and 24 months **No difference among intervention groups** Graft primary patency at 1 month
	ASA 1500 mg/d versus prostaglandins (PGE1) 0.2 ng/kg/min; vein bypass	**No difference among intervention groups** Early occlusion
	Clopidogrel 75 mg/d plus ASA 75-100 mg/d versus ASA 75-100 mg/d	**Benefits with clopidogrel plus ASA** Primary patency in prosthetic bypasses at 24 months; amputation in prosthetic bypasses **No difference among intervention groups** Amputation of venous bypasses; mortality for venous or prosthetic bypasses; primary patency in venous bypasses at 24 months; minor, mild or major bleeding for prosthetic bypasses; major bleeding for venous bypasses **Higher risk with clopidogrel plus ASA** Minor or mild bleeding for venous bypasses

Continue...

Table 2. Continuation.

Review	Interventions	Main results
Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery[7]	VKA versus placebo	**Benefits with VKA** Occlusion in venous bypasses at 6 months; occlusion in prosthetic bypasses at 5 years; limb loss in venous bypasses at 5 years; limb salvage for venous bypasses at 6 months; limb loss for venous or prosthetic bypasses at 3, 6 and 24 months and 5 years; mortality for venous or prosthetic bypasses at 12 months **No difference among intervention groups** Occlusion in venous bypasses at 3, 12 and 24 months and 5 years; occlusion in prosthetic bypasses at 3, 6, 12 and 24 months; limb loss in venous or prosthetic bypasses at 3, 6, 12, 24 months and 5 years for prosthetic; mortality in venous or prosthetic bypasses at 3, 6, 12 and 24 months and 5 years
	VKA versus ASA 80 mg/d or ASA 1000 mg/d plus DIP 225 mg/d	**Benefits with VKA** Occlusion in venous bypasses at 3, 6, 12 and 24 months **Benefits with ASA plus DIP** Occlusion in prosthetic bypasses at 6, 12 and 24 months **No difference among intervention groups** Occlusion in prosthetic bypasses at 3 months
	LMWH (enoxaparin) 40 mg versus UFH 5000 IU (intraoperative)	**Benefits with LMWH** Occlusion in venous or prosthetic bypasses at 10 and 30 days **No difference among intervention groups** Occlusion in venous or prosthetic bypasses at 24 hours
	LMWH (dalteparin) 2500 IU versus ASA 900 mg/d plus DIP 300 mg/d	**Benefits with LMWH** Occlusion in venous or prosthetic bypasses at 6 and 12 months
	LMWH (dalteparin) 5000 IU versus placebo	**No difference among intervention groups** Occlusion in venous or prosthetic bypasses at 1, 3 and 12 months
	UFH 5000 IU versus antithrombin 1500 IU	**Benefits with UFH** Intraoperative occlusion of venous or prosthetic bypasses. **No difference among intervention groups** Occlusion in venous or prosthetic bypasses at 1 month
	LMWH (enoxaparin) 40 mg/d versus dextran 2500 ml plus heparin 5000 IU	**No difference among intervention groups** Early occlusion in venous or prosthetic bypasses

Continue...

Table 2. Continuation.

Review	Interventions	Main results
Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion after peripheral endovascular treatment[8]	ASA 50-330 mg/d plus DIP 75-400 mg/d versus placebo	**Benefits with ASA (330 mg)/DIP** Occlusion/restenosis at 6 months **No difference found among interventions** Occlusion/ restenosis at 1, 3 and 6 months (other doses) and 12 months; amputation, mortality and bleeding at the puncture site at 1 month **Higher risk with ASA (1000 mg/d) plus DIP** Gastrointestinal side effects at 12 and 24 months
	ASA 150-990 mg/d plus DIP 225-400 mg/d versus VKA	**No difference found** Occlusion/restenosis at 1, 3, 6, 12, 24 and 36 months
	Clopidogrel 75 mg/d plus ASA 100 mg/d versus LMWH (dalteparin) 5000 IU followed by warfarin	**No difference found** Occlusion/restenosis at 24 hours and 1, 6, 12 and 18 months **Higher risk with LMWH followed by warfarin** Major bleeding
	Ticlopidine 1000 mg/d versus VKA	**No difference found** Occlusion/restenosis at 12 months **Higher risk with ticlopidine** Gastrointestinal side effects
	Cilostazol 200 mg/d plus ASA 100 mg/d versus ticlopidine 200 mg/d plus ASA 100 mg/d	**Benefits with cilostazol plus ASA** Occlusion/restenosis at 36 months. **No difference found** Occlusion/restenosis at 12 and 24 months; amputation, mortality and side effects at 36 months
	LMWH (therapeutic nadroparin) plus ASA 200 mg/d versus UFH (heparinization followed by ASA)	**Benefits with LMWH versus UFH** Occlusion/restenosis at 3 weeks and 3 and 6 months (femoropopliteal arteries); occlusion/restenosis at 12 months for patients with critical ischemia **No difference found among interventions** Occlusion/restenosis at 3 weeks and 3 and 6 months (arteries of the pelvis); pseudoaneurysm hematoma and amputation
	LMWH (dalteparin) 2500 IU/d plus ASA 100 mg/d versus ASA 100 mg/d	**Benefit with LMWH plus ASA** Occlusion/restenosis at 12 months for critical ischemia **No difference found among interventions** Occlusion/restenosis at 12 months for intermittent claudication

ASA = acetylsalicylic acid, VKA = vitamin K antagonists, DIP = dipyridamole, LMWH = low molecular weight heparin, UFH = unfractionated heparin, AMI = acute myocardial infarction, PGE1 = prostaglandin E1.

ANTIPLATELET AGENTS FOR PREVENTING THROMBOSIS AFTER PERIPHERAL ARTERIAL BYPASS SURGERY

The purpose of the review[8] was to evaluate the effects of antiplatelet agents for preventing thrombosis in patients who underwent femoropopliteal or femorodistal bypass surgery. The outcomes included graft patency and treatment complications. Sixteen randomized controlled trials (RCTs) (total of 5,683 participants) were included. The main findings were as follows.

Acetylsalicylic acid (ASA) or ASA plus dipyridamole (DIP) versus placebo or nothing, for venous bypass or prosthetic bypass

Primary venous graft patency: benefit through treatment with ASA or ASA plus DIP for outcomes at 12 months (odds ratio, OR: 0.69; 95% confidence interval, CI: 0.48 to 0.99; 2 RCTs; 642 patients); no difference among intervention groups at 1 or 3 months (OR: 0.85; 95% CI: 0.54 to 1.35; 2 RCTs; 342 patients) or 6 or 24 months (OR: 1.03; 95% CI: 0.32 to 3.28; 2 RCTs; 620 patients).

Primary prosthetic graft patency: benefit through treatment with ASA or ASA plus DIP for outcomes at 1 month (OR: 0.14; 95% CI: 0.04 to 0.51; 3 RCTs; 157 patients), 3 or 6 months (OR: 0.21; 95% CI: 0.11 to 0.41; 4 RCTs; 122 patients) or 9 or 12 months (OR: 0.19; 95% CI: 0.1 to 0.36; 4 RCTs; 122 patients).

No differences were found among the groups for the following outcomes: mortality (evaluated in 4 RCTs with 799 patients); limb amputation (evaluated in 1 RCT with 148 patients); gastrointestinal symptoms (evaluated in 6 RCTs with 952 patients); severe bleeding (evaluated in 2 RCTs with 598 patients); mild bleedings (evaluated in 1 RCT with 148 patients); or wound or graft infection (evaluated in 1 RCT with 549 patients).

ASA or ASA plus DIP versus pentoxifylline, for venous bypass or prosthetic bypass

Gastric intolerance: benefit through use of pentoxifylline (OR: 18.04; 95% CI: 5.07 to 64.17; 1 RCT; 118 patients).

No differences were found among the groups for the following outcomes: primary graft patency at 1, 3, 6 or 12 months, mortality, limb amputation, gastric bleeding and dizziness (evaluated in 1 RCT with 118 patients).

ASA plus DIP versus indobufen, for venous bypass or prosthetic bypass

No differences were found among the groups for the following outcomes: primary graft patency at 1, 3, 6, 9 or 12 months (evaluated in 1 RCT with 112 patients).

ASA or ASA plus DIP versus vitamin K antagonists (VKA), for venous bypass or prosthetic bypass

No differences were found among the groups for the following outcomes: primary graft patency at 3, 6, 12 or 24 months and limb amputation (evaluated in 2 RCTs with 2,781 patients); or cardiovascular events and mortality (evaluated in 1 RCT with 2,690 patients).

ASA plus DIP versus low molecular weight heparin (LMWH), for venous bypass or prosthetic bypass

Mortality: benefit through treatment with ASA plus DIP (OR: 0.18; 95% CI: 0.04 to 0.86; 1 RCT; 200 patients).

No differences were found among the groups for the following outcomes: primary graft patency at 6 or 12 months (evaluated in 1 RCT with 200 patients).

Ticlopidine versus placebo, for venous bypass

Primary venous graft patency: benefit through use of ticlopidine at 6 months (OR: 0.26; 95% CI: 0.11 to 0.63; 1 RCT; 243 patients) or 12 or 24 months (OR: 0.37; 95% CI: 0.21 to 0.67; 1 RCT; 243 patients); no difference among the intervention groups at 1 month (OR: 3.0; 95% CI: 0.12 to 74.37; 1 RCT; 243 patients).

ASA versus prostaglandin (E1), for venous bypass

Early occlusion: no difference among the intervention groups (evaluated in 1 RCT with 100 patients).

ASA versus naftidrofuryl

No differences were found among the groups for the following outcomes: primary graft patency, dizziness, gastric bleeding and mortality (evaluated in 1 RCT with 99 patients).

Clopidogrel plus ASA versus ASA alone

Primary prosthetic bypass patency: benefit through use of clopidogrel plus ASA for outcomes at 24 months (OR: 0.53; 95% CI: 0.32 to 0.88; 1 RCT; 253 patients).

Amputation in prosthetic bypass: benefit through use of clopidogrel plus ASA (OR: 0.44; 95% CI: 0.21 to 0.91; 1 RCT; 253 patients).

Minor bleeding in venous bypass: benefit through use of ASA (OR: 2.46; 95% CI: 1.33 to 4.53; 1 RCT; 598 patients).

Mild bleeding in venous bypass: benefit through use of ASA (OR: 5.75; 95% CI: 1.26 to 26.17; 1 RCT; 598 patients).

No differences were found among the groups for the following outcomes: amputation for venous bypass and primary venous bypass patency at 24 months (evaluated in 1 RCT with 598 patients); mortality for venous or prosthetic bypasses (evaluated in 1 RCT with 851 patients); minor bleeding for prosthetic bypass, mild bleeding for prosthetic bypass and major bleeding for prosthetic bypass (evaluated in 1 RCT with 253 patients); or major bleeding for venous bypass (evaluated in 1 RCT with 598 patients).

Conclusions from this review

Treatment with ASA or ASA plus DIP had a positive effect on the patency of patients undergoing venous and prosthetic bypass

surgery, especially on prosthetic bypasses, with benefit for outcomes at 1, 3, 6, 9 and 12 months. For venous bypass, the benefit was observed only for the 12-month endpoint. However, this superiority needs further investigation.

A single study evaluated the effect of ticlopidine versus placebo in venous bypass surgery. The results showed improvements at 6, 12 and 24 months after treatment. Thus, the only antiplatelet agent with better effect on venous bypass patency was ticlopidine.

The association of clopidogrel plus ASA versus ASA alone, which was evaluated in a single study, did not show any favorable effects for treatment with ASA plus Clopidogrel for outcomes at 24 months in venous bypass surgery, but favorable results were reported for prosthetic bypass surgery.

The results from this review need to be carefully interpreted since many of the analyses were obtained from a single study and with different dosages.

ANTITHROMBOTIC AGENTS FOR PREVENTING THROMBOSIS AFTER INFRAINGUINAL ARTERIAL BYPASS SURGERY

This review[9] aimed to determine the efficacy of antithrombotic agents in patients with peripherical arterial disease (intermittent claudication and critical ischemia) who underwent femoropopliteal or femorodistal bypass surgery. Fourteen RCTs (total of 4,970 participants) were included. The main findings were as follows.

VKA versus placebo

Occlusions in venous bypass surgery: lower number of occlusions (benefit) through treatment with VKA for outcomes at 6 months (OR: 0.4; 95% CI: 0.17 to 0.96; 3 RCTs; 143 patients); no differences among the groups for outcomes at 3 or 12 months (OR: 0.75; 95% CI: 0.49 to 1.14; 4 RCTs; 650 patients) or 24 months or 5 years (OR: 1.0; 95% CI: 0.71 to 1.4; 3 RCTs; 568 patients).

Occlusions in prosthetic bypass surgery: lower number of occlusions (benefit) through treatment with VKA for outcomes at 5 years (OR: 0.43; 95% CI: 0.26 to 0.73; 2 RCTs; 140 patients); no differences among the groups for outcomes at 3 or 6 months (OR: 0.87; 95% CI: 0.2 to 2.82; 1 RCT; 33 patients) or 12 or 24 months.

Limb loss in venous bypass surgery: benefit through treatment with VKA for outcomes at 5 years (OR: 0.29; 95% CI: 0.14 to 0.6; 2 RCTs; 179 patients); no differences among the intervention groups for outcomes at 3, 6, 12 or 24 months.

No differences were found among the groups for the following outcomes: limb loss in prosthetic bypass surgery at 3, 6 or 12 months (evaluated in 1 RCT with 33 patients) or 24 months or 5 years; or mortality in venous or prosthetic bypass surgery at 3, 6 or 12 months (evaluated in 2 RCTs with 268 patients) or 24 months or 5 years.

VKA versus ASA or ASA plus DIP

Occlusions in venous bypass surgery: lower number of occlusions (benefit) through treatment with VKA for outcomes at 3 months (OR: 0.65; 95% CI; 0.46 to 0.92; 2 RCTs; 1,637 patients), 6 or 12 months (OR: 0.65; 95% CI: 0.49 to 0.85; 2 RCTs; 1,640 patients) or 24 months (OR: 0.59; 95% CI: 0.46 to 0.76; 2 RCTs; 1,640 patients).

Occlusions in prosthetic bypass surgery: lower number of occlusions (benefit) through treatment with ASA plus DIP for outcomes at 6 months (OR: 1.46; 95% CI: 1.08 to 1.98; 1 RCT; 1,104 patients) or 12 or 24 months (OR: 1.41; 95% CI: 1.11 to 1.8; 1 RCT; 1,104 patients); no differences among the intervention groups at 3 months.

LMWH versus unfractionated heparin (UFH)

Occlusions in venous or prosthetic bypass surgery: lower number of occlusions (benefit) through treatment with LMWH in outcomes at 10 or 30 days (OR: 0.54; 95% CI: 0.33 to 0.9; 2 RCTs; 507 patients); no differences among the intervention groups at 24 hours.

LMWH versus ASA plus DIP

Occlusions in venous or prosthetic bypass surgery: lower number of occlusions (benefit) through treatment with LMWH in outcomes at 6 or 12 months (OR: 0.52; 95% CI: 0.29 to 0.96; 1 RCT; 300 patients).

LMWH versus placebo

Occlusions in venous or prosthetic bypass surgery: no differences among the intervention groups in outcomes at 1, 3 or 12 months (evaluated in 1 RCT with 207 patients).

UFH versus antithrombin

Occlusions in venous or prosthetic bypass surgery: lower number of occlusions (benefit) through UFH in the intraoperative period (OR: 55.0; 95% CI: 1.86 to 1622.6; 1 RCT; 13 patients); no differences among the intervention groups at one month.

LMWH versus dextran plus heparin

Early graft occlusion: no differences among the intervention groups (evaluated in 1 RCT with 277 patients) for venous or prosthetic bypasses.

Conclusion from this review

This review suggested that the effectiveness of antithrombotic medications depends on the type of graft used (venous or prosthetic).

Patients undergoing venous bypass surgery are likely to benefit more from VKA than from platelet inhibitors, while patients undergoing prosthetic bypass surgery are likely to benefit more

from antiplatelets (ASA) than from VKA. To support this information and rule out divergences, studies that are more homogenous, with larger samples and detailed descriptions of the participants' characteristics, are needed.

Regarding treatment with LMWH versus UFH, the results were marginal and further studies with more patients are needed, for better comparisons.

For LMWH versus ASA plus DIP, better patency was found in the LMWH group, but this advantage was observed for patients with critical ischemia and not for patients with claudication. Further studies are needed in order to confirm these results.

ANTIPLATELET AND ANTICOAGULANT DRUGS FOR PREVENTION OF RESTENOSIS/REOCCLUSION AFTER PERIPHERAL ENDOVASCULAR TREATMENT

This review[10] evaluated whether any antithrombotic drug was more effective in preventing restenosis or reocclusion after endovascular treatment, in comparison with any antithrombotic drug, no treatment, placebo or vasoactive drugs. Twenty-two RCTs (3,529 participants in total) were included. The main findings were as follows.

ASA plus DIP versus placebo

Occlusions/restenosis: lower numbers of occlusions/restenosis (benefit) through treatment with ASA 330 mg at 6 months (OR: 0.4; 95% CI: 0.19 to 0.87; 1 RCT; 133 patients). No differences were found with regard to immediate occlusion or primary occlusion at 1, 3 or 6 months (including with different doses of 330 mg) or 12 months.

Occlusions/restenosis with high or low doses of ASA plus DIP: no differences among the intervention groups at 1 month (OR 1.45; 95% CI: 0.63 to 3.35; 3 RCTs; 748 patients) or 3, 6, 12 or 24 months.

Gastrointestinal side effects: higher number of side effects through treatment with high doses of ASA plus DIP at 12 or 24 months (OR: 1.85; 95% CI: 1.15 to 2.98; 2 RCTs; 575 patients).

No differences were found among the groups for the following outcomes: amputations, mortality and bleeding at a puncture site at 1 month (evaluated in 1 RCT with 223 patients).

ASA plus DIP versus VKA

Occlusions/restenosis: no differences among the intervention groups at 1, 3, 6, 12, 24 or 36 months (evaluated in 2 RCTs with 289 patients).

Clopidogrel plus ASA versus LMWH followed by warfarin

Occlusions/restenosis: no differences among the intervention groups at 24 hours or 1, 6, 12 or 18 months (evaluated in 1 RCT with 103 patients).

Risks of major bleeding: higher for treatment with LMWH followed by warfarin (OR: 0.08; 95% CI: 0.01 to 0.63; 1 RCT; 103 patients).

Ticlopidine versus VKA

Occlusions/restenosis: no differences among the intervention groups at 12 months (evaluated in 1 RCT with 197 patients).

Side effects: higher number of side effects through use of ticlopidine (OR: 6.48; 95% CI: 2.27 to 20.55; 1 RCT; 103 patients). Treatment was suspended for 34% of the patients due to gastrointestinal side effects.

Cilostazol plus ASA versus ticlopidine plus ASA

Occlusions/restenosis: lower numbers of occlusions/restenosis (benefit) through treatment with cilostazol plus ASA for outcomes at 36 months (OR: 0.4; 95% CI: 0.19 to 0.83; 1 RCT; 127 patients); no differences among groups with outcomes at 12 or 24 months.

No differences were found among the groups for the following outcomes: amputations, mortality and side effects, all with a follow-up of 36 months (evaluated in 1 RCT with 127 patients).

LMWH (nadroparin) plus ASA versus UFH plus ASA

Occlusions/restenosis: lower numbers of occlusions/restenosis (benefit) through treatment with LMWH (nadroparin) at 3 weeks (OR : 0.3; 95% CI: 0.13 to 0.68; 1 RCT; 110 patients), 3 months (OR: 0.32; 95% CI: 0.15 to 0.7; 1 RCT; 100 patients) or 6 months (OR : 0.16; 95% CI: 0.07 to 0.4; 1 RCT; 110 patients) for femoropopliteal arteries; or 12 months for patients with critical ischemia (OR: 0.15; 95% CI: 0.06 to 0.42; 1 RCT; 79 patients). No differences in occlusions/restenosis were found at 3 weeks or 3 or 6 months for pelvic arteries.

No differences were found among the groups for the following outcomes: hematoma < 10 cm, pseudoaneurysms at 3 weeks or amputations at 6 months (evaluated in 1 RCT with 172 patients).

LMWH (dalteparin) plus ASA versus ASA alone

Occlusions/restenosis: lower numbers of occlusions/restenosis (benefit) through treatment with LMWH plus ASA at 12 months for patients with critical ischemia (OR: 0.15; 95% CI: 0.06 to 0.42; 1 RCT; 79 patients). This benefit was not observed for patients with intermittent claudication (OR: 1.73; 95% CI: 0.97 to 3.08; 1 RCT; 196 patients).

Conclusions from this review

The authors concluded that there was limited evidence to suggest that occlusions/restenosis after six months of endovascular treatment were reduced through use of antiplatelet drugs, in comparison with placebo/controls.

The best evidence points to use of dipyridamole plus ASA, cilostazol plus ASA and low molecular weight heparin (with or without ASA).

Cilostazol plus ASA was superior to ticlopidine, and LMWH plus ASA was superior to ASA, in assessing restenosis/occlusion at 12 months after the start of intervention.

The clinical trials included in this systematic review were small, and the side effects could not be consistently evaluated.

A single study[11] evaluated the use of ASA plus clopidogrel compared with LMWH plus warfarin, but without evidence of superiority for either of the treatments. Use of ASA plus clopidogrel seems to have off-label indications mainly in the United States. RCTs evaluating use of ASA plus clopidogrel for acute coronary syndrome showed significant reductions in cardiovascular deaths (AMI or stroke), but they showed that this treatment led to increased risk of major bleeding.

DISCUSSION

This study included three Cochrane systematic reviews.[8-10] No evaluation using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) criteria was done in any of the reviews included in this study. This evaluation is now mandatory for publication of systematic reviews in the Cochrane Library.

The results in **Table 2** can be used for guidance for healthcare professionals and managers, but it needs to be borne in mind that future studies may substantially change the results that have been published so far.

For patients revascularized with prostheses, there was a benefit from use of ASA plus clopidogrel, and especially from use of ASA alone or ASA plus DIP. This benefit was not observed in relation to venous grafts.[8]

For venous bypass surgery, the best results were observed through use of ticlopidine. For both venous and prosthetic bypass surgery, the results need to be carefully interpreted because they were based on few studies.[8]

Patients undergoing venous bypass surgery are likely to benefit more from VKA than from platelet inhibitors. Comparing use of LMWH versus use of ASA plus DIP, better results were found in the LMWH group, but these results were observed in patients with critical ischemia and not in patients with claudication. Further studies are needed to confirm these results.

Patients undergoing prosthetic bypass surgery are likely to benefit more from antiplatelet (ASA) than from VKA.[9]

For patients undergoing endovascular procedures, the best results came from use of ASA plus DIP, from cilostazol plus ASA and from LMWH. Cilostazol plus ASA was superior to ticlopidine; and LMWH plus ASA was superior to ASA.

CONCLUSION

This study included three Cochrane systematic reviews that provided evidence regarding use of antiplatelets and anticoagulants in lower-limb revascularization in patients with lower-limb PAD. Patients who underwent venous or prosthetic bypass surgery were included, as well as patients who received endovascular treatments.

We noticed that patients undergoing prosthetic graft revascularization presented better outcomes through use of antiplatelet agents. Patients undergoing venous graft revascularization showed better outcomes through use of anticoagulants. In patients undergoing endovascular treatment, use of both antiplatelet and anticoagulant medication proved to be beneficial.

However, the lack of use of the GRADE approach in the reviews included compromised the certainty of our evaluation of the evidence. Updates to these reviews are needed in order to assess the implications of these treatments for clinical practice, among patients with PAD.

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Address for correspondence:
Silfayner Victor Mathias Dias
Av. Cascata, 123
Jardim Maria Izabel — Marília (SP) — Brasil
CEP 17515-300
Tel. (+55 11) 94440-3464
E-mail: silfayner@gmail.com

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General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.

10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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