ISSN 1516-3180

São Paulo Medical Journal/Evidence for Health Care, 2016 october 6; 134(6):469-557

São Paulo Medical Journal

EVIDENCE FOR HEALTH CARE

Medline, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/ Sciences Edition (impact factor 0.955) and EBSCO Publishing

December 1 - Volume 134 - Number 6

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- Prevalence of vitamin B12 deficiency in type 2 diabetic patients using metformin

Cross-sectional study:

- Cutoffs and cardiovascular risk factors associated with neck circumference among community-dwelling elderly adults

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ORGANIZATION

Founded in 1932, a bimonthly publication of the Associação Paulista de Medicina
e-mail: revistas@apm.org.br

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Desktop publishing: Zeppelini Editorial (www.zeppelini.com.br).
Listed in: Medline, Lilacs, SciELO, Science Citation Index Expanded and Journal Citation Reports/Sciences Edition (impact factor 0.588) and EBSCO publishing.
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• One-year subscription for the year 2016: individual US$ 165; institutional US$ 230.

Scientific Council

Diretoria Executiva da Associação Paulista de Medicina (Triênio 2014-2017)

Knowing for whom the bell tolls: acting locally and thinking globally. Brazil, Latin America and the Global Burden of Diseases, 2015

Sabendo por quem os sinos dobram: atuando localmente e pensando globalmente. Brasil, América Latina e a carga global de doenças, 2015

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"No man is an Iland, intire of it selfe; every man is a peece of the Continent, a part of the maine; if a Clod bee washed away by the Sea, Europe is the lesse, as well as if a Promontorie were, as well as if a Mannor of thy friends or of thine owne were; any mans death diminishes me, because I am involved in Mankinde; And therefore never send to know for whom the bell tolls; It tolls for thee" – John Donne (1572-1623) Devotions upon Emergent Occasions

The Global Burden of Diseases, Injuries and Risk Factors (GBD) study is an initiative from the Institute for Health Metrics and Evaluation of the University of Washington, with unrestricted grants from the Melinda and Bill Gates Foundation. The GBD study has been developing two concepts to enable geographical and temporal trend comparisons. These are the number of years of life lost (YLLs) and number of years of life lived with disability (YLDs). Combination of these two indicators reveals the number of disability-adjusted life-years (DALYs). Moreover, the GBD study is publishing data relating to risk factors. A more detailed description of these indexes can be found in the special issue of The Lancet dated October 7, 2016. The data presented below are based on the results of the articles addressing YLL,[1] YLD,[2] DALY[3] and risk factors.[4]

The world can be divided geopolitically in several ways, but there is one grouping that is applied by most agencies: the category of Latin American and Caribbean countries. It represents 50 independent countries and a few colonies with 640 million inhabitants. However, two-thirds of this population and three-quarters of the gross product is concentrated in four countries: Brazil, Mexico, Colombia and Argentina. We will discuss the differences in the GBD indexes among these four countries (**Table 1**).

MORTALITY

The ranking of the five most important causes of YLLs shows how important the burden of coronary heart disease and stroke is, both worldwide and in these four countries, for both sexes. The coronary heart disease (CHD) values were similar among the four countries, but the risk of death due to stroke was significantly higher in Brazil for men and women than in Argentina, Colombia and Mexico.

Two particular causes in Latin American and the Caribbean countries are violence and road traffic, which are ranked within the top five causes of deaths, in contrast to the global data. The road traffic death rate was highest in Brazil (24 per 100,000) followed by Colombia (17), Mexico (17) and Argentina (14). However, the proportion of pedestrian deaths was greater in Colombia (62%) followed by Mexico (44%), Brazil (35%) and Argentina (28%). Violence is a characteristic of Latin American and Caribbean countries: the age-adjusted homicide rates

(per 100,000) in 2015 were 34 in Colombia, 28 in Brazil and 17 in Mexico, but only 6 in Argentina. Another four Latin American and Caribbean countries had higher rates that these: Venezuela, El Salvador, Honduras and Guatemala. The proportion of homicides due to firearms was significantly different: Colombia (78%), Brazil (69%), Mexico (59%) and Argentina (50%).

Another difference observed was the importance of chronic kidney disease (CKD) and diabetes in Mexico. The risk of death due to CKD in Mexico was three times higher than in Argentina, Brazil and Colombia.

YEARS LIVING WITH DISABILITY

Both globally and in these four Latin American and Caribbean countries, an impressive amount of time is lost through disability relating to back and neck disorders, sensory problems, anxiety and depression and skin complaints. However, in contrast to the other countries, diabetes appears as one of the greatest causes of YLDs in Mexico.

DALYS

DALYs are derived from a combination of YLLs and YLDs. They show that CHD is the most important cause in Brazil and Argentina, as also seen worldwide, and that it is the second biggest cause in Colombia and Mexico. Violence is the top cause in Colombia and diabetes leads the causes of DALYs in Mexico. Neck and back pain and psychiatric disorders have similar impact with regard to DALYs, compared with cardiovascular diseases.

RISK FACTORS

Hypertension is the most important risk factor globally, and in Brazil, Argentina and Colombia, but not in Mexico. The combination of obesity and diabetes is important in all Latin American and Caribbean countries, especially in Mexico, with an association with chronic kidney disease. Smoking was ranked second in the world and in Argentina, fourth in Brazil and fifth in Colombia. Alcohol use was classified as one of the five most important risk factors in Brazil, Colombia and Mexico.

WHAT IS NEW IN GBD 2015?

A relatively large amount of information about mortality and DALYs is available, but the impact of non-lethal conditions on increasing YLDs and DALYs deserves more attention from the Brazilian health authorities. São Paulo Medical Journal dedicated three editorials[5-7] and four articles[8-11] to the important topic of lumbar pain. Depression, anxiety and skin disorders need to be more appropriately ranked as priorities for research worldwide,

Table 1. Description of the causes of years of life lost (YLL), years of living with disability (YLD) and disability-adjusted life-years (DALY) for all countries and for Brazil, Argentina, Colombia and Mexico

Global	Brazil	Argentina	Colombia	Mexico
CHD	CHD	CHD	Violence	CHD
Stroke	Violence	LRI	CHD	CKD
LRI	Stroke	Stroke	Road injuries	Diabetes
NN pretem	Road injuries	Road injuries	Congenital	Violence
Diarrhea	NN pretem	Congenital	Stroke	Road injuries
Years of living with disability (YLD)				
Back and neck	Back and neck	Back and neck	Back and neck	Back and neck
Sensory problems	Depression	Depression	Sensory problems	Sensory problems
Depression	Sensory problems	Sensory problems	Depression	Diabetes
Iron	Anxiety	Skin	Skin	Skin
Skin	Skin	Anxiety	Anxiety	Iron
Disability-adjusted life-years (DALY)				
CHD	CHD	CHD	Violence	Diabetes
Stroke	Violence	Back & neck	CHD	CHD
LRI	Stroke	LRI	Back & neck	CKD
Back & neck	Road injuries	Stroke	Sensory problems	Back and neck
NN pretem	Back and neck	Depression	Depression	Sensory problems
Risk factors				
Hypertension	Hypertension	Hypertension	Hypertension	Diabetes
Smoking	Obesity	Smoking	Obesity	Obesity
Diabetes	Diabetes	Obesity	Diabetes	Hypertension
Obesity	Smoking	Diabetes	Alcohol use	Renal dysfunction
Childhood malnutrition	Alcohol use	Dyslipidemia	Smoking	Alcohol use

CHD = coronary heart disease; LRI = lower respiratory infection; CKD = chronic kidney disease; NN pretem = neonatal preterm disorders sensory disabilities.

and the focus of medical care needs to be shifted to primary care, such that it is not managed only by medical specialists.

WHAT ARE THE PRIORITIES FOR ARGENTINA, BRAZIL, COLOMBIA AND MEXICO?

In relation to the epidemiological profile of chronic diseases, GBD 2015 makes it possible to establish five priorities in Latin America and Caribbean countries:

1. Alcohol intake reduction: High alcohol consumption is strongly associated with car and motorcycle crashes. Latin America and Caribbean governments are notoriously lenient with regard to punishing individuals who drive under the influence of alcohol beverages. Moreover, deadly interpersonal violence is also related to alcohol abuse.[12,13]
2. Hypertension: Reduction of high blood pressure can reduce racial and social disparities regarding deaths due to cardiovascular diseases. In all countries, it is essential:
    1. to improve awareness, treatment and control of hypertension;
    2. to reduce sodium intake;
    3. to spread the use of automatic sphygmomanometer devices with greater precision and accuracy;[14,15]
    4. to deliver antihypertensive drugs free of charge (shifting from thiazides to chlorthalidone or indapamide); and
    5. to take special care of individuals with resistant hypertension, who account for 3% of the adult population.[16]
3. CHD secondary prevention: CHD is the leading cause of death, and the first cause of DALYs in Argentina and Brazil and the second one in Colombia and Mexico. The high prevalence rates of people with CHD implies to amplify national program addressing secondary prevention including smoking quitting and free delivery of aspirin, statins, and angiotensin-converting-enzyme (ACE) inhibitors.[17]
4. Obesity-diabetes prevention: The prevalence of overweight and obesity in Mexico has been increasing at an alarming rate, with high rates of adverse outcomes relating to diabetes. However, although it is easy to put forward proposals for curbing the obesity epidemic (reduction of calorie intake and increase of physical activity), such proposals are very ineffective. One strategy should be to focus on childhood, so as to avoid obesity among the next generation of teenagers and young adults.[18]
5. CKD screening: Renal failure in Mexico and Central America leads to high rates of DALYs. This is thought to be due to the high prevalence rate of diabetes in Mexico and of Mesoamerican nephropathy due to heat stress or intoxication with herbicides.[19,20] Although there is no consensus regarding CKD screening through determination of serum creatinine and urinary albumin, verification of the cost-effectiveness of early diagnosing of CKD is urged.[21,22]

CONCLUSION

The complexity of the "health-disease" process implies that there is a need to plan and think globally, while acting locally. The most important lesson is that there is only one island: the Earth. And also, the bell tolls for everyone.

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Sources of funding: Not declared
Conflict of interest: Not declared

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Prevalence of vitamin B12 deficiency in type 2 diabetic patients using metformin: a cross-sectional study

Prevalência de deficiência de vitamina B12 em pacientes diabéticos do tipo 2 usando metformina: um estudo transversal

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KEY WORDS:
Diabetes mellitus.
Vitamin B 12 deficiency.
Metformin.
Proton pump inhibitors.
Histamine H2 antagonists.

PALAVRAS-CHAVE:
Diabetes mellitus.
Deficiência de vitamina B 12.
Metformina.
Inibidores da bomba de prótons.
Antagonistas dos receptores histamínicos H2.

ABSTRACT

CONTEXT AND OBJECTIVE: The prevalence of vitamin B12 deficiency varies from 5.8% to 30% among patients undergoing long-term treatment with metformin. Because of the paucity of data on Brazilian patients, this study aimed to determine the frequency of B12 deficiency and related factors among Brazilian patients with type 2 diabetes mellitus (T2DM) using metformin.

DESIGN AND SETTING: Cross-sectional study at a public university hospital.

METHODS: Patients with T2DM and a control group of non-diabetics were included. Serum B12 levels were measured and biochemical B12 deficiency was defined as serum levels < 180 pg/ml. Associations between B12 deficiency and age, duration of T2DM, duration of use and dosage of metformin, and use of proton pump inhibitors (PPIs) or histamine H2 antagonists were determined.

RESULTS: 231 T2DM patients using metformin (T2DM-met) and 231 controls were included. No difference in the frequency of PPI or H2-antagonist use was seen between the groups. B12 deficiency was more frequent in the T2DM-met group (22.5% *versus* 7.4%) and this difference persisted after excluding PPI/H2-antagonist users (17.9% *versus* 5.6%). The factors that interfered with serum B12 levels were PPI/H2-antagonist use and duration of metformin use ≥ 10 years. Use of PPI/H2-antagonists was associated with B12 deficiency, with an odds ratio of 2.60 (95% confidence interval, 1.34-5.04).

CONCLUSIONS: Among T2DM patients, treatment with metformin and concomitant use of PPI/H2-antagonists are associated with a higher chance of developing B12 deficiency than among non-diabetics.

RESUMO

CONTEXTO E OBJETIVO: A prevalência de deficiência de vitamina B12 varia de 5,8% a 30% nos pacientes em tratamento a longo prazo com metformina. Devido à escassez de dados em pacientes brasileiros, este estudo determinou a frequência de deficiência de B12 e fatores relacionados em pacientes brasileiros com diabetes *mellitus* tipo 2 (DM2) usando metformina.

TIPO DE ESTUDO E LOCAL: Estudo transversal em hospital público universitário.

MÉTODOS: Pacientes com DM2 e um grupo controle de não diabéticos foram incluídos. Os níveis séricos de vitamina B12 foram dosados e deficiência bioquímica de B12 foi definida como níveis séricos < 180 pg/ml. Foi investigada a associação entre deficiência de B12 e idade, duração do DM2, duração do uso e dose de metformina, uso de inibidores de bomba de prótons (IBP) ou antagonistas dos receptores histamínicos H2 (antagonistas-H2).

RESULTADOS: 231 pacientes DM2 usando metformina (DM2-met) e 231 controles foram incluídos. Não houve diferença na frequência de uso de IBP/antagonistas-H2 entre os grupos. Deficiência de B12 foi mais frequente no grupo DM2-met (22,5% *versus* 7,4%) e essa diferença persistiu após exclusão dos usuários de IBP/antagonistas-H2 (17,9% *versus* 5,6%). Fatores que interferiram nos níveis séricos de B12 foram: uso de IBP/antagonistas-H2 e duração do uso de metformina ≥ 10 anos. O uso de IBP/antagonistas-H2 associou-se com deficiência de B12, com um risco relativo de 2,60 (95% intervalo de confiança, 1,34-5,04).

CONCLUSÕES: Considerando pacientes com DM2, o tratamento com metformina e uso concomitante de IBP/antagonistas-H2 estão associados com maior chance de desenvolver deficiência de B12 quando comparado aos não diabéticos.

INTRODUCTION

Metformin is considered to be the first-choice therapy for type 2 diabetes mellitus (T2DM) due to its efficacy in decreasing insulin resistance and cardiovascular risk.[1-4] Despite its known efficacy and favorable safety profile, there are non-negligible side effects such as vitamin B12 malabsorption.[5]

Vitamin B12, or cyanocobalamin, is found in foods of animal origin and has an important role in deoxyribonucleic acid (DNA) synthesis and in many biochemical reactions. The prevalence of B12 deficiency varies from 5.8% to 30% among patients undergoing long-term treatment with metformin.[6-13] Identifying B12 deficiency is clinically relevant since several conditions may be associated with this, such as megaloblastic anemia, neuropathy, cognitive dysfunction, memory loss, irritability, dementia, extrapyramidal signs and increased risk of osteoporosis.[14-17]

To date, only one study has estimated the prevalence of B12 deficiency among Brazilian T2DM patients using metformin.[11] That study was conducted in southern Brazil and found that B12 deficiency occurred in 6.9% of the patients.

OBJECTIVE

Because of the reported association between metformin use and B12 deficiency, its high morbidity and the paucity of data among Brazilian patients, the present study aimed to determine the frequency of biochemical B12 deficiency and its related factors among T2DM patients using metformin who were followed up at an endocrinology outpatient clinic in a public university hospital in southeastern Brazil.

METHODS

Study design

This was a cross-sectional study at a public university hospital.

Study population

T2DM patients were recruited from the outpatient endocrinology clinic at a public university hospital, over a 24-month period. A substantial proportion of these patients are referred to our hospital by primary care centers in the same municipality. The control group consisted of non-diabetic individuals, who were matched for sex and age and were recruited in the same outpatient clinic and at the Blood Donation Center of this hospital. All subjects entered the study after they had given their written informed consent, in accordance with a protocol approved by the Ethics Committee (protocol number: 0019.0.258.000I).

The inclusion criteria for the patients' group were that they needed to have T2DM, be older than 18 years of age and have been using metformin for at least three years. Patients and controls were excluded from the study if they had a history of partial or total gastrectomy, malabsorptive diseases, B12 supplementation during the three months prior to enrollment in the study or documented pernicious anemia, or if they were vegetarians or pregnant women.

Methods

During a regular scheduled visit to the outpatient clinic or to the Blood Donation Center, the subjects were informed about the study. Subsequently, after they had agreed to participate and had signed the informed consent, a medical interview was conducted and blood samples were collected. Demographic data such as age and sex were noted, as well as the following parameters: T2DM duration, metformin use (duration and dose), use of proton pump inhibitors (PPIs) or type 2 histamine receptor blockers (H2-antagonists), smoking habits and alcohol consumption. Smoking habits were divided into current and non-smokers. Patients were defined as "alcohol consumers" if their average consumption was one to two drinks per day. Laboratory data included serum B12 levels, hemoglobin (Hb) and mean corpuscular volume (MCV). We did not obtain dietary histories, nor did we document the prevalence of neuropathy.

Serum B12 levels were quantified using a chemiluminescent enzyme immunoassay (Access Immunoassay Systems, Beckman Coulter Inc., CA, USA). The reference values were 180-914 pg/ml, with an analytical sensitivity of 50 pg/ml. Biochemical B12 deficiency was defined as serum levels < 180 pg/ml. Anemia was defined as Hb < 13 g/dl for males and < 12 g/dl for females, based on WHO guidelines.[18] Macrocytosis was characterized as mean corpuscular volume (MCV) > 100 fl.[19]

Statistical analysis

Power analysis indicated that 231 patients were required to determine a 20% prevalence of B12 deficiency in T2DM patients (with 95% confidence interval, CI, of ± 5%). The results are presented as medians with interquartile range for continuous variables and count with proportions for categorical variables. Associations between B12 deficiency and categorical variables were determined using the chi-square test. Associations between continuous variables and B12 deficiency were determined by means of the Mann-Whitney U test. The Spearman rank correlation coefficient (r_s) was used to evaluate the correlation between numerical variables. A multivariate analysis using logistic regression was performed to identify factors independently associated with B12 deficiency. The covariates chosen for the multivariate model were known or hypothesized biological factors that would affect B12 levels. Analyses were performed using SPSS version 11.0 for Windows (SPSS, Inc. Chicago, IL, USA).

RESULTS

Participants' characteristics

A total of 462 subjects were included from June 2012 to June 2014, comprising 231 T2DM patients who were using metformin (T2DM-met) and 231 controls. The patients' and controls' characteristics are shown in **Table 1**.

In comparing the T2DM-met and control groups, no difference in the frequency of PPI or H2-antagonist use was seen. However, the median serum B12 level was lower in the T2DM group (272 versus 348 pg/ml; P < 0.001) (**Figure 1**). Considering the T2DM-met patients, B12 levels were significantly lower in PPI or H2-antagonist users compared with T2DM-met patients that did not use PPI or H2-antagonist (210 versus 292 pg/ml; P = 0.002) (**Figure 2**).

After excluding PPI or H2-antagonist users among the patients and controls, the serum B12 levels were still significantly lower in the T2DM-met group (292 versus 358 pg/ml; P = 0.001).

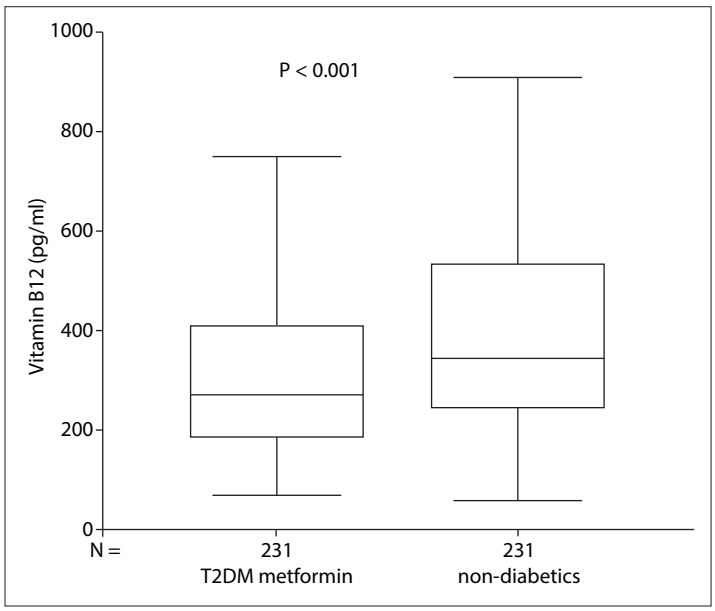

Figure 1. Vitamin B12 serum levels in diabetic patients using metformin and non-diabetics.

Frequency of vitamin B12 deficiency

Biochemical B12 deficiency was more frequent in the T2DM-met group than in the control group (22.5% versus 7.4%; P < 0.001).

After excluding PPI or H2-antagonist users among the patients and controls, the frequency of B12 deficiency continued to be significantly higher in the T2DM-met group (17.9% versus 5.6%; P = 0.001).

Factors associated with vitamin B12 deficiency

Table 2 shows key comparisons of variables between patients with and without B12 deficiency. Comparing patients with and without B12 deficiency, there were no differences with regard to age, sex, T2DM duration or metformin use (duration and dose). PPI or H2-antagonist use was more frequent among the B12-deficient patients (40.4% versus 20.7%; P = 0.004). A weak negative correlation between serum B12 levels and the duration of metformin use (r = -0.18; P = 0.006) was seen. However, no correlation was found between serum B12 levels and the daily dose of metformin.

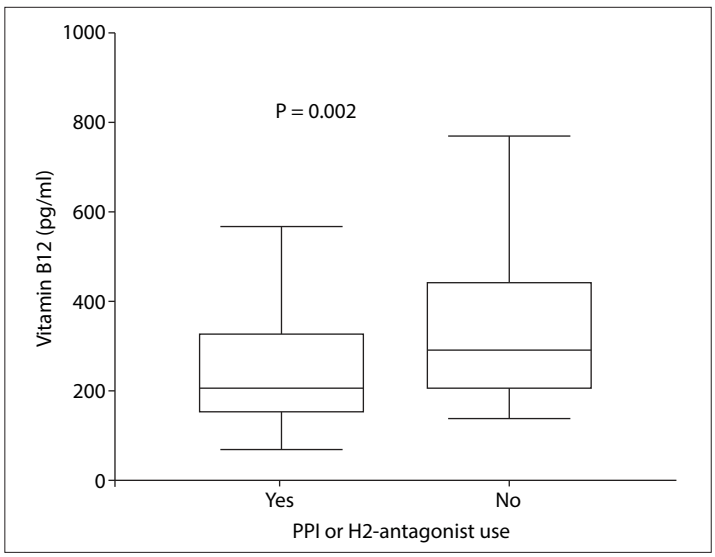

Figure 2. Vitamin B12 serum levels in diabetic patients using metformin with or without proton pump inhibitors or H2-antagonist use.

Table 1. General characteristics of patients and controls

	T2DM-met (n = 231)	Controls (n = 231)	P-value
Age (years)	60 (55-68)	62 (54-69)	0.870
Sex (male, %)	n = 64 (27.7%)	n = 77 (33.3%)	0.225
Proton pump inhibitor or H2-antagonist use (%)	n = 58 (25.1%)	n = 70 (30.3%)	0.213
Serum vitamin B12 (pg/ml)	272 (186-417)	348 (248-534)	< 0.001
Vitamin B12 deficiency (%)	n = 52 (22.5%)	n = 17 (7.4%)	< 0.001

Data are expressed as medians (with interquartile range) for continuous variables and as counts (with proportions) for categorical variables. T2DM-met: Type 2 diabetes mellitus patients using metformin.

Table 2. Clinical and laboratory characteristics of patients with and without vitamin B12 deficiency

Characteristic	Vitamin B12 deficiency (-) (n = 179)	Vitamin B12 deficiency (+) (n = 52)	P-value
Age (years)	61.0 (55.0-67.0)	62.5 (57.0-70.0)	0.339
Sex (male, %)	24.6%	17.2%	0.230
Diabetes duration (years)	11 (6-20)	13 (10-18)	0.413
Duration of metformin use (years)	8 (5-10)	10 (7-13)	0.088
Daily dose of metformin (mg)	1,700 (1,500-2,550)	2,000 (1,500-2,550)	0.252
H2-antagonist or PPI use (%)	n = 37 (20.7%)	n = 21 (40.4%)	0.004
Anemia (%)	n = 56 (31.3%)	n = 12 (23.1%)	0.378
MCV (fl)	89.0 (87.4-92.6)	89.4 (87.3-99.4)	0.153
Macrocytosis (%)	n = 1 (0.6%)	n = 5 (9.6%)	< 0.001

Data are expressed as medians (with interquartile range) for continuous variables and as counts (with proportions) for categorical variables. PPI = proton pump inhibitor, MCV = mean corpuscular volume.

When the duration of metformin use was classified as < 10 years or ≥ 10 years, the prevalence of biochemical B12 deficiency was higher in the T2DM-met group ≥ 10 years (28.0% versus 17.7%; P = 0.04).

The factors that significantly interfered with serum B12 levels after multiple regression were PPI or H2-antagonist use and duration of metformin use ≥ 10 years. PPI or H2-antagonist use was associated with biochemical B12 deficiency (odds ratio [OR] 2.60; 95% CI: 1.34–5.04).

Consequences of vitamin B12 deficiency

Among the T2DM-met patients with B12 deficiency (n = 52), anemia was seen in 23.1% (n = 12). The prevalence of anemia did not differ between T2DM-met patients with and without B12 deficiency (23.1% versus 31.3%; P = 0.378). Considering all the T2DM-met patients with anemia (n = 68), three (4.4%) had macrocytic, 60 (88.2%) had normocytic and five (7.4%) had microcytic anemia.

Macrocytosis was significantly more frequent in the B12-deficient group (9.6% versus 0.6%; P < 0.001). However, the MCV did not differ between T2DM-met patients with and without B12 deficiency (89.4 versus 89.0; P = 0.153).

In analyzing only the T2DM-met patients with B12 deficiency, macrocytic anemia was only found in two patients, while three others had macrocytosis with normal red blood cell counts.

DISCUSSION

The serum levels of vitamin B12 were significantly lower in the T2DM-met group than in the control group, even after excluding PPI and H2-antagonist users. Similarly, the PPI and H2-antagonist users (T2DM-met and control groups) had lower serum B12 levels than patients who did not use these medications. These findings suggest that PPI/H2-antagonists and metformin have an additive effect with regard to promoting vitamin B12 malabsorption. Both of these categories of medications are widely used by patients, sometimes without medical prescription, and their use should not be overlooked. When clinically indicated, their use should be monitored because of the possibility of vitamin B12 malabsorption and its consequences.

The prevalence of B12 deficiency among T2DM-met patients was significantly higher than in the control group matched for to sex and age (22.5% versus 7.4%). Previous studies have found similar results, but the mechanisms involved in this deficiency are not well established.[7,20,21] Some evidence has supported the hypothesis that metformin-induced B12 malabsorption is due to enhanced bacterial overgrowth or to modification of the intestinal microbiota.[14,22,23] In addition, metformin interferes with calcium-dependent membrane action and with the secretion of B12-intrinsic fator *per se*. Since the B12-intrinsic factor complex uptake by the ileal cell surface receptor is a calcium-dependent process, both mechanisms possibly cause a decrease in B12 absorption.[5,24]

One factor significantly associated with B12 deficiency was found: simultaneous use of metformin with PPI or H2-antagonists. The association between B12 deficiency and PPI or H2-antagonist use supports the notion that reduced gastric acidity has a role as a predisposing factor for B12 malabsorption. Both of these drugs decrease acid secretion by the parietal cells, and gastric acid produced by these cells is required for cleavage of vitamin B12 from dietary sources.[25-27] Although several other studies have reported similar findings,[25-27] this association is not always present.[6,12,13,28,29] For example, Nervo et al.[11] did not find any association between serum B12 levels and use of omeprazole. Nevertheless, considering the possible additive effect between metformin and PPI or H2-antagonists in relation to B12 absorption, caution should be used when these drug classes are combined.

Concerning the duration of metformin use, there was a non-significant trend towards an association between B12 deficiency and longer duration of metformin use (≥ 10 years versus < 10 years). There have been reports of decreased serum B12 levels occurring as early as three to four months after the beginning of metformin treatment.[24,30] However, according to most reports, vitamin B12 deficiency occurs only after five to ten years of metformin use.[20,31] This delay in the onset of B12 deficiency may be due to the significant hepatic stores of this vitamin.[28,32]

To date, only one study has estimated the prevalence of B12 deficiency among Brazilian patients with T2DM using metformin.[11] The study was conducted by Nervo et al. in the southern region of Brazil and included 144 T2DM patients using metformin. They found that B12 deficiency occurred in 6.9% of their patients. Similarly to our study, it was conducted in a single center and with a hospital-based sample. However, there was no control group and they did not find any association between serum B12 levels and use of PPI.[11] Several factors might explain the low frequency of B12 deficiency found by Nervo et al.[11] It is well known that protein intake in southern Brazil is higher than in the southeastern region.[33] Also, a lower cutoff was used for the definition of B12 deficiency (169 pg/ml), which might have underestimated the frequency of this vitamin deficiency. Finally, the median duration of metformin use was four years, which is half the median duration found in our study.

Vitamin B12 deficiency is related to a number of comorbidities, such as peripheral neuropathy and megaloblastic anemia.[34] The prevalence of anemia and mean corpuscular volume did not differ between T2DM-met patients with and without B12 deficiency (23.1% versus 31.3% and 89.4 fl versus 89.0 fl, respectively). The high rates of anemia in this particular sample might be related to several factors. The older age of our patients is one possible explanation, since it has been reported that the prevalence of anemia is higher in older age groups.[35] Also, normocytic anemia was the most common presentation (83.3% and 89.2%, respectively) in both groups of patients, with and without B12 deficiency. Considering normocytic anemia, chronic inflammation must be highlighted as a possible cause, since it is associated with the release of proinflammatory cytokines.[36] A population-based cohort study carried out in São Paulo, Brazil, that only included individuals older than 65 years showed that 35.1% of the cases of persistent anemia could be attributed to chronic inflammation.[37] Although chronic kidney disease is known to be a cause of anemia, we did not include patients with estimated glomerular filtration rate less than 60 ml/min. However, other coexisting conditions, such as thalassemic or sickle cell trait and iron deficiency may explain not only anemia but also the lack of correlation between B12 deficiency and MCV.[38-40] In this circumstance, neutrophil hypersegmentation is an important clue to the presence of B12 deficiency.[40] Macrocytosis was present in only 9.6% of T2DM-met patients with B12 deficiency. Similarly, de Groot-Kamphuis et al.[12] showed that biochemical B12 deficiency does not predict the emergence of megaloblastic anemia. This leads to an important caveat: there may be a discrepancy between B12 deficiency and its clinical manifestations, such that the deficiency of B12 that would be needed to cause macrocytosis is mild compared with the deficiency that is needed to cause to anemia. The clinical importance of mild, preclinical cobalamin deficiency is still uncertain. Therefore, well-designed studies are needed to clarify whether monitoring of serum B12 levels in T2DM-met patients brings any real benefit and is cost-effective.

There were several limitations to our study. First, external validity is a concern, because this was a single-center, hospital-based sample and it may have differed significantly from the typical diabetic patients in the community. Second, considering the continental size of Brazil and the differences in dietary habits, our findings may not reflect the reality of other regions. Third, the cross-sectional design limited us to describing the association between metformin use and B12 deficiency. Additional longitudinal studies are needed in order to prove any causality in this association. Fourth, the serum levels of methylmalonic acid and homocysteine were not assessed. Both of these are B12 metabolic intermediaries and their serum concentrations (in both of them) or urinary concentrations (methylmalonic acid) are elevated in cases of B12 deficiency, due to decreased metabolic rates. For this reason, assessment of these markers is helpful when serum B12 levels are equivocal or borderline, thus serving as biochemical markers that reflect intracellular B12 deficiency.[34,41,42] Measuring homocysteine and methylmalonic acid would be helpful in distinguishing patients who have been incorrectly classified with regard to B12 deficiency (false positives and false negatives). Finally, because of the difficulty in excluding potential causes of peripheral neuropathy other than diabetes and B12 deficiency, the prevalence of neuropathy and its possible association with B12 deficiency were not evaluated.

CONCLUSIONS

This cross-sectional study conducted in southeastern Brazil confirms that in patients with T2DM, long-term treatment with metformin and concomitant use of PPI/H2-antagonists are associated with higher chances of developing biochemical vitamin B12, in comparison with non-diabetics.

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Sources of funding: None
Conflict of interests: None

Date of first submission: July 11, 2015
Last received: November 18, 2015
Accepted: November 21, 2015

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DOI: 10.1590/1516-3180.2016.0068160416

Body Dysmorphic Symptoms Scale for patients seeking esthetic surgery: cross-cultural validation study

Escala de Sintomas da Dismorfia Corporal para pacientes que buscam a cirurgia plástica: estudo de validação cultural

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KEY WORDS:
Body dysmorphic disorders.
Body image.
Surgery, plastic.
Psychiatry.
Therapeutics.

PALAVRAS-CHAVE:
Transtornos dismórficos corporais.
Imagem corporal.
Cirurgia plástica.
Psiquiatria.
Terapêutica.

ABSTRACT

CONTEXT AND OBJECTIVE: Rhinoplasty is one of the most sought-after esthetic operations among individuals with body dysmorphic disorder. The aim of this study was to cross-culturally adapt and validate the Body Dysmorphic Symptoms Scale.

DESIGN AND SETTING: Cross-cultural validation study conducted in a plastic surgery outpatient clinic of a public university hospital.

METHODS: Between February 2014 and March 2015, 80 consecutive patients of both sexes seeking rhinoplasty were selected. Thirty of them participated in the phase of cultural adaptation of the instrument. Reproducibility was tested on 20 patients and construct validity was assessed on 50 patients, with correlation against the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder.

RESULTS: The Brazilian version of the instrument showed Cronbach's alpha of 0.805 and excellent inter-rater reproducibility (intraclass correlation coefficient, ICC = 0.873; P < 0.001) and intra-rater reproducibility (ICC = 0.939; P < 0.001). Significant differences in total scores were found between patients with and without symptoms (P < 0.001). A strong correlation (r = 0.841; P < 0.001) was observed between the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder and the Body Dysmorphic Symptoms Scale. The area under the receiver operating characteristic curve was 0.981, thus showing good accuracy for discriminating between presence and absence of symptoms of body dysmorphic disorder. Forty-six percent of the patients had body dysmorphic symptoms and 54% had moderate to severe appearance-related obsessive-compulsive symptoms.

CONCLUSIONS: The Brazilian version of the Body Dysmorphic Symptoms Scale is a reproducible instrument that presents face, content and construct validity.

RESUMO

CONTEXTO E OBJETIVO: Rinoplastia é uma das operações mais procuradas por indivíduos com o transtorno dismórfico corporal. O objetivo deste estudo foi adaptar culturalmente e validar a Body Dysmorphic Symptoms Scale.

DESENHO E LOCAL: Estudo de validação cultural desenvolvido no ambulatório de cirurgia plástica de um hospital universitário público.

MÉTODOS: Oitenta pacientes consecutivos de ambos os gêneros que desejavam submeter-se à rinoplastia foram selecionados entre fevereiro de 2014 e março de 2015. Trinta pacientes participaram da fase de adaptação cultural do instrumento. A reprodutibilidade foi testada em 20 pacientes e a validade de construto em 50 pacientes, correlacionando-se a escala com a Yale-Brown Obsessive Compulsive Scale para transtorno dismórfico corporal.

RESULTADOS: A versão brasileira do instrumento mostrou alfa de Cronbach de 0,805 e excelente reprodutibilidade interobservador (coeficiente de correlação intraclasse, CCI = 0,873; P < 0,001) e intraobservador (CCI = 0,939; P < 0,001). Houve diferença significante entre os escores totais de pacientes com e sem sintomas (P < 0,001). Observou-se forte correlação (r = 0,841; P < 0,001) entre a Yale-Brown Obsessive Compulsive Scale para transtorno dismórfico corporal e a Body Dysmorphic Symptoms Scale. A área sob a curva característica de operação do receptor (ROC) foi de 0,981, revelando boa acurácia para discriminar a presença de sintomas para transtorno dismórfico corporal; 46% dos pacientes apresentaram sintomas do transtorno dismórfico corporal e 54% dos pacientes apresentaram sintomas obsessivo-compulsivos moderados a graves relacionados com a aparência.

CONCLUSÃO: A versão brasileira da Body Dysmorphic Symptoms Scale é um instrumento reprodutível que apresenta validade de face, conteúdo e construto.

INTRODUCTION

More than 221,000 rhinoplasty procedures (or nose operations) were performed worldwide in 2013, mainly among Caucasians; about 163,600 of these procedures were performed on women.[1] Rhinoplasty is often sought by young people between 13 and 34 years of age.[1-5] Patients between 13 and 19 years account for 5% of all surgical cosmetic procedures performed.[1,2] This shows the high level of social acceptance of esthetic surgery in general and of rhinoplasty in particular, as a means of physical enhancement in a culture in which physical attractiveness is highly valued, thus leading to greater concern regarding appearance based on an ideal standard body.[4] However, the social importance of physical appearance also makes it difficult to diagnose body dysmorphic disorder.[4]

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), body dysmorphic disorder can be described as preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to other people, and compulsive or repetitive behavior (e.g. checking one's appearance in a mirror, excessive grooming, skin picking and seeking reassurance) or mental acts (e.g. comparing one's appearance with that of others) in response to concerns regarding appearance. It causes clinically significant distress or impairment in important areas of functioning, with symptoms that are poorly explained by normal concerns regarding physical appearance or by concerns regarding body fat or weight, among individuals meeting diagnostic criteria for eating disorders. Body dysmorphic symptoms may be associated with muscle dysmorphia. Patients with body dysmorphic disorder may show different degrees of insight regarding their body.[4,6]

Rhinoplasty is one of the most sought-after esthetic surgical procedures. Typical candidates include people with ethnically characteristic noses, teenagers and individuals with body dysmorphic disorder,[3-5,7-11] which thus shows the social aspect of rhinoplasty. Rhinoplasty improves appearance through enhancing facial harmony. The inherent risks associated with the surgical process include respiratory problems, visible or palpable irregularities and dissatisfaction with the final outcome. Individuals with psychological or neurobiological vulnerability are more likely to show dissatisfaction with the surgical results, because their perception of the physical defect may be a symptom or contributory factor for development of a mental disorder.[3,4] Rhinoplasty is also one of the cosmetic surgical procedures most frequently involved in lawsuits.[5,7,9,10,12-14]

Despite indications of improvement in psychosocial wellbeing following rhinoplasty, the prevalence of body dysmorphic disorder in patients seeking this surgical procedure ranges from 12% to 33%[10,13,15-18] and 52%.[4] Although the prevalence of psychiatric disorders among rhinoplasty patients seems inconsistent in the literature and requests for rhinoplasty should not be considered to be a symptom of a psychiatric disorder, screening for psychological conditions in selecting candidates for surgery is essential for a successful surgical cosmetic outcome.[4,19-22]

Excessive concern for appearance may conceal psychopathological states that are not always easily identified and which may lead to iatrogenic and medico-legal problems if neglected.[20,22] The Body Dysmorphic Symptoms Scale is a specific instrument that measures psychopathological symptoms of body dysmorphic disorder.[23] It is a short and easy-to-administer scale that captures specific information about body dysmorphic symptoms. Thus, cross-cultural validation of this patient-reported outcome measurement may help in relation to rapid screening for and identification of body dysmorphic disorder. Psychological disorders may not only affect the emotional and social life of patients, but also influence their satisfaction with the results from surgery.[24,25]

OBJECTIVE

To translate into Brazilian Portuguese, culturally adapt and validate the Body Dysmorphic Symptoms Scale, by testing the psychometric properties, reproducibility and validity of the instrument, and to assess body dysmorphic disorder and levels of obsessive-compulsive symptoms among patients seeking esthetic surgery.

METHODS

This cross-cultural validation study was approved by our institution's Research Ethics Committee (approval no. 428.965/13) and was conducted in accordance with the Brazilian Ethical Review System for research involving human beings. It also conformed to the World Medical Association's Declaration of Helsinki (June 1964) and subsequent amendments. Written informed consent was obtained from all patients or their parents or legal representatives after the procedures had been fully explained to them and prior to their inclusion in the study; anonymity was assured.

Patients of both sexes at any age, seeking rhinoplasty and showing physical appearance associated with clinically significant subjective distress, were recruited at the plastic surgery outpatient clinic of a public university hospital in Brazil between February 2014 and March 2015. A psychologist with expertise in body dysmorphic disorder, who was also one of the authors of this study, performed the clinical assessment on all patients, in accordance with the descriptions in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).[6]

Patients who were unable to understand the interview questions, those with severe physical deformities as a result of obesity, bariatric surgery, tumors or other conditions, those with psychotic disorders or previous history of body dysmorphic disorder, and those who had undergone psychiatric or psychological treatment were not included in the study.

The traditional protocol for determining an adequate sample size based on power analysis is not useful when the primary hypothesis focuses on psychometric measurement properties.[26] A sample size of at least 50 and not more than 100 subjects is adequate for representing and evaluating the psychometric properties of social construct measurements.[26] Thus, a total of 80 consecutive patients who met the study criteria were selected, of whom 30 participated in the cultural adaptation of the scale; 20 were included in the reliability analysis on the final version of the instrument; and these 20, together with 30 different patients, participated in the construct validity assessment against the Brazilian-Portuguese version of the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder. No patient declined to participate.

The cultural adaptation, reliability and validity phases of the study followed the methodology of Guillemin et al.[27-29] and Gandek and Ware.[30]

The psychologist with expertise in body dysmorphic disorder also applied the cross-culturally validated Brazilian-Portuguese version of the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder to patients participating in the construct validity study.[31]

The Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder is a 12-item semi-structured clinician-rated instrument that is designed to measure severity of body dysmorphic disorder symptoms among individuals showing excessive preoccupation and subjective distress with physical appearance.[31] It is an outcome measurement for clinical studies and for treating body dysmorphic disorder.[32] The 12 items are rated on a 0-4 scale, where 0 indicates no symptom and 4 indicates extreme body dysmorphic symptoms. The first 10 items assess excessive preoccupation, obsessions and compulsive behavior associated with dissatisfaction with physical appearance. The first three items are based on the body dysmorphic disorder diagnostic criteria and assess preoccupation, impairment of overall functioning, and subjective distress, which is related both to excessive preoccupation and to compulsive behavior. Items 11 and 12 assess insight and avoidance, respectively. The total score is calculated as the sum of ratings for the 12 items, thus yielding a maximum score of 48.[31] The cutoff score of 19 for the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder has been correlated with sensitivity of 0.865 and specificity of 0.731.[31]

The Body Dysmorphic Symptoms Scale

The Body Dysmorphic Symptoms Scale is a 10-item self-report measurement of psychopathological symptoms of body dysmorphic disorder among people with excessive concern and anxiety about their physical appearance who seek cosmetic surgery.[23] The following are examples of the items: "Are you seriously concerned that one part of your body is defective?", "Do you avoid looking at yourself in the mirror to be less worried?" and "Do you try to hide or camouflage your defect with your hands, hair, makeup, or clothing?" Each item is answered "yes" or "no". The overall score is the sum of positive responses. High scores indicate the presence of psychopathological factors associated with dissatisfaction with body image and symptoms of body dysmorphic disorder.[23]

The present study was conducted after Dr. Perugi, the main author of the original version of the Body Dysmorphic Symptoms Scale,[23] granted us permission to translate, culturally adapt and validate the instrument for Brazilian Portuguese.

Translation

The Body Dysmorphic Symptoms Scale was translated from English into Brazilian Portuguese by two independent translators. Only one of the translators was informed about the study objectives, so as to achieve a conceptual rather than a literal translation of the scale. Both translations were evaluated by a multidisciplinary committee formed by two plastic surgeons, a psychiatrist and two psychologists with extensive experience of body image disorder and selection of candidates for cosmetic surgery. All items were checked by the multidisciplinary committee for possible mistakes made during the translation and were evaluated for content validity. A consensus Brazilian-Portuguese version of the instrument was then obtained by combining elements from both translations.[27]

Idiomatic, semantic, conceptual and cultural equivalences were considered during the translation phase. The consensus version in Brazilian Portuguese was then back-translated into English by two independent translators who were unaware of the original tool or purpose of the study. Both back-translated versions were evaluated and compared with the original one by the same multidisciplinary committee, in order to correct possible errors or discrepancies made during back-translation.[28] This analysis resulted in development of the consensus version of the Body Dysmorphic Symptoms Scale in Brazilian Portuguese, which was appropriately adapted to the linguistic and cultural context of the target population, while maintaining all the essential characteristics of the original instrument in English.[29]

Cross-cultural adaptation or pretesting

During the cultural adaptation phase, a psychologist with a doctoral degree and expertise in body dysmorphic disorder administered the consensus version of the Body Dysmorphic Symptoms Scale to the first 10 candidates for rhinoplasty and supervised a second psychologist during application of the instrument to the next 20 candidates. Interviews were conducted face to face. The cultural adaptation phase served to train the second psychologist for the inter-rater reliability phase.

The Body Dysmorphic Symptoms Scale was administered to 30 patients to test possible failures of the respondents to comprehend the items. After providing informed consent, the participants each had the opportunity to express their comprehension of the scale and suggest any changes that they considered necessary. All of the patients understood that the scale items were related to concerns and dissatisfaction with physical appearance.

In this phase, the face and content validity of the instrument were determined through a consensus reached by the multidisciplinary committee. Face validity evaluates whether the instrument measures what it was designed to measure and content validity relates to the degree to which each item is relevant in measuring the target content.[30,33] The final version (**Appendix 1**) was obtained when the patients, translators and healthcare professionals reached a consensus.[29,34]

Psychometric evaluation

After translation and cultural adaptation, the final version of the instrument was tested for reliability among 20 patients and for construct validity among the 20 patients together with 30 different patients, for a total of 50 patients.

Reliability

Test-retest reliability (reproducibility) is the ability of an instrument to produce stable or similar results from repeated administration when no change to the patient characteristics has occurred. It evaluates the extent to which variation in scores between assessments reflects real differences rather than random fluctuation.[30,33]

The instrument was assessed by means of test-retest procedures in three interviews conducted by two independent interviewers (two experienced psychologists). Twenty patients were interviewed by psychologist #1 and the interview was repeated three hours later on the same day by psychologist #2. Two weeks later, the instrument was administered to the same patients by psychologist #1 only. Inter and intra-rater reliability analyses were performed. This phase of testing was used to verify the precision of the instrument for measuring the properties for which it was designed.[28,29]

Validity

Construct validity is the process in which the correlation of a measurement with other variables is tested for theoretical consistency. In determining the construct validity, hypothesis testing indicates the direction and strength of the expected relationship.[30,33] Our hypothesis was that preoccupation with physical appearance and excessive levels of body investment, together with clinically significant distress, among patients seeking cosmetic surgery, may be associated with symptoms of body dysmorphic disorder, which may be present at different levels of severity. Construct validity was assessed among 50 patients (20 patients who participated in the reliability analysis together with 30 different patients) using convergent and discriminant validity analyses. Convergent validity was tested by correlating the Body Dysmorphic Symptoms Scale with the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder scores. Discriminant validity was determined by comparing the mean Body Dysmorphic Symptoms Scale scores of patients with and without body dysmorphic disorder symptoms.

A cutoff point for symptom severity and the corresponding sensitivity and specificity values were estimated through the receiver operating characteristic curve, which was constructed based on the clinical evaluation of body dysmorphic disorder, in accordance with the descriptions in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Statistical analysis

Cronbach's alpha was used to evaluate the internal consistency of the reliability of the instrument.

Test-retest reliability and convergent validity were estimated using Pearson's correlation coefficient (r) and the intraclass correlation coefficient (ICC).

Discriminant validity was determined using Student's t-test for independent samples.

A cutoff point for symptom severity and the corresponding sensitivity and specificity values were estimated through the receiver operating characteristic curve. The kappa coefficient was also calculated.

The Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA) and Stata 12 software (StatCorp, College Station, Texas, USA) were used for data analysis. All statistical tests were performed at a significance level of 5% ($P < 0.05$). Data were expressed as mean ± standard deviation (SD).

RESULTS

The Brazilian-Portuguese version of the Body Dysmorphic Symptoms Scale (**Appendix 1**) was administered to 80 patients. The flow diagram showing the initial recruitment and the final sample of patients is shown in **Figure 1**. The patients did not have any doubts about the items, which were considered easy to understand and clearly formulated. The mean time taken to respond to the questionnaire was five minutes.

Thirty-seven patients (37/80; 46%) met the diagnostic criteria for body dysmorphic disorder, according to the Body Dysmorphic Symptoms Scale, and 27 patients (27/50; 54%) showed moderate to severe appearance-related obsessive-compulsive symptoms.

The mean Body Dysmorphic Symptoms Scale score was 7.5 ± 1.0 (range, 6-9; $t = 12.3$; $P < 0.001$).

Overall, most patients were women (80%), Caucasians (75%) and single (58.8%). The mean age was 33.4 ± 11.8 years (range, 14-65); 55.1% reported spending three or more hours a day concerned about their physical appearance and 79% of patients reported that they began to experience body dissatisfaction during childhood and adolescence. Thus, the time that elapsed from the onset of body dissatisfaction to the patient's decision to seek cosmetic treatment was about 15 years. Also, 52.5% had completed high school education and 21% were semi-skilled workers.

The instrument showed good internal consistency (Cronbach's alpha = 0.805). All items contributed favorably towards the internal consistency of the scale (**Table 1**).

The corrected item-total correlation was greater than 0.4, except for items 2, 9 and 10, thus indicating that the consistency between item scores and the overall score of the instrument was acceptable (**Table 1**).

According to the Body Dysmorphic Symptoms Scale, 56 patients (70%) reported that they compulsively checked their appearance in a mirror; 54 (67.5%) often tried to camouflage the perceived defect with their hands, hair or excessive makeup; 65 (81.3%) had previously sought esthetic surgical procedures; 30 (37.5%) were dissatisfied with the results from the previous esthetic surgery; 56 (70%) showed self-referential perceptions due to exaggeration of the perceived defect; and 54 (67.5%) had poor insight regarding their perceived defects, believing that they had real physical deformities for which esthetic surgery was needed. Psychosocial impairment was identified in 25 patients (31.3%), who avoided affective and social relationships; while 33 patients (41.3%) avoided looking in the mirror, thus showing aversion to their own image. Six patients (7.5%) showed aggressive and violent behavior towards their relatives and friends, and 12 (15%) were so distressed that they were at the point of having suicidal thoughts.

The Body Dysmorphic Symptoms Scale demonstrated excellent inter-rater reliability (r = 0.909; ICC = 0.873; P < 0.001) and intra-rater reliability (r = 0.956; ICC = 0.939; P < 0.001), as seen in **Table 2**.

There were significant differences in Body Dysmorphic Symptoms Scale scores between patients with and without body dysmorphic symptoms (P < 0.001). Patients without body dysmorphic symptoms had significantly lower Body Dysmorphic Symptoms Scale scores than those with body dysmorphic symptoms (**Figure 2**).

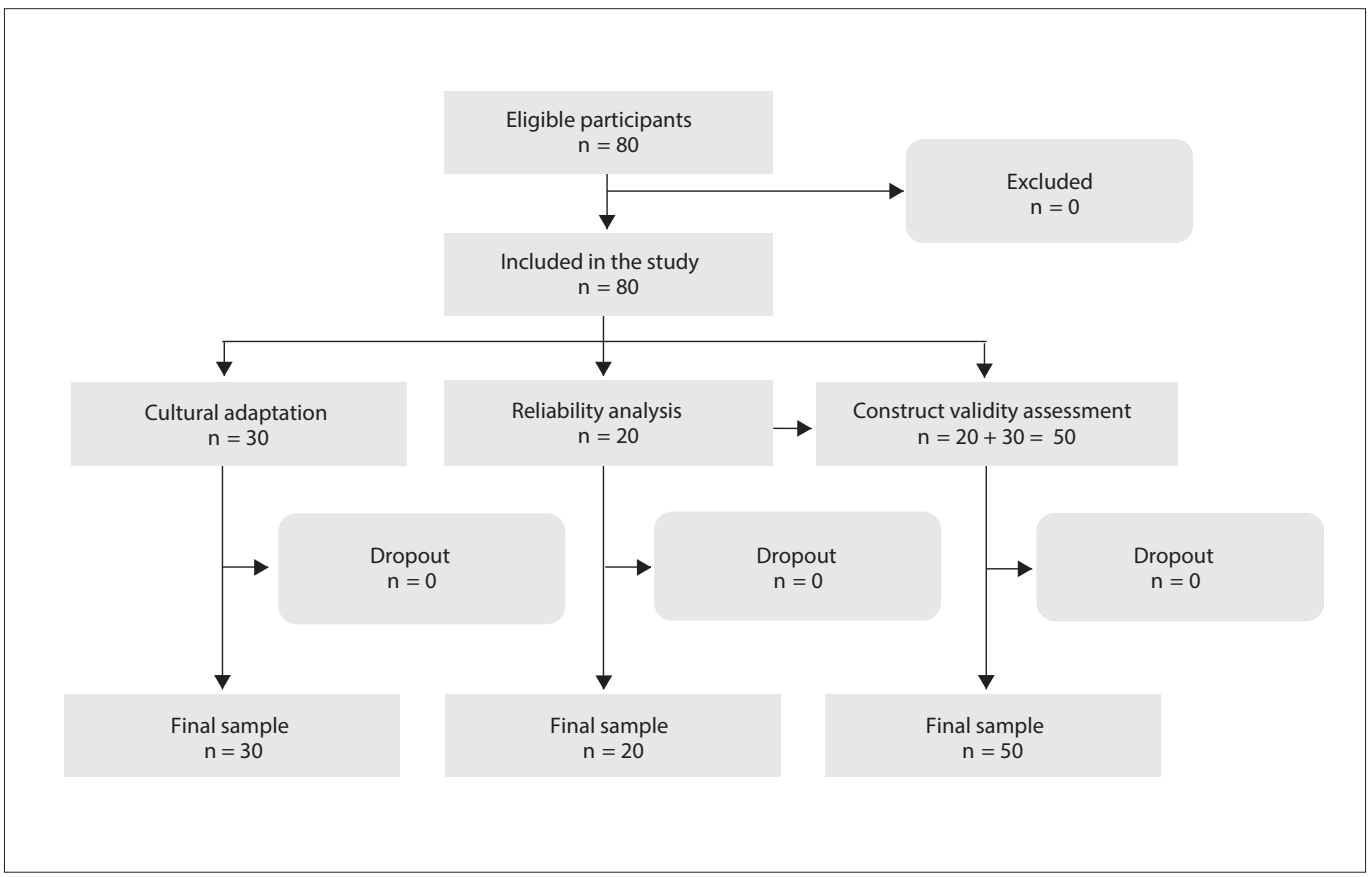

Figure 1. Flow diagram showing the initial recruitment and final sample of patients.

A strong positive correlation (r = 0.841; P < 0.001) was found between the Body Dysmorphic Symptoms Scale and the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder (**Figure 3**).

A cutoff score of 6 was determined for the Body Dysmorphic Symptoms Scale using the receiver operating characteristic curve (**Figure 4**); this was associated with sensitivity of 1.0 and specificity of 0.86. Scores of 6 and above indicate the presence of

Table 1. Internal consistency analysis for the Body Dysmorphic Symptoms Scale (n = 80)

Items Cronbach's alpha = 0.805		Corrected item-total correlation	Cronbach's alpha if item deleted
1	Are you seriously concerned that part of your body is not esthetically pleasing?	0.631	0.770
2	Do you perform long, detailed checking of yourself, carefully evaluating the part of your body that you do not like?	0.354	0.803
3	Do you completely avoid looking at yourself in the mirror and seeing this part that displeases you?	0.408	0.798
4	Do you believe that people are looking at you, especially at the part of your body that displeases you?	0.591	0.775
5	Do you try to hide the part of your body that concerns you by using makeup, clothing or other resources?	0.592	0.774
6	Do you believe that esthetic surgery can dramatically change your life, correcting the defect that concerns you?	0.450	0.792
7	Have you neglected or felt discouraged about performing your usual activities because of the defect that concerns you?	0.523	0.783
8	Have you previously received any treatments or undergone any surgery to correct this defect without obtaining satisfactory results?	0.587	0.775
9	Does this defect make you angry, impatient or aggressive, especially towards your relatives, friends or coworkers?	0.283	0.806
10	Are there are times when you feel so distressed with the defect that you see no meaning in life and wish to die?	0.370	0.799

Table 2. Inter and intra-rater reliability for the Body Dysmorphic Symptoms Scale

Reliability	Intraclass correlation	95% confidence interval	P-value
Intra-rater	0.939	[0.855; 0.975]	< 0.001
Inter-rater	0.873	[0.712; 0.947]	< 0.001

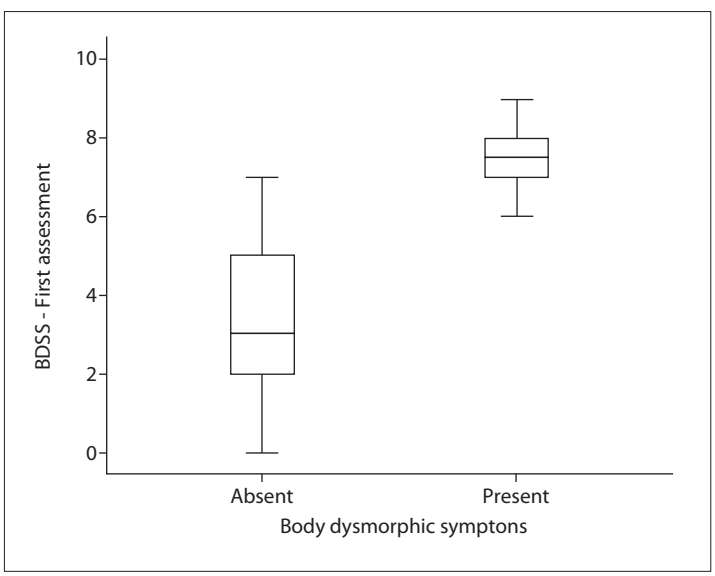

Figure 2. Distribution of patients with and without body dysmorphic symptoms, according to the Body Dysmorphic Symptoms Scale (BDSS).

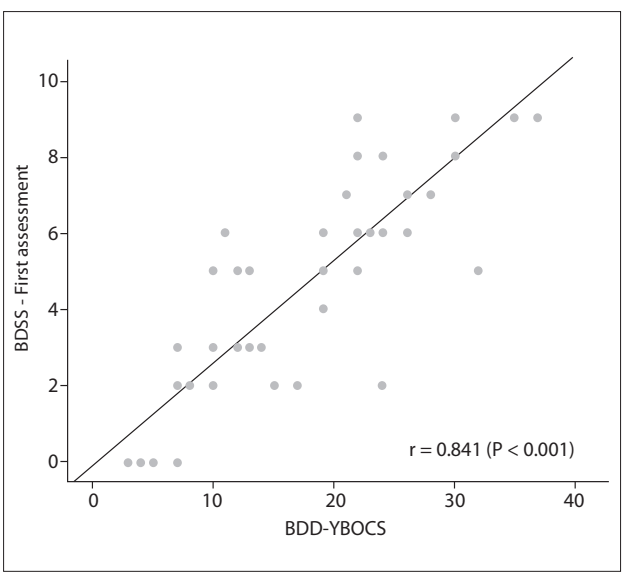

Figure 3. Correlation between the Body Dysmorphic Symptoms Scale (BDSS) and the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder (BDD-YBOCS).

psychopathological characteristics that were associated with dissatisfaction with body image and symptoms of body dysmorphic disorder. The area under the receiver operating characteristic curve (ROC) was 0.981, thus suggesting that the Body Dysmorphic Symptoms Scale presented very good accuracy for discriminating between presence and absence of body dysmorphic symptoms.

The kappa coefficient between the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder (for a cutoff point of 19) and the Body Dysmorphic Symptoms Scale (for a cutoff point of 6) was 0.721, thus showing that there was strong agreement between the cutoff points for severe body dysmorphic symptoms.

The final Brazilian version of the instrument was named Body Dysmorphic Symptoms Scale-Unifesp-EPM or BDSS-Unifesp-EPM (Escala de Sintomas da Dismorfia Corporal - Unifesp-EPM, in Brazilian Portuguese).

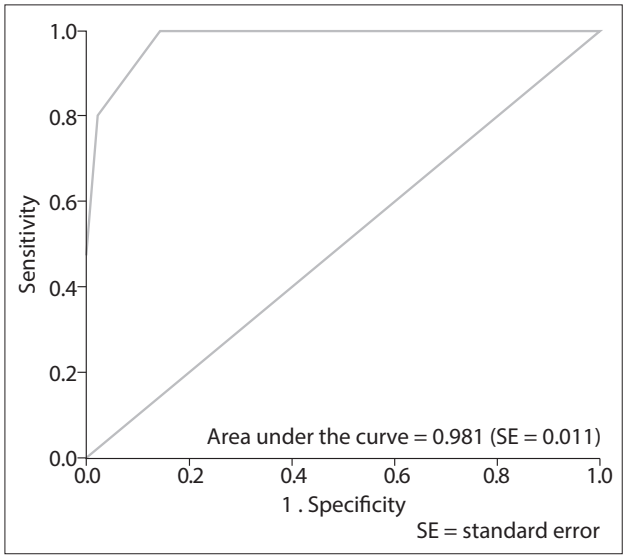

Figure 4. Receiver operating characteristic curve for the Brazilian version of the Body Dysmorphic Symptoms Scale.

DISCUSSION

The Body Dysmorphic Symptoms Scale was translated into Brazilian Portuguese, culturally adapted and tested for reliability and construct validity. The general guidelines for cross-cultural adaptation of instruments were followed in order to ensure the quality of the cross-culturally adapted Brazilian version of the Body Dysmorphic Symptoms Scale (**Appendix 1**). Healthcare professionals who were experienced in managing patients with body dysmorphic disorder and rhinoplasty patients participated in the evaluation on this instrument.[27]

The Brazilian-Portuguese version of the Body Dysmorphic Symptoms Scale was validated in a population sample of 80 cosmetic surgery patients and showed excellent internal consistency, test-retest reliability and intra-rater reliability. However, it was not possible to compare these results with those of the original scale or with the scientific literature because the psychometric properties of the scale were not assessed by the authors of the instrument,[23] or by Mühlbauer et al.,[35] who proposed a modification of item 6 regarding unrealistic expectations and called the instrument the Modified Pisa Body Dysmorphic Symptoms Scale.

The psychometric properties of the Body Dysmorphic Symptoms Scale were evaluated for the first time in the present study. A cutoff score of 6, which was determined using the receiver operating characteristic curve, was able to discriminate between patients with body dissatisfaction and those with body dysmorphic disorder. The cutoff score of 6 was associated with sensitivity of 1.0 and specificity of 0.86, thus indicating that the Brazilian version of the Body Dysmorphic Symptoms Scale is a specific instrument for identifying body dysmorphic symptoms. This tool may be used preoperatively, in screening the candidates for esthetic surgery procedures.

In order to assess construct validity, it is recommended in the literature that the instrument should be compared against a similar tool, so as to evaluate the relationships of comparable constructs with similar operational concepts.[30] Thus, the Body Dysmorphic Symptoms Scale was compared against the cross-culturally validated Brazilian-Portuguese version of the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder, which measures the degree of dissatisfaction with a given physical feature and the severity of body dysmorphic symptoms.[31] The strong correlation between the two instruments indicates that the Body Dysmorphic Symptoms Scale was able to measure the severity of body dysmorphic symptoms, and that both instruments are able to detect patterns of neurocognitive deficits (obsessive thoughts and compulsive behavior) that are present in body dysmorphic symptoms. However, the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder is a semi-structured, longer and more complex tool that is designed to be applied by professionals who do not have much background within mental health, with regard to selecting patients who are seeking esthetic and surgical procedures, whereas the Body Dysmorphic Symptoms Scale is a short and easy-to-administer scale that also captures specific information about body dysmorphic symptoms.

The assessment of discriminant validity showed that there was a significant difference in mean Body Dysmorphic Symptoms Scale scores between patients with and without body dysmorphic symptoms. A larger number of patients reported high scores for items 1, 2, 4, 5 and 6, thus showing dissatisfaction with their body image with regard to compulsive behavior (e.g. checking their appearance in a mirror and excessive grooming) and mental acts (e.g. comparing their appearance with that of others) in combination with subjective distress, which are the factors that most

interfere with the overall functioning of patients with body dysmorphic disorder. The levels of subjective distress and psychosocial impairment that are associated with physical appearance may be the most important parameters to be assessed among cosmetic surgery patients.[22] About 81% of the patients believed that cosmetic surgery would solve all their problems relating to the distress caused by their physical appearance (item 6), and 67% of the patients were convinced that a perceived defect was really present and had fixed ideas about their perception (item 1). This belief appeared to be related to exaggeration of the defect rather than to a delusional perception, but in 70% of the patients it enhanced self-referential ideas (item 4).[4,19]

Items 2, 9 and 10 of the Body Dysmorphic Symptoms Scale presented corrected item-total correlation values of less than 0.4, which suggested that these items had a weak correlation with the other items of the scale. This may have related to the presence of body dysmorphic symptoms (as described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, in the diagnostic criteria for body dysmorphic disorder A and B) in this population (item 2), and may have indicated that the patients in this study did not have any auto or hetero-aggressive behavior (items 9 and 10). In fact, 70% of the patients responded positively to item 2 and only 7.5% and 15% responded positively to items 9 and 10, respectively, which were the items with the lowest scores in the instrument.

The prevalence of body dysmorphic symptoms was 46% in the study sample (according to the Body Dysmorphic Symptoms Scale), and 54% of the patients had moderate to severe appearance-related obsessive-compulsive symptoms, according to the Yale-Brown Obsessive Compulsive Scale for Body Dysmorphic Disorder. Most of the patients began to experience body dissatisfaction during childhood and adolescence, and were spending three or more hours a day on appearance-related concerns and behavior, and showed higher levels of subjective distress. The fact that 58.8% of the patients were single, 52.5% had only completed secondary education and 21% were semi-skilled workers may suggest that the disorder caused psychosocial impairment over time among these patients. Picavet et al.[13] identified moderate to severe appearance-related obsessive-compulsive symptoms in 33% of their patients seeking rhinoplasty, also using the Yale-Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder. The high prevalence of body dysmorphic symptoms found in the present study is similar to those found in previous studies.[3,4]

The participants' mean age was 33 years at the time of the interview, which was not associated with the onset of body dysmorphic symptoms and thus was consistent with the literature.[1-5,13,23] The time that elapsed from the onset of body dissatisfaction to the patient's decision to seek cosmetic treatment (about 15 years) was very similar to that of patients seeking mental health treatment, thus showing the different behaviors and profiles of this population.[36] In other words, patients with body dysmorphic disorder may take different paths; those who seek cosmetic surgery will not necessarily seek psychiatric treatment later.[36] Most of the patients were women and Caucasians, which is in agreement with previous studies.[1,4]

The limitations of this study include its small sample size and the fact that most of the patients were women. In addition, the study was conducted on a clinical population that usually has greater disease severity, given that higher rates of disease severity have been observed in clinical samples than in the general population.[37-39] This may have affected the cutoff score on the Body Dysmorphic Symptom Scale, which may be different in other situations. Further studies with a larger number of patients and involving multiple centers are necessary in order to evaluate and compare the prevalence of body dysmorphic symptoms among patients seeking plastic surgery, so as to enable development of care and treatment strategies for this population.

CONCLUSION

The cross-culturally validated Brazilian-Portuguese version of the Body Dysmorphic Symptoms Scale is a reliable instrument that shows face, content and construct validity. It is a useful tool that can contribute towards screening candidates with body dysmorphic disorder for cosmetic surgery. The prevalence of moderate to severe body dysmorphic and appearance-related obsessive-compulsive symptoms is high among patients seeking esthetic rhinoplasty.

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Sources of funding: None
Conflicts of interest: None

Date of first submission: March 16, 2016
Last received: April 6, 2016
Accepted: April 16, 2016

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Appendix 1. Translated version of the Body Dysmorphic Symptoms Scale

1. Você está seriamente preocupado(a) de que uma parte do seu corpo é defeituosa?	
( ) sim	( ) não
2. Você se observa no espelho de forma atenta e repetida?	
( ) sim	( ) não
3. Você evita olhar-se no espelho para não ficar tão preocupado(a)?	
( ) sim	( ) não
4. Você se preocupa que outras pessoas possam estar observando, falando ou zombando de seu defeito?	
( ) sim	( ) não
5. Você tenta esconder ou camuflar seu defeito com as mãos, maquilagem ou roupas?	
( ) sim	( ) não
6. Você acredita que uma cirurgia plástica poderá mudar radicalmente a sua vida, corrigindo o defeito que lhe incomoda?	
( ) sim	( ) não
7. Você negligenciou suas atividades normais por causa do defeito?	
( ) sim	( ) não
8. Este defeito lhe causa raiva, impaciência, agressividade, principalmente no relacionamento com parentes, amigos ou colegas de trabalho?	
( ) sim	( ) não
9. Nesses momentos, você quebra algum objeto, dá murros ou chuta paredes e portas?	
( ) sim	( ) não
10. Seu desespero é tamanho a ponto de desejar morrer, ferir-se ou prejudicar-se em função desse desespero?	
( ) sim	( ) não

Medication and nutritional supplement use before and after bariatric surgery

Utilização de medicamentos e suplementos nutricionais antes e após a cirurgia bariátrica

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KEY WORDS:
Bariatric surgery.
Comorbidity.
Pharmaceutical preparations.
Gastric bypass.
Obesity, morbid.

PALAVRAS-CHAVE:
Cirurgia bariátrica.
Comorbidade.
Preparações farmacêuticas.
Derivação gástrica.
Obesidade mórbida.

ABSTRACT

CONTEXT AND OBJECTIVE: Bariatric surgery has been an effective alternative treatment for morbid obesity and has resulted in decreased mortality, better control over comorbidities and reduced use of drugs. The objective of this study was to analyze the impact of bariatric surgery on medication drug and nutritional supplement use.

DESIGN AND SETTING: Longitudinal study of before-and-after type, on 69 morbidly obese patients in a public hospital in Porto Alegre.

METHODS: Through interviews, the presence of comorbidities and use of drugs with and without prescription were evaluated.

RESULTS: Among the 69 patients interviewed, 85.5% had comorbidities in the preoperative period, with an average of 2.3 (± 1.5) per patient. The main comorbidities reported were hypertension, diabetes and dyslipidemia. 84.1% of the patients were using prescribed drugs in the preoperative period. The mean drug use per patient was 4.8, which decreased to 4.4 after the procedure. The surgery enabled significant reduction in use of most antidiabetic (84%), antilipemic (77%) and antihypertensive drugs (49.5%). On the other hand, there was a significant increase in use of multivitamins and drugs for disorders of the gastrointestinal tract. The dosages of most of the drugs that continued to be prescribed after surgery were decreased, but not significantly.

CONCLUSION: After bariatric surgery, there were increases in the use of vitamins, gastric antisecretory drugs and antianemic drugs. Nevertheless, there was an overall reduction in drug use during this period, caused by suspension of drugs or dose reduction.

RESUMO

CONTEXTO E OBJETIVO: A cirurgia bariátrica tem sido uma alternativa efetiva de tratamento para a obesidade mórbida, resultando na diminuição da mortalidade, melhor controle das comorbidades e redução no uso de medicamentos. O objetivo deste estudo foi analisar o impacto da cirurgia bariátrica sobre a utilização de medicamentos e suplementos nutricionais.

TIPO DE ESTUDO E LOCAL: Estudo longitudinal do tipo antes e depois com 69 pacientes obesos mórbidos em um hospital público de Porto Alegre.

MÉTODOS: Nas entrevistas, foram avaliados a presença de comorbidades e o uso de medicamentos com e sem prescrição médica.

RESULTADOS: De 69 pacientes entrevistados, 85,5% apresentaram comorbidades no período pré-cirúrgico, média de 2,3 (± 1,5) por paciente. As principais comorbidades relatadas foram hipertensão, diabetes e dislipidemias. 84,1% dos pacientes estavam em uso de medicamentos sob prescrição médica, no período pré-cirúrgico. A média de uso de medicamentos por paciente foi de 4,8, reduzindo para 4,4 após o procedimento. A cirurgia proporcionou diminuição significativa do uso da maioria dos antidiabéticos (84%), antilipêmicos (77%) e anti-hipertensivos (49,5%). Por outro lado, observou-se aumento significativo na utilização de multivitamínicos e medicamentos para desordens do trato gastrointestinal. A maior parte dos medicamentos que continuaram sendo prescritos após a cirurgia teve sua dose reduzida, no entanto, esta redução não foi significativa.

CONCLUSÃO: Após a cirurgia bariátrica, observou-se aumento na utilização de vitaminas, antisecretores gástricos e antianêmicos. No entanto, de forma geral, houve redução na utilização de medicamentos neste período, ocasionada pela suspensão de medicamentos ou redução de doses.

INTRODUCTION

Chronic non-communicable diseases are one of the biggest public health issues today.[1] Obesity stands out in this regard and has been officially acknowledged by the World Health Organization (WHO) as a chronic disease.[2]

The number of obese individuals has been increasing worldwide and has reached an average of 30% of the adult population in some countries.[3] In Brazil, poor dietary habits have been reflected in the population's health and in increasing prevalence of overweight. More than half of all Brazilians (51%) are now overweight, and 17% of these individuals are obese.[1]

Fighting this rapid growth is one of the biggest challenges for world health, given that obesity is frequently associated with a vast array of comorbidities, such as systemic arterial hypertension, type 2 diabetes mellitus, dyslipidemia, obstructive sleep apnea, cardiovascular diseases and some types of cancer.[4-8] Most patients with high blood pressure are overweight,[9] and hypertension is six times more frequent among obese individuals than among those with normal weight.[10]

The alternatives to clinic treatment for reducing weight among patients with morbid obesity are limited, and the long-term outcomes are relatively inefficient.[11] Bariatric surgery seems to be a viable option for treating morbid obesity, since it has been shown to be effective in maintaining the weight loss. A significant improvement in comorbidities and even their regression may be observed in most patients who undergo this surgical procedure for weight loss.[10] This surgical procedure has been shown to enable control over glucose levels, even leading to remission of diabetes.[12] The quick and sustained improvement in glucose homeostasis that this procedure provides has made it the gold-standard metabolic procedure and treatment for diabetic patients with morbid obesity.[13] Comorbidity reductions are reflected in diminished drug use during the postoperative period, and discontinuation of drug therapy for some diseases, thus resulting in reduced expenditure on drugs and other healthcare services.[10,14-18]

In addition, bariatric surgery extends survival, decreases occurrences of cardiovascular events and is also associated with greater reduction of mortality due to cardiovascular diseases, myocardial infarction, stroke, diabetes and cancer, in comparison with obese individuals who do not undergo this surgery.[10,19,20] The reduction in the risk of myocardial infarction, stroke and adverse cardiovascular events is approximately 50% after this surgery, in comparison with individuals who did not undergo the procedure.[19]

If, on the one hand, bariatric surgery reduces the need for medication to treat comorbidities; on the other hand, the restrictive and disabsorptive procedures involved pose a higher risk of deficiencies of vitamins and minerals.[21] However, studies assessing drug use and their respective dosages after bariatric surgery are still scarce.

OBJECTIVE

Within this context, this study aimed to assess the impact of bariatric surgery on medication drug use among morbidly obese patients, before and after the procedure, focusing mainly on the number of drugs used, drug classes and posology.

METHODS

This was a longitudinal study of before-and-after type, carried out between 2008 and 2011 in the endocrinology clinic of the service for assisting morbidly obese individuals at Hospital Nossa Senhora da Conceição (HNSC) in the city of Porto Alegre, which works under the National Health System (Sistema Único de Saúde, SUS). Through this service, four to five operations per month are performed on patients coming from several regions of the state of Rio Grande do Sul. The clinic offers care provided by physicians (endocrinologist, surgeon and psychiatrist), psychologists, nutritionists and nurses.

The patients eligible for surgical treatment are those with BMI greater than 40 kg/m² or greater than 35 kg/m² in association with comorbidities, after failure in applying traditional measures for weight loss. They need to be psychologically capable of following dietary orientation during the postoperative period, as well as presenting absence of endocrine causes of obesity.[22-24]

The sample size was estimated to be 52 patients, taking into consideration the reduction in drug use for treating hypertension and cardiovascular disease (HT/CVD) that has been reported in the literature.[25] The reduction in drug use expected after the intervention was 49%. Considering the probability that some patients would be lost from the follow-up, it was decided to increase the sample size by 30%. Thus, after the research project had been approved by the HNSC Research Ethics Committee (report no. 146/08), and after potential participants had signed an informed consent statement authorizing data use, 69 individuals with morbid obesity (convenience sampling), who were waiting for biliopancreatic diversion with duodenal switching (BPD-DS) and Roux-en-Y gastric bypass (RYGBP), were interviewed.

Individuals aged over 18 years with class III obesity (body mass index, BMI, greater than 40 kg/m²) and those with BMI greater than 35 kg/m² in association with comorbidities, who were willing to participate in the study, had presented stable obesity for at least five years and had had at least two years of previous inefficient clinical treatment, were included in this study. Patients who did not adhere to preoperative monitoring appointments, had comprehension difficulties (which made them unable to make decisions) or had already undergone another surgical

procedure with the aim of losing weight (gastric sleeve) were excluded from the study.

Data were gathered through 40-minute interviews that were conducted with all patients one day before the procedure and again six months after it. A structured questionnaire was used to assess the variables of gender, age, weight, drug use, reasons for undergoing the surgery and comorbidities. To confirm the presence of comorbidities, drug use, weight and height, some data from the patients' records were used.

Information on drug use at the time of the interviews was initially gathered through the open question "What medications do you take?" For each drug, the name, daily dose, indication and whether its use was through self-medication or prescription were registered. To minimize data loss through forgetfulness, the participants were also asked about their drug use by specifying organs or systems (for example: "Do you take any drug for heart disease?").

The proportion of patients using each drug was calculated taking into consideration the total number of patients using the drug at each time: preoperatively, n = 69; postoperatively, n = 64. To evaluate dose variability, the sum of the doses of each drug divided by the number of patients using this drug at each time was calculated.

The data were double-input into the Epi Data 2.1a. software. They were analyzed through the Statistical Package for the Social Sciences (SPSS) version 18.0 and the Winpepi software. Comparative and descriptive analyses were performed, expressing frequency, average, standard deviation and P-values. McNemar's chi-square test was applied to compare the numbers of patients using drugs before and after the procedure. Student's t test was applied to analyze the dosages. P values ≤ 0.05 were considered significant.

RESULTS

During the preoperative period, 69 patients who were scheduled to undergo bariatric surgery were monitored. There were no refusals to participate. However, after the procedure, there was a loss of five cases: four patients did not return to the consultations in the hospital and one patient died. The majority of the patients participating in this study were women (91.3%) and married (46.5%). Their mean age was 42.3 (± 10.4); they had a mean of 9 (± 2.3) years of education and had undergone a mean of 4 (± 1.3) years of preoperative monitoring. Their mean BMI before the operation was 51.07 (± 7.8) kg/m², and after the operation it was 35.9 (± 7.2) kg/m² (**Table 1**).

During the preoperative period, 85.5% of the patients presented one to five comorbidities associated with obesity, with a mean of 2.33 (± 1.47) per patient. The patients between 20 and 25 years of age did not present any comorbidities. On the other hand, comorbidities were present in all patients aged over 49 years. Hypertension, diabetes, high cholesterol level, hypothyroidism, arthrosis/arthritis, asthma, depression and circulatory problems were the main issues reported prior to surgery. After the procedure, significant reductions in hypertension and diabetes were observed. Dyslipidemia, hypothyroidism, arthrosis/arthritis and depression presented reductions, but not significantly (**Table 2**).

The surgical technique most often used was gastric bypass (91.4%). The subjects mentioned the following as the main reasons for undergoing the surgery: desire to have better health (42.9%), desire for better quality of life (11.1%), desire for weight loss (11.1%), tiredness (6.3%), difficulty in moving around (6.3%), sore legs (4.8%), backache (3.2%) and prejudice (3.2%).

Among the 69 patients interviewed before the surgery, 84.1% reported using drugs through medical prescription, whereas 73.9% did this through self-medication. At the time of the postoperative assessment, 82.6% and 50.7% took drugs, respectively with and without prescription. Use of 328 drugs was observed before the operation, with an average of 4.8 drugs per patient,

Table 1. Characteristics of patients undergoing bariatric surgery at Hospital Nossa Senhora da Conceição between 2008 and 2011 (n = 69)

Baseline characteristics		Mean (SD), % (n)
Mean age (years)		42.3 (10.4)
School education (years)		9 (2.3)
Preoperative monitoring (years)		4 (1.3)
Marital status	Married	62.3% (43)
	Single	37.7% (26)
Gender	Female	91.3% (63)
	Male	8.7% (6)
BMI	Preoperative	51.1 (7.8) kg/m²
	Postoperative	35.9 (7.2) kg/m²

SD = standard deviation; BMI = body mass index.

Table 2. Main comorbidities shown at pre and postoperative assessments

Comorbidities	Preoperative number of patients with comorbidities n = 69	Postoperative number of patients with comorbidities n = 64
Hypertension	45 (65.2%)	19 (29.7%)*
Diabetes	20 (28.9%)	4 (6.3%)*
Dyslipidemias	11 (15.9%)	4 (6.3%)
Hypothyroidism	9 (13%)	6 (9.4%)
Arthrosis/arthritis	9 (13%)	4 (6.3%)
Depression	8 (11.6%)	6 (9.4%)

*P ≤ 0.05 (chi-square test).

whereas after the operation this use reduced to 284 drugs, with an average of 4.4 per patient.

A significant reduction in the use of antihypertensive drugs (49.5%) was observed, except for propranolol. Decreases in the use of antidiabetic (84%), antidepressant (30%), antilipemic (50%), muscle relaxant (33.3%), painkiller (35.3%) and anti-inflammatory (78.5%) drugs were also observed, and these decreases were significant for the following drugs: metformin, fluoxetine, simvastatin, acetylsalicylic acid (ASA), diclofenac and paracetamol. On the other hand, there were significant increases in the use of vitamin supplements and drugs relating to disorders of gastrointestinal tract, such as omeprazole (**Table 3**).

Moreover, reductions in daily dosages were observed for antidiabetic, antilipemic, antidepressant, antithrombotic and most antihypertensive drugs. The differences observed in relation to the dosages were not significant.

DISCUSSION

Our results showed that use of antidiabetic, antihypertensive, painkiller, antilipemic and antidepressant drugs had decreased by the time of the assessment six months after surgery. However, increases in the numbers of drugs used to treat gastrointestinal disorders, anemia and vitamin deficiency were observed.

Among the patients who kept on using drugs after the surgery, reductions in dosages were observed in most of the cases, mainly in relation to antihypertensive drugs (except for hydrochlorothiazide), antidiabetic drugs and antidepressants; however, these reductions were not significant.

Table 3. Differences observed in relation to the main therapeutic classes, drugs and mean daily dosages used before and after bariatric surgery

Therapeutic class/ system	Drug	Patients using drugs n (%)		P*	Mean prescribed daily dosage, mg (SD)		Dosage difference %
		Pre (n = 69)	Post (n = 64)		Pre	Post	
Antihypertensive	Hydrochlorothiazide	30 (43.5)	17 (24.6)	0.001	26.27 (± 6.94)	29.38 (± 18.87)	+11.8
	Captopril	26 (37.7)	15 (21.7)	0.003	85.96 (± 41.04)	67.67 (± 47.09)	-21.28
	Propranolol	10 (14.5)	6 (8.7)	0.125	104 (± 50.60)	80 (± 25.30)	-23.08
	Enalapril	9 (13.0)	2 (2.9)	0.016	26.11 (± 17.10)	25 (± 21.21)	-4.25
	Others	22 (31.9)	9 (13.0)	-	None	None	None
Antidiabetic	Metformin	18 (26.1)	3 (4.3)	0.000	1802.78 (± 784.5)	850	-52.85
	Insulin	3 (4.3)	1 (1.4)	0.500	45.67 (± 47.18)	30	-34.31
	Others	4 (5.8)	0	-	None	None	None
Antidepressive	Fluoxetine	27 (39.1)	16 (23.2)	0.013	63.65 (± 32.11)	48 (± 25.97)	-24.6
	Citalopram	8 (11.6)	4 (5.8)	0.125	40 (± 17.73)	36.67 (± 5.77)	-8.3
	Others	5 (7.2)	8 (11.6)	-	None	None	None
Antilipemic	Simvastatin	13 (18.8)	3 (4.3)	0.006	23.85 (± 9.61)	23.33 (± 15.27)	-2.18
Antithrombotic	Acetylsalicylic acid	7 (10.1)	1 (1.4)	0.031	133.33 (± 51.64)	100	-24.9
	Others	1 (1.4)	2 (2.9)	-	None	None	None
Anti-inflammatory	Diclofenac	7 (10.1)	1 (1.4)	0.031	116.67 (± 57.73)	None	None
	Ibuprofen	6 (8.7)	1 (1.4)	0.125	300 (± 300)	None	None
	Others	1 (1.4)	1 (1.4)	-	None	None	None
Painkillers	Paracetamol	39 (56.5)	19 (29.7)	0.001	821.48 (± 592.29)	1000 (± 707.11)	+21.73
	Metamizole	5 (7.2)	11 (15.9)	0.109	500	500	None
	Others	7 (10.1)	2 (2.9)	-	None	None	None
Muscle relaxants	Carisoprodol	6 (8.7)	6 (8.7)	1.000	None	None	None
	Orphenadrine	6 (8.7)	2 (2.9)	0.289	None	None	None
Respiratory system†		11 (15.9)	5 (7.25)	-	None	None	None
Vitamins and mineral supplements	Multivitamins	1 (1.4)	39 (56.5)	0.000	None	None	None
Antianemic	Folic acid	1	4 (5.8)	0.250	None	None	None
	Cyanocobalamin	-	3 (4.3)	-	None	None	None
	Others	-	3 (4.3)	-	None	None	None
Gastric antisecretory agents	Omeprazole	9 (13.0)	31 (44.9)	0.000	24.44 (± 8.82)	22.92 (± 8.06)	-6.22

SD = standard deviation; *McNemar's chi-square test; †oxymetazoline (1 patient), xylometazoline (1), salbutamol (2), fenoterol (1), salmeterol and fluticasone (1), formoterol and budesonide (2), beclometasone (1), dexchlorpheniramine (1) and loratadine (1).

Antidiabetic drugs

The number of patients using antidiabetic drugs decreased by 84% during the postoperative period. Reductions in mean daily dosages of antidiabetic drugs were also observed. Our results are consistent with those of other authors. Maciejewski et al.[26] reported that there was a 50% reduction in the use of antidiabetic drugs within one year after bariatric surgery. Additionally, Potteiger et al.[27] and Narbro et al.[28] reported that there were significant reductions in the numbers and cost of drugs used to treat diabetes relating to obesity, after surgery. Importantly, the features of the population and the follow-up period need to be taken into account in assessing these proportions, because the impact of surgery on antidiabetic drug use may vary according to these factors.[29]

The great majority of the patients with type 2 diabetes experience more favorable results from clinical examinations, after undergoing bariatric surgery. The mortality rate associated with diabetes has also been significantly reduced.[10] A more recent study that assessed the long-term effects of bariatric surgery on diabetic patients observed that glucose control and remission from diabetes were possible in 89.2% and 64.7% of the patients, respectively.[30] Similar findings had already been reported previously.[31]

Furthermore, reduction of diabetes has been found to occur more frequently among patients who underwent gastric bypass surgery that excluded the duodenum from the nutrient pathway and changed the bowel metabolism, thus reducing insulin resistance faster.[32] Therefore, the significant decrease in antidiabetic drug use observed in our study might be related to the surgical technique used on most subjects (91%).

Recent studies have also suggested that the remission mechanism of this comorbidity in the postoperative period may be categorized into two groups: unconnected with weight loss and connected with it. Although weight loss is an aspect common to all techniques, gastric bypass has shown improvement in diabetes over the short term, regardless of weight loss.[33,34] The underlying mechanisms for this are still being studied.[35-42]

Metformin, the most widely used antidiabetic drug, is absorbed slowly and incompletely by the gastrointestinal tract, mainly from the small intestine onwards. Studies suggest that this drug reaches saturation of absorption, since its concentration in the plasma does not increase with administration of ever-higher dosages.[43]

Metformin dosage has to be carefully individualized, based on patients' tolerance and response. Side effects, especially gastrointestinal effects, are observed in approximately 5 to 50% of the patients and seem to be related to dosage.[43]

Regarding pharmacokinetics, few studies have focused on antidiabetic drug absorption after bariatric surgery. However, Aron-Wisnevsky[44] observed that metformin bioavailability seems to increase after gastric bypass, thus increasing the risk of toxicity. Therefore, the decrease in dosage observed in our study might be partly related to these findings.

Antihypertensive drugs

A reduction in the number of patients using antihypertensive drugs during the postoperative period was observed (49.5%) The mean daily dosages became smaller for most drugs, except for hydrochlorothiazide. Increases in dosage may be due to exclusion of other antihypertensive drugs. According to the BAROS system (Bariatric Analysis and Reporting Outcome System), arterial hypertension is resolved after bariatric surgery when patients continue to use diuretics alone.[45,46]

Regarding the reduction in the number of patients who were using antihypertensive drugs, our findings were similar to those reported by other authors.[26-28,47,48] Partial or complete improvement was shown within 12 months after undergoing bariatric surgery, especially among the patients who had undergone gastric bypass,[10,47] thus reducing the need for antihypertensive drugs.[49,50] It seems again that our results were somehow related to the technique used for the majority of our patients, i.e. gastric bypass.

Reductions in plasma catecholamines and renin activity brought about by weight loss is associated with decreased sympathetic activity, and is likely to be a determining factor for controlling hypertension.[51-53] Thus, it can be suggested that these factors may have contributed towards decreased antihypertensive drug use after loss of excessive weight due to the bariatric surgery.

Antilipemic drugs

Approximately 50% of the patients undergoing surgery for weight loss present dyslipidemia, which is a major factor relating to morbidity and mortality rates.[16,54] Weight loss significantly improves patients' lipid profiles. Reductions in triglycerides, total cholesterol and low-density lipoprotein (LDL) levels, and increases in high-density lipoprotein (HDL) occur. Within less than one year, most patients who previously needed lipid-lowering drugs are able to discontinue their use.[16]

Our results confirm the findings from previous studies.[16,54] A marked decrease in the number of patients using simvastatin was observed. These results suggest that not only was the surgery effective for weight loss, but also it was an efficient alternative for treating dyslipidemia among these severely obese individuals. Improvement in lipid profile is related to the technique used, and disabsorptive techniques cause more significant changes. However, the mechanisms involved in dyslipidemia reduction following bariatric surgery have not been clarified yet.[10]

Regarding the dosage of antilipemic drugs, there are some reports on atorvastatin in the literature, suggesting that its

bioavailability increases after the surgical procedure, thus allowing reduction of the dosage.[44] Nevertheless, it is not known whether the same occurs with simvastatin. In our study, for patients who continued using simvastatin after surgery, there was no clinically significant reduction in daily dosage use.

Multivitamins and antianemic drugs

Multivitamin supplementation is recommended during the postoperative period, in order to correct nutritional deficiencies,[55,56] especially those relating to vitamins B12, A and D, thiamine, folate and minerals such as iron, zinc and calcium.[57,58] Such deficiencies frequent occur after bariatric surgery and relate to decreased food intake and physiological changes produced by the surgery.[59,60]

Gastric bypass changes how food passes along the gastrointestinal tract and leads to poor nutrient absorption, given that food is exposed to the jejunum earlier than usual, through exclusion of part of the gastric and duodenal surface.[61] The absorbent surface area and solubility, and consequently drug bioavailability, are affected by this technique.[44,57]

Our results support previous findings in that they indicated that there was a significant increase in vitamin use that might be related to the surgical technique (91%), as well as decreased food intake after the surgery. Furthermore, an increase in the use of antianemic drugs during the postoperative period was observed. Iron deficiency during this period was very evident.[21]

Gastric antisecretory agents

Unlike our study, in which a significant increase in the use of antisecretory agents was observed, Crémieux[55] and Fontana and Wohlgemuth[62] reported reductions in the use of these drugs for up to three years after the surgery. This decrease might be connected with the reduced occurrence of gastroesophageal reflux over time, which might remain stabilized for up to three years. The difference in the results reported by these authors,[55] in comparison with our study, might be associated with the duration of the postoperative follow-up among the patients and with the standard of service rendered.

Development of stomach ulcers is one of the biggest and most common complications associated with the gastric bypass technique,[63,64] and it is reported in 1% to 20% of the patients after surgery.[65,66] Stomach ulcers may develop over the short term, possibly associated with technical problems at the intervention site.[67] They are usually located in the damaged intestinal mucosa, unable to withstand acidity; they may also be located near the anastomosis.[66] Stapling during the surgery, use of anti-inflammatory drugs or presence of *Helicobacter pylori* (*H. pylori*) during the preoperative period may provoke development of late ulcers. Previous reports in the literature suggest that *H. pylori* damages the mucosal barrier, and that this damage persists into the postoperative period. This induces exacerbation of the ulcer, even if the organism has already been treated.[63,68,69] All these factors may have influenced the increased prescription of antisecretory drugs observed in this study.

Antidepressants

There are few studies relating to the effect of bariatric surgery on the use of drugs that act on the central nervous system. One of the reasons for this is the screening that is done on patients before they undergo bariatric surgery, given that the presence of moderate or severe psychosis or dementia is one of the exclusion criteria.[55] Unlike most other studies, ours showed that the use of antidepressants decreased among the patients after the surgical procedure. Use of some classes of antidepressants, especially selective serotonin reuptake inhibitors, has been indicated as an adjunct in treatments for obesity.[43] This factor may be related to the decrease observed in our study.

Lopes[70] and Segal et al.[71] also observed a tendency towards improvement in their patients' psychological functioning. Nevertheless, it is known that some psychiatric disorders may emerge during this period.

Over the long term, some authors have observed that several psychiatric conditions have been causes of death during the postoperative period, usually through suicide. Depression has been reported to be one of the most frequent late complications (23.4%).[72-75]

van Hout et al.[76] pointed out that the psychiatric effects of bariatric surgery might take from 6 to 24 months to emerge. It has been suggested that the levels of anxiety and depression probably will not be significantly different six months after surgery,[77] and that improvements in depressive conditions might only be observed 12 months after the surgery.[78]

Regarding the daily dosage, decreases were observed in relation to both fluoxetine and citalopram. According to previous reports in the literature, these effects may occur through discontinuation of use of selective serotonin reuptake inhibitors (SSRIs). Therefore, abrupt discontinuation of these drugs should be avoided whenever possible.[43] The small reductions in antidepressant use and daily dosages observed in our study may have been partially related to this, since complete withdrawal of these drugs may have serious effects.

Anti-inflammatory drugs and painkillers

The high frequency of use of anti-inflammatory drugs during the preoperative period may be explained by the fact that obesity contributes towards development of inflammatory diseases in the joints. Moreover, anti-inflammatory drugs are efficient possibly because obesity is a proinflammatory condition.[79]

Inflammatory diseases of the joints are more common in obese people probably precisely due to their overweight condition. Therefore, the need for these drugs decreases through surgery,[80] given that patients have less need for them, for treating pain, fever and inflammation, after they have lost some excess weight.

The use of anti-inflammatory drugs decreased by 78.5%, which corroborated previous findings. Furthermore, there was also a 35.3% reduction in the use of painkillers, and 33.3% regarding muscle relaxants. Among the painkillers, only for dipyrone was there an increase in consumption, which may have been due to the standard prescription issued by the surgical team during the postoperative period. It is possible that this medical prescription may have influenced the choice of analgesic in self-medication situations. It is important to point out that these last two drug classes were the ones most often used in self-medication, thus suggesting that bariatric surgery decreased the need for their use among the patients.

Our results support and reinforce previous findings in the literature regarding the impact of bariatric surgery on the use of some drug classes.[28,31]

One limitation of our study was the small sample size. However, few studies have assessed dosage reductions among the drugs that continue to be used after bariatric surgery.[81,82] Consequently, the data presented in this study provide further details of the benefits of this procedure for patients.

Within this context, there is a need for more comprehensive studies with larger sample sizes and longer follow-up, especially in Brazil, where studies correlating weight loss with drug use, with pharmacokinetic assessments before and after bariatric surgery, are still scarce. Moreover, these studies need to address other factors that may have influenced the increase or decrease in use of some drug classes, such as adherence to treatment, side effects, access to drugs and economic factors, among others.

With the rampant growth of obesity, implementation of prevention policies is also a relevant approach to be considered within public health management, so as not only to prevent obesity but also to prevent its complications due to associated comorbidities, drug use, side effects, reduced quality of life and even societal prejudice.

CONCLUSION

Based on the data obtained, bariatric surgery was observed to enable decreased need for some of the drug classes used, and also adjustment of the dosages of the drugs that continued to be prescribed. On the other hand, new drug classes were included in the patients' therapeutic plans, such as vitamins, drugs for gastrointestinal tract disorders and antianemic drugs, as a result of the limitations imposed by the procedure.

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Sources of funding: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior/CNPq (Procedural no. 479383/2008-1)
Conflict of interest: None

Date of first submission: November 23, 2015
Last received: April 24, 2016
Accepted: May 3, 2016

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Frequency of pain and eating disorders among professional and amateur dancers

Frequência de dor e distúrbios alimentares entre bailarinos profissionais e amadores

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KEY WORDS:
Musculoskeletal pain.
Feeding and eating disorders.
Bulimia.
Anxiety.
Dancing.

PALAVRAS-CHAVE:
Dor musculoesquelética.
Transtornos da alimentação e da ingestão de alimentos.
Bulimia.
Ansiedade.
Dança.

ABSTRACT

CONTEXT AND OBJECTIVE: The pursuit of perfection can cause anxiety and lead dancers to exceed their physical limits. The aim here was to evaluate the prevalence of pain symptoms and eating disorders among professional and amateur dancers.

DESIGN AND SETTING: Observational cross-sectional study; Curitiba, PR, Brazil.

METHODS: Data on 150 professional and non-professional practitioners of ballet, jazz and street dance were collected through specific questionnaires: Brief Pain Inventory-Short Form (BPI-SF), Eating Attitudes Test-26 (EAT-26), Bulimic Investigatory Test Edinburgh (BITE) and State-Trait Anxiety Inventory-T-6 (STAI-T-6).

RESULTS: Pain was observed in 58.6% of the sample, equally between professionals and amateurs (P = 0.19). Ballet dancers had more lower-limb pain than the other groups (P = 0.05). EAT-26 showed a tendency towards more eating disorders among the amateurs (P = 0.06). Higher risk of eating disorders was found among ballet dancers (P = 0.004) and jazz practitioners (P = 0.02) than among street dancers. Amateurs had more symptoms on the BITE scale (P < 0.0001), more pain (P = 0.002) and higher anxiety (P < 0.0001). Eating disorders were more common among females (P = 0.01) and singles (P = 0.02). Professionals were more satisfied with their own body image than amateurs (P < 0.001).

CONCLUSIONS: Pain symptoms were found in almost half of the sample, equally among professionals and amateurs as well as between the three dance styles. Female and singles had more eating disorders. Those with eating disorders had higher levels of pain and anxiety.

RESUMO

CONTEXTO E OBJETIVO: Buscar a perfeição pode causar ansiedade e levar bailarinos a ultrapassar seus limites físicos. O objetivo foi avaliar a prevalência de sintomas dolorosos e distúrbios alimentares entre bailarinos profissionais e amadores.

TIPO E LOCAL: Estudo transversal observacional; Curitiba, PR, Brasil.

MÉTODOS: Dados de 150 praticantes profissionais e não profissionais de *ballet*, *jazz* e *street dance* foram coletados por meio de questionários específicos: Brief Pain Inventory-Short Form (BPI-SF), Eating Attitudes Test-26 (EAT-26), Bulimic Investigatory Test Edinburgh (BITE) e State-Trait Anxiety Inventory-T-6 (STAI-T-6).

RESULTADOS: Encontrou-se dor em 58,6% da amostra, igualmente entre profissionais e amadores (P = 0,19). Praticantes de *ballet* tinham mais dor em membros inferiores que os demais (P = 0,05). No EAT-26, encontrou-se uma tendência para mais transtornos alimentares entre os amadores (P = 0,06). Alto risco para transtornos alimentares apareceu naqueles que praticavam o *ballet* (P = 0,004) e *jazz* (P = 0,02) mais do que *street dance*; amadores tinham mais sintomas no BITE (P < 0,0001), mais dor (P = 0,002) e ansiedade (P < 0,0001). Transtornos alimentares foram mais comuns em mulheres (P = 0,01) e solteiros (P = 0,02). Bailarinos profissionais estavam mais satisfeitos com sua imagem corporal do que amadores (P < 0,001).

CONCLUSÕES: Encontrou-se sintomatologia dolorosa em quase metade da amostra, tanto em bailarinos profissionais como amadores, bem como nos três estilos de dança. Mulheres e pessoas solteiras tiveram mais transtornos alimentares. Aqueles com distúrbios alimentares tinham níveis mais elevados de dor e ansiedade.

INTRODUCTION

Dance is one of the most primitive forms of artistic expression. Dancers use their own bodies to communicate ideas and feelings. Therefore, it is natural that they seek the ideal physical shape, in order to practice their art with perfection. This search often leads them to subject their bodies to strenuous exercise and restrictive diets that turn them into a risk group for eating disorders and musculoskeletal injuries.[1-5]

Dancing ballet is demanding. It requires athletic ability and aerobic endurance, muscular strength, flexibility, good joint stability and neuromuscular coordination. The movements are complex and may involve a great range of motion. Therefore, mobility, static and dynamic strength, stability and equilibrium are necessary for extended periods. In addition, jumps may cause major impact on the feet. For these reasons, ballet dancers frequently overload bone structures, muscles and periarticular ligaments.[3,6]

Jazz and street dance require agility, since these forms explore the dynamics of body movements. Such movements need to be sharp to allow fast and accurate changes in body position, which requires neuromotor control, strength, speed, coordination, flexibility and balance.[7] Thus, strain injuries are also common in this group of dancers.[8]

According to Arabia et al.[3] the highest incidence of musculoskeletal injuries appears among dancers between 8 and 16 years of age. The risk factors include poor postural behavior, anatomical anomalies, improper dance technique, little training and muscle imbalance. In addition, practicing on oblique, slippery and unstable floors, as well as alternating scenarios between high brightness and darkness, and use of fog or smoke on stage, contribute to injuries. Very low body weight in association with low bone mass may favor stress fractures.[3,4]

In a study by Azevedo et al.[9] that included 100 dancers, the risk factors for injury were: physical and general fatigue (mentioned by 53%); and unsuitable floors for dance practice and continuous repetition of demanding choreographic movements (both mentioned by 43.9%). The dancers indicated that the following items might prevent musculoskeletal problems: proper floors on stages and studios; and health professionals integrated into the dance company.

Early diagnosis and correct treatment of musculoskeletal injury are important because chronic pain has negative effects on individuals' physical and mental state alike, thereby impairing quality of life.[10]

Dancers are also at risk of developing eating disorders because of the stringent requirements of physical performance and body esthetics. The onset of an eating disorder is mostly influenced by body image, more than by the individual's weight.[5] According to Hsu et al.,[11] the variables involved in misperception of body image are gender, psychiatric disorders, age, maternal attitude (mainly among children and adolescents) and psychiatric disorders. Teenagers are the group most affected within this context, possibly because of their changes in lifestyle and self-confidence as they mature into adulthood. Misperception of weight has been correlated with lower satisfaction with life and poor self-rated health. Likewise, an association between perfectionism and eating disorder symptoms has been found.

Insufficient daily calorie intake over a long period generates loss of muscle mass, menstrual irregularities and inadequate bone mineralization.[4] Eating disorders in dancers are known to be common, but the exact rates remain to be clarified. They may differ according to the region studied given that dietary habits may be influenced by cultural, social and economic factors.[12]

Evaluating painful symptoms and eating disorders among dancers allows researchers to find out about their routines, the environment within which they live and work and their quality of life. Such analyses can provide knowledge about the amount of physical and emotional stress to which these individuals are subjected and may contribute towards better understanding, recognition, diagnosis and treatment of pain and eating disorders in this population. Furthermore, very little is known about amateur dancers, since most studies have been conducted among professionals. Within this context, the present study aimed to investigate the prevalence of pain and eating disorders among dancers. It also aimed to detect whether there are differences in these issues among dancers practicing different dance styles and between professionals and amateurs.

OBJECTIVE

The present study aimed to ascertain the prevalence of pain and eating disorders among dancer in one institution. It also aimed to determine whether any differences in these two issues exist among dancers practicing different dance styles and between professionals and amateurs, and to compare such characteristics between dancers presenting high and low risk of eating disorders.

METHODS

This study was approved by the local Research Ethics Committee, and the participants or their legal guardians accepted the informed consent statement. This was an analytical cross-sectional study on a completely random sample formed by professional and amateur dancers aged 13 years and over. It was conducted through online virtual or paper versions of questionnaires applied at two dance schools in Curitiba, Paraná, Brazil. The sample comprised 150 dancers who were practicing ballet, jazz and street dance. All participants answered the questionnaires anonymously. Some dancers (n = 52) were invited to answer printed questionnaires that were distributed according to their order of arrival at classes and were later on collected by the school clerk. The online questionnaires (n = 98) were answered through an online form that had been specially designed for this study and advertised through social media (the dancers' Facebook and

internet groups). Only four of the invited dancers refused to participate: three of them claimed that they did not have time; the other one did not give any reason.

The participants of this study were asked to fill out the Brief Pain Inventory-Short Form (BPI-SF).[8] The BPI-SF contains questions that evaluate pain, its intensity and its interference in normal activities. It is scored on a scale from 0 to 10 points, where 0 means the lowest and 10 the highest pain or interference in daily activities, mood, sleep and relationships. It also analyzes the usage of pain medication.

The Eating Attitudes Test-26 (EAT-26)[13-15] and Bulimic Investigatory Test Edinburgh (BITE)[13] were used to assess eating disorders. EAT-26 contains 26 questions concerning eating attitudes, and its total score can range from 0 to 78 points. Scores ≥ 20 mean high risks of an eating disorder. This instrument investigates food selection, knowledge about calorie intake, perceptions about how other people evaluate the subject's dietary habits, vomiting and its frequency, and self-control regarding the amount and frequency of food intake.

The BITE questionnaire has two scales: one on symptoms and the other on their severity. This questionnaire investigates the frequency of meals, food intake, fasting habits and body self-image. The symptom scale goes from 0 to 30 points and subjects with scores ≥ 20 are regarded as having a high risk of eating compulsion or bulimia; scores from 10 to 19, intermediate risk; and < 10, low risk. On the other hand, the severity scale ranges from 0 to 39 points, such that scores ≥ 5 express the need to investigate eating disorders and scores ≥ 10 reveal the need to treat eating disorders or bulimia.

The State-Trait Anxiety Inventory-6 (STAI-T-6)[16] assesses self-report items pertaining to anxiety. Its scores can range from 6 to 24 points and higher scores indicate higher levels of anxiety.

All the questionnaires used had previously been translated and validated for the Portuguese language.[8,13-16]

For the statistical analysis, the data were gathered into contingency and frequency tables. The distribution was judged by means of the Kolmogorov-Smirnov test and central trend measurements were expressed as means and standard deviations in normal samples and as medians and interquartile ranges (IQR) in non-Gaussian samples. For analyses on nominal data, we used Fisher's test and chi-square tests. For analyses on associations of numerical data, we used the Kruskal-Wallis test (for sets of three samples) and the Mann-Whitney test (for sets of two samples). The significance level of 5% was used and calculations were done with the aid of the GraphPad Prism software, version 5.0.

RESULTS

a) Descriptive analysis on the sample

Between May and August 2015, 150 dancers were interviewed: 48 professionals (members of dance companies) (32%) and 102 amateurs (68%). Regarding dance styles, 56% reported practicing classical ballet, 62.6% jazz dance and 24.6% street dance.

Comparisons of the epidemiological data and habitual dance styles between the professional and non-professional dancers are presented in **Table 1**. It can be seen that the professional dancers were practicing for more hours/week and that the

Table 1. Comparison of epidemiological data and dancing habits between professional and non-professional dancers

Sociodemographic characteristics	Total (n = 150)	Professionals (n = 48)	Amateurs (n = 102)	P*
Age group (years)				
> 20	55 (36.6%)	17 (35.4%)	38 (30.3%)	0.25†
20-25	60 (40%)	16 (33.3%)	44 (23.5%)	
< 25	35 (23.3%)	15 (31.2%)	20 (19.6%)	
Gender				
Male	23 (15.3%)	13 (27%)	10 (9.8%)	**0.006†**
Female	127 (84.6%)	35 (72.9%)	92 (90.1%)	
Weekly dance hours	1-45	3-32	1-45	**< 0.0001‡**
Median (IQR)	6 (4.0-12.0)	11.5 (6.0-25.0)	6 (3.75-9.00)	
Age at start of dancing (years)	2-32	2-32	2-24	0.38‡
Median (IQR)	11 (7.0 to 16.0)	11.5 (7.0-15.25)	10 (6.0-16.0)	
Education				
Higher education	88 (58.6%)	28 (58.3%)	60 (58.8%)	0.36†
Secondary school	49 (32.6%)	15 (31.2%)	34 (33.3%)	
Primary education	7 (4.6%)	4 (8.3%)	3 (2.9%)	
No data	6 (4%)	1 (2.0%)	5 (4.9%)	
Marital status				
Married or stable relationship	17 (11.3%)	4 (8.3%)	13 (12.7%)	0.89§
Single or divorced	133 (88.6%)	44 (91.6%)	89 (87.2%)	

*Refers to professionals versus amateurs; †Chi-square test; ‡Mann-Whitney test; §Fisher test.
IQR = interquartile range.

proportion of male subjects was higher among the professionals than among the amateurs.

b) Pain evaluation

In the pain analysis using the BPI-SF, 87/150 (58%) of the participants declared that they had some kind of musculoskeletal pain (60.4% of the professionals versus 56.8% of the amateur group; with P = 0.19). In 82/150 (53.3%), the pain was mild, in 9/150 (6%) moderate and in 1/150 (0.6%) severe.

Figure 1 indicates the locations that were most affected. It can be seen that the highest rates of pain were in the spinal region and lower limbs. The most affected places were the spine (lower back: 44%; cervical spine: 25.3%; middle back: 28.6%), lower limbs (left knee: 32%; right knee: 27.3%; left thigh: 28%) and shoulder (right shoulder: 19.3%; left shoulder: 21.3%). Comparison of the pain regions showed that there was no statistical difference between professional and amateur dancers; however, classical ballet practitioners had more pain in the lower limb than did jazz and street dance practitioners (P = 0.05).

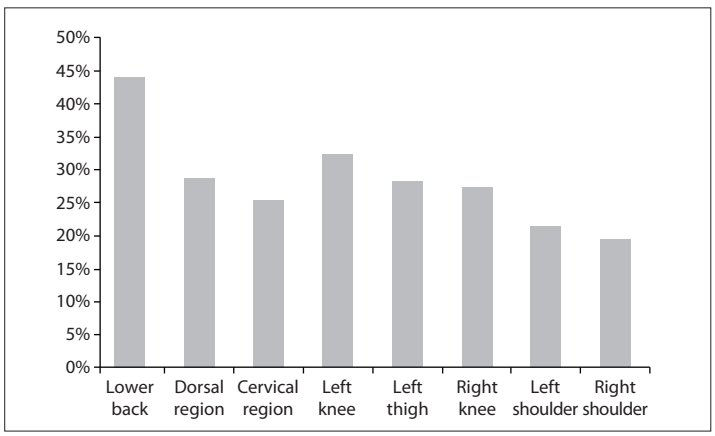

Figure 1. Most common sites affected by musculoskeletal pain among dancers (n = 150).

Regarding pain treatment methods (use of analgesics, anti-inflammatory drugs hormonal therapy or physical methods), professional dancers used more physical methods (such as physiotherapy, acupuncture, massage, etc.) than did the amateurs (P = 0.05).

Table 2 shows a comparison of the impact of pain on daily activities between the professional and non-professional dancers. In comparing the pain component by means of BPI-SF between the three dance forms, no significant difference (P = 0.65) was found.

c) Evaluation of dietary habits

Analysis on dietary habits using the EAT-26 questionnaire showed that 52/150 (34.6%) of all the participants had results consistent with a high risk of eating disorders and 98/150 (65.3%) had a low risk. This comparison of the sample with high and low risks of eating disorders according to EAT-26 is in **Table 3**. It shows that females and ballet dancers had higher risk of presenting eating disorders, while single or divorced dancers and jazz practitioners had less risk.

Figure 2 shows a comparison of the anxiety scale (STAI-T-6) results between subjects with high and low risk of eating disorders.

Interpretation of the results from the BITE scale for eating compulsion or bulimia showed that high scores were found in 14.6% of the sample and average scores in 43.3%. Severity domain analysis on this scale showed that 15.3% of the dancers had clinically significant values and 6% had very high scores. Professionals and amateurs had the same risk of bulimia (P = 0.39) and the

Table 2. Comparison of pain according to BPI-SF (Brief Pain Inventory-Short Form) between professional dancers and amateurs

Items analyzed (BPI-SF)	Professional dancers (n = 48)	Non-professional dancers (n = 102)	P*
VAS (last 24 h)	0-10	0-10	0.87
Median (IQR)	3.0 (2.0-5.0)	3.0 (2-5.0)	
Interference of pain with general activities	0-9	0-10	0.38
Median (IQR)	2.0 (0-3.0)	1.0 (0-3.0)	
Interference of pain with mood	0-10	0-10	0.79
Median (IQR)	1.0 (0-2.75)	1.0 (0-3.0)	
Interference of pain with walking	0-9	0-9	0.57
Median (IQR)	0 (0-1.0)	0 (0-2.0)	
Interference of pain with work	0-10	0-10	**0.02**
Median (IQR)	1.0 (0-3.0)	0 (0-2.0)	
Interference of pain with social relationships	0-7	0-10	0.16
Median (IQR)	0 (0-1.0)	0 (0-2.0)	
Interference of pain with sleep	0-10	0-10	0.21
Median (IQR)	0 (0-2.0)	0 (0-4.0)	
Interference of pain with enjoyment of life	0-8	0-9.0	0.80
Median (IQR)	0 (0-1.0)	0 (0-10)	

*Mann-Whitney test; VAS = visual analogue scale; IQR = interquartile range.

Table 3. Comparison of dancers with high and low risk of eating disorders according to the EAT-26 questionnaire (Eating Attitudes Test-26)

	High risk (n = 52)	Low risk (n = 98)	P
Age			
< 20	22 (42.3%)	33 (33.6%)	0.53
20-25	18 (34.6%)	42 (42.8%)	
> 25	12 (23.0%)	23 (23.4%)	
Gender			
Female	49 (94.2%)	78 (79.5%)	**0.01**
Male	3 (5.7%)	20(20.4%)	
Marital status			
Single or divorced	43 (82.6%)	92 (93.8%)	**0.02**
Married or stable relationship	9 (17.3%)	6 (6.1%)	
Age at start of dancing (years) – range	3-30	2-32	0.45
Median (IQR)	10 (7.0-15.0)	12.0 (6.0-16.0)	
Number of practice hours/week – range	1-32	2-45	0.07
Median (IQR)	6 (4.0-10.0)	7.50 (4.0-14.0)	
Dance style			
Ballet	40 (76.9%)	52 (53.0%)	**0.004**
Jazz	26 (50%)	67 (68.3%)	**0.03**
Street dance	10 (19.2%)	27 (27.5%)	0.26
Working status			
Professionals	12 (20.6%)	37 (37.7%)	0.06
Amateurs	40 (68.9%)	61 (62.2%)	

Tests: Fisher; Chi-square; Mann Whitney; STAI-T-6 = State-Trait Anxiety Inventory T-6.

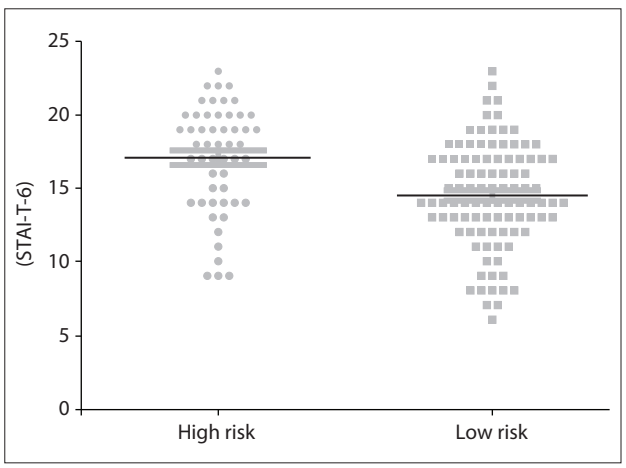

Figure 2. Comparison of anxiety scale (STAI-T-6) results among dancers with high and low risk of eating disorders (P < 0.0001; Mann-Whitney).

frequency of meals (breakfast, lunch, dinner and snacks) was the same in both groups (all meals with P = non-significant).

There was no difference in body mass index between the professional and non-professional dancers (P = 0.28), and also no differences among the three dance styles studied (P = 0.33). However, investigation of personal views of current weight versus ideal weight showed that the amateurs were less satisfied with their own body image than were the professionals (P < 0.001).

DISCUSSION

Our results showed that more than half of the sample analyzed had some kind of musculoskeletal pain and that dance style did not affect dancers' perceptions regarding appearance. Moreover, as expected, pain among the professional dancers played an important role regarding interference with their work. However, the number of hours a week dance practice was highly variable in both professional and amateur groups. Eating disorders were observed in almost one third of the study sample, mainly occurring among females, ballet practitioners and those with high levels of anxiety. Interestingly, eating disorders were less common among singles and jazz practitioners. It was also observed that almost 20% of the dancers presented a risk of bulimia and that this risk was equally distributed between professionals and amateurs. Finally, it could be seen that the amateur dancers showed great dissatisfaction with their own body image.

Physical activity reduces pain levels[10] and, moreover, the act of dancing relieves tension and day-to-day stress. However, despite its benefits for physical fitness and pleasure, dancing requires hours of training and it takes years to improve performance, which may generate situations of stress and anxiety. The search for perfection may lead to excessive physical activity, which possibly leads to musculoskeletal injuries. This cycle ultimately allows the act of dancing to be considered to be an important occupational disease.[2,17] Furthermore, as part of the physically active population, dancers are prone to accidents.[2]

Almost 100% of retired dancers who belonged to the ballet companies American Ballet and New York City Ballet were found to have had at least one injury during their careers.[18]

Pain cannot be objectively assessed by tests, and its evaluation depends on the patient's report.[10] This serves to emphasize the importance of applying instruments that can quantify perceived pain and its repercussions on dancers' daily lives and work, such as the BPI-SF questionnaire used here.

As stated earlier, more than half of the dancers had some sort of musculoskeletal pain and the most common injury sites were the lower spine, followed by the middle back and cervical regions and lower limbs. These results agree with those of the study by Dore and Guerra,[8] on 141 professional ballet dancers who showed similar affected regions (low back, knees, neck and left hip/thigh). It can be stated that the high prevalence of pain in the low back and legs is due to the classical dance position of extreme external rotation of the lower limbs, which leads to hyperlordosis, and also to the weight supported on the toes through tip and half-tip positions. Weak abdominal muscles and tight thoracolumbar fascia may favor this, thus increasing the chance of injury from a curved back and arabesques. Accordingly, ballet dancers were the ones who had most pain in the lower limbs. However, in relation to the other regions, including the lower back, there were significant differences among the dance styles studied. This suggests that further studies should be conducted in order to evaluate the causes of pain in these regions, since the positions and repetitions used in different types of dance diverge from one style to another. We believe that jazz dancers reported more pain in the lower limbs than did street dancers because of the high similarities between jazz positions and those performed in classical ballet.

Regarding the intensity of pain, although reports of mild pain prevailed in the present study (53.3%), Dore and Guerra[8] found high levels of pain in 70.2% of the dancers. They also demonstrated the influence of pain on work activities. In our comparison between professional and amateur dancers, we found a significant difference in the interference with work produced by pain ($P = 0.02$), such that this relationship was closer among the professionals. We therefore reiterate the above authors' assertion that painful symptoms interfere significantly in the work activities of dancers, especially among professionals, since they use their bodies as a work tool. Thus, it is necessary to implement or enhance measures to prevent injury and improve the treatment of existing lesions, and to place dancers under constant monitoring by healthcare professionals. The presence of medical staff in dance companies helps to reduce injuries and the number of days off work due to illness, and saves financial resources among dancers.[4] According to the literature, the most successful model is built up through a multidisciplinary team that includes dance teachers, doctors, physiotherapists, massage therapists, Pilates instructors, sports psychologists and sports nutritionists.[18]

Eating disorders are entities of multifactorial origin with higher occurrence rates among teenagers and young women, and with significant prevalence in the general population. It is also important to point out that late diagnosis, due to denial of the situation, ultimately leads to health impairment.[19] In the present study, almost one third of the dancers (34.6%) were at risk of eating disorders, half of them with high scores. We also found that younger people, females, single individuals and classical ballet practitioners were more vulnerable to this condition. Guimarães et al.[20] also found that a high proportion of classical ballet dancers had eating disorders and showed dissatisfaction with body image. In the present study, the BMI of dancers of all styles was found to be within the normal range. Despite this, 54.1% of the professional dancers and 96% of the amateur dancers classified themselves as being overweight. This shows that acknowledgment of body image seems to be disturbed mainly in the amateur group. Individuals with eating disorders, and specifically bulimia, usually place extreme value on their body shape and weight. They have erroneous physical perceptions, difficulty in identifying emotions, low self-esteem, a low threshold for frustration, impaired impulse control and high levels of anxiety.[21] The requirement for dancers to maintain an extremely low weight is closely linked to the athletes' triad (eating disorders, amenorrhea and osteoporosis).[3,4]

Unfortunately, the lack of references involving jazz and street dance styles hinders comparisons of the present data with other samples, which thus suggests that there is a need for more studies within this context. The same applies to the group of amateur dancers, which was the larger group in the present study and also showed a great degree of musculoskeletal pain and eating behavior disorders.

Finally, this study provides some knowledge about the lives of dancers and shows that this group needs support with regard to both of the situations studied: prevention of musculoskeletal pain and counseling to improve dietary habits. This study also highlights that this guidance is needed not only by professionals but also by amateurs, who are at similar risk of both musculoskeletal lesions and eating disorders. However, lastly, this was only a small cross-sectional study. For a better panorama to be provided, this study needs to be replicated with larger samples that are evaluated by a multidisciplinary team that should include psychologists in order to better understand the relationship between the problems observed and their causes.

CONCLUSIONS

Painful symptoms were commonly observed and found at similar rates among professional and amateur dancers, and also among dancers practicing the three styles that were studied. The back and lower limbs were the regions most affected by pain, which had greater interference with work activities among professional dancers.

Almost one third of the dancers were at risk of developing eating disorders, which were more commonly seen among young and single females. Regarding self-awareness of the body, amateur dancers had worse body image perceptions than the professionals. Dancers presenting a high risk of eating disorders had higher levels of pain and anxiety than those at low risk.

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Sources of funding: None
Conflict of interest: None

Date of first submission: March 24, 2016
Last received: May 9, 2016
Accepted: May 31, 2016

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DOI: 10.1590/1516-3180.2016.0139140616

A five-year review of vertical HIV transmission in a specialized service: cross-sectional study

Revisão de cinco anos da transmissão vertical do HIV em um serviço especializado: estudo transversal

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KEY WORDS:
HIV.
Infectious disease transmission, vertical.
Women's health.
Child health.
Hospital records.

PALAVRAS-CHAVE:
HIV.
Transmissão vertical de doença infecciosa.
Saúde da mulher.
Saúde da criança.
Registros hospitalares.

ABSTRACT

CONTEXT AND OBJECTIVE: Healthcare professionals need to instill the process of prevention, control and treatment of people infected with HIV into care practice. Through maintaining preventive treatment among HIV-infected pregnant women, it has been demonstrated that prophylactic antiretroviral therapy, scheduled cesarean section and the prohibition of breastfeeding significantly reduce vertical HIV transmission. This study aimed to assess the rates of vertical HIV transmission in a specialized service and identify the factors associated with it.

DESIGN AND SETTING: Cross-sectional study developed at the University Hospital of Santa Maria (RS), Brazil.

METHODS: A cross-sectional study was conducted on a sample of 198 notification forms and medical records of HIV-positive pregnant women and exposed children.

RESULTS: The vertical transmission rate was 2.4%, and three children had been infected by vertical HIV transmission. The statistically significant risk factor was the use of injectable drugs. Delayed reporting of pregnancy, absence of antiretroviral therapy during pregnancy, lack of proper prenatal care, incapacity to perform viral load detection tests and CD4+ T cell counts and obstetric and maternal clinical complications were reported.

CONCLUSIONS: The vertical transmission rate was high and the recommended intervention measures were not adopted in full. Adequate prophylactic measures need to be implemented in HIV-positive pregnant women prenatally and during the antenatal, delivery and postpartum periods.

RESUMO

CONTEXTO E OBJETIVO: Os profissionais de saúde precisam introduzir o processo de prevenção, controle e tratamento das pessoas infectadas com HIV na prática assistencial. Manter o tratamento preventivo em gestantes infectadas pelo HIV demonstra que a terapia antirretroviral profilática, a cesariana programada e a proibição da amamentação reduzem significativamente a transmissão vertical do HIV. Este estudo tem como objetivo avaliar as taxas de transmissão vertical do HIV em um serviço especializado e identificar os fatores associados.

TIPO DE ESTUDO E LOCAL: Estudo transversal desenvolvido no Hospital Universitário de Santa Maria (RS), Brasil.

MÉTODOS: Estudo transversal foi conduzido utilizando amostra de 198 fichas de notificação e prontuários de mulheres grávidas HIV-positivas e crianças expostas.

RESULTADOS: A taxa de transmissão vertical foi de 2,4%, e três crianças foram infectadas por transmissão vertical do HIV. O fator de risco estatisticamente significativo foi o uso de drogas injetáveis. Comunicação tardia da gravidez, ausência de terapia antirretroviral durante a gravidez, falta de cuidados pré-natais adequados, incapacidade de realizar testes virais de detecção de carga e contagem de células T CD4+ e complicações clínicas obstétricas e maternas foram relatadas.

CONCLUSÕES: A taxa de transmissão vertical foi elevada e medidas de intervenção recomendadas não foram adotadas na íntegra. Medidas profiláticas adequadas precisam ser implementadas em mulheres grávidas HIV-positivas no pré-natal e durante os períodos pré-natal, intraparto e pós-parto.

INTRODUCTION

Vertical transmission of human immunodeficiency virus (HIV) is characterized by passage of the virus from the mother to the child through the placenta during pregnancy, at the time of childbirth or through breastfeeding.[1-4] Children with HIV infection who develop acquired immunodeficiency syndrome (AIDS) stand out within the context of the epidemic. Its epidemiological growth is due to the feminization process and the increased survival rate among individuals infected through vertical transmission.[5,6]

In Brazil, the first cases of vertical transmission were reported in 1985.[7] The Brazilian Ministry of Health uses the incidence rates among children under five years of age as an indicator for monitoring vertical transmission. Between 1980 and 2013, 12,551 cases of AIDS in children under 13 years of age who had been exposed to vertical transmission were reported in the notification information system.[1]

Screening of pregnant women and early implementation of antiretroviral prophylaxis are issues that require more attention.[8] Healthcare professionals need to instill the process of prevention, control and care of people infected with HIV into general practice. Through administering preventive treatment among HIV-infected pregnant women, it has been demonstrated that prophylactic antiretroviral therapy, scheduled cesarean section and prohibition of breastfeeding significantly reduces HIV transmission from mother to child.[9,10]

OBJECTIVE

This study aimed to assess the rate of vertical HIV transmission in a specialized service and identify the factors associated with it.

METHODS

A cross-sectional study was conducted between 2008 and 2012 at the University Hospital of Santa Maria, Rio Grande do Sul, Brazil, where HIV-infected pregnant women gave birth. The study was approved by the Research Ethics Committee of the Paulista School of Nursing (CAEE No: 16395413.4.0000.5505), in accordance with Resolution 466/2012 of the National Health Council and also with international rules.

The study participants were identified through records kept in the information system for notifiable diseases and through the medical records of HIV-positive women. The sample comprised the entire population of children at this hospital who were exposed to HIV between 2008 and 2012. Miscarriages and cases of stillbirths among pregnant women infected with HIV were excluded.

The primary variable was the prevalence of vertical HIV transmission. Secondary variables included sociodemographic variables (maternal age, maternal education, city of residence, area of residence and occupation of the mother); maternal exposure to HIV (sexual partners, partner's HIV status and use of injectable drugs); pregnancy, prenatal care, early prenatal care, antiretroviral therapy during pregnancy, treatment regimen, reasons for not performing antiretroviral prophylaxis during pregnancy, maternal HIV viral load (PCR-RNA) and CD4+ T cell counts during pregnancy; complications during pregnancy (clinical, obstetric and coinfections); management during delivery (delivery type, delivery performance of municipality, use of injectable antiretrovirals, rupture of membranes, episiotomy, lactation inhibitors, quick tests before delivery and pregnancy outcome); and finally, care of the newborn (early administration of oral zidovudine, full-time use of oral zidovudine, breastfeeding, cross lactation, viral load, HIV screening test and confirmatory rapid anti-HIV serological test).

Descriptive statistics (absolute frequency, mean, median, standard deviation, minimum and maximum) of the independent variables were performed to characterize the HIV-infected pregnant women and exposed children. The dependent variable was used to calculate the rate of vertical HIV transmission. Fisher's exact test and nonparametric Mann-Whitney tests were used to assess the associations between the dependent and independent variables.

We used the chi-square test to compare quantitative variables between HIV-positive and HIV-negative children and binary logistic regression to verify the risk factors for vertical HIV transmission. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 21.0. For each point estimate, 95% confidence intervals were derived, and a statistical significance level of 5% was used.

RESULTS

Over the study period, there were 198 eligible cases of HIV-infected women who gave birth in the institution. Therefore, 198 children were exposed to HIV during pregnancy. The baseline characteristics of the pregnant women and exposed children are shown in **Table 1**.

The prevalence of vertical transmission in this population was 2%, and 98% of the exposed children underwent chemoprophylaxis; 99% were not breastfed.

Among the possible risk factors for HIV transmission, there were significant associations with use of injectable drugs by the pregnant woman, confirmation of HIV infection during prenatal exams, antiretroviral drug use during pregnancy, viral load result, CD4+ T cell counts or presence of associated infections (**Table 2**).

Through assessing the clinical characteristics of the pregnant women infected with HIV, it was found that 39.4% had obstetric complications, 36.4% suffered from coinfections and 30.8% demonstrated presence of maternal clinical complications.

Regarding the number of hours after birth at which antiretroviral therapy was started for the child, a statistically significant difference ($P = 0.03$) was found between those infected with HIV and those that were not infected.

Table 1. Baseline characteristics of HIV-infected pregnant women and exposed children (n = 198) at the University Hospital of Santa Maria (RS), Brazil, between 2008 and 2012

Characteristics	Median (minimum-maximum)
Pregnant women	n (%)
Age in years	27 (14-45)
Schooling in years	7 (0-18)
Fixed sexual partner	75 (37.9)
Sexual partner infected with HIV	33 (16.7)
Injectable drug abuse	19 (9.6)
Use of lactation inhibitor	195 (97.0)
First prenatal consultation held in the first trimester	27 (13.6)
Vaginal birth	41 (20.7)
Threat of abortion	7 (3.5)
Anemia	6 (3.0)
Intrauterine growth restricted	2 (1.0)
Maternal hypertension	10 (5,1)
Disruption of membranes before delivery	24 (12.1)
Maternal infection with syphilis	10 (5.1)
Maternal infection with toxoplasmosis	25 (12.6)
Maternal infection with hepatitis C virus	14 (7.1)
Maternal urinary infection	19 (9.6)
Preterm labor	36 (18.2)
Presence of vaginal infections	22 (11.1)
Time (in hours) of membrane rupture, median (minimum-maximum)	5 (1-648)
Viral load detectable	81 (40.9)
CD4+ T lymphocyte count, mean (standard deviation)	465.9 (249.5)
Children exposed	
Infected with HIV	4 (2.0)
Did not breastfeed	196 (99.0)
No cross-lactation	198 (100.0)
Underwent chemoprophylaxis	194 (98.0)

DISCUSSION

In Brazil, the prevalence of vertical HIV transmission is 1%. However, the rate seen in the hospital service examined here was 2%, which is more than double the national average. It was observed that this rate was 3.4 times higher than the prevalence in this service, over the period between 2002 and 2006, when it was 0.7%. Some of the factors that may have influenced the increase in vertical transmission are late notification of pregnancies of infected women for the health service, absence of the use of antiretroviral therapy during pregnancy, lack of perception of prenatal complications, obstetric complications and quality of maternal clinics. In 2012, the detection rate for AIDS in children under 5 years of age was 3.4/100,000. This rate has been used as an indicator to monitor vertical HIV transmission.[11-13]

The present study did not allow identification of risk factors for vertical transmission, mainly because of absence of data in the files. However, there is evidence that clinical and immunological factors (recent infection, vaginal infections, viral load of pregnant women and low CD4+ count), obstetric issues (vaginal delivery and premature birth), factors relating to the newborn (breastfeeding and antiretroviral prophylaxis for newborns), absence of antiretroviral therapy during pregnancy and behavioral factors (young maternal age and use of drugs by pregnant women) influence vertical transmission.[14]

With regard to clinical and immunological factors, it was found in this study that 36.4% of the pregnant women had recent infections and 11.1% had vaginal infections. Both types of infection boost vertical transmission because they weaken immunity in the pregnant woman and fetus and therefore result in greater amounts of secretions with high viral load at the time of delivery.[14-17] This demonstrates the importance of early diagnosis and subsequent treatment in order to reduce the risk factors for vertical transmission.

Since the hospital service examined here provides care for cases of high complexity and mainly caters to pregnant women at high risk prenatally, only 22% of the women underwent vaginal delivery and 28.3% gave birth prematurely. The high rate of

Table 2. Clinical characteristics of pregnant women infected with HIV at the University Hospital of Santa Maria (RS), Brazil, between 2008 and 2012

Variables	OR	CI		P†
		Lower	Upper	
Injectable drug use by pregnant women: no*; yes	1.11	0.90	0.96	0.03
Confirmation of HIV infection: before prenatal period*; prenatal/pregnancy	0.59	1.05	5.31	0.04
Antiretroviral drug use during pregnancy: yes*; no	1.92	1.16	22.30	0.02
Viral load result: detectable; undetectable*	0.71	1.04	11.76	0.04
CD4+ T cell count: up to 350*; 351 or more	1.32	-0.02	0.10	0.05
Presence of associated infections: no*; yes	1.25	1.06	22.87	0.02
Viral load result: detectable; undetectable*	1.15	0.00	0.01	0.02

*Reference; †Binary logistic regression; OR = odds ratio; CI = confidence interval.

premature births shown in this study may be associated with the antiretroviral therapy, which has been shown to increase the risk of premature delivery.[9,10,12,14,16]

With regard to risk factors relating to the newborn, 1.5% of the newborns in this study were breastfed and 97.1% underwent chemoprophylaxis. There is evidence that breastfeeding without antiretroviral treatment for the mother or the child increases the risk of vertical transmission by 91%. One factor that helps reduce the possibility of vertical transmission is the use of medication to inhibit lactation, and 95.9% of the pregnant women in this study were found to be using this medication.[4,8,12,14-18]

Use of antiretroviral drugs during pregnancy increases the CD4+ T lymphocyte cell counts and consequently reduces the viral load, thereby decreasing the risk of intrauterine vertical transmission. This should be combined with early detection of HIV infection in pregnant women. However, 38.3% of the women in this study were diagnosed with infection prenatally or later. Only 33.3% of the pregnant women received adequate prenatal care starting from the first trimester of pregnancy, and this lack of care can contribute towards the risk of vertical transmission, abortion and perinatal mortality.[9,10,15-17]

Injectable drug abuse, which doubles the risk of vertical transmission and increases the risk of abortion sixfold,[10] was seen in the cases of 9.6% of the pregnant women in this study. For pregnant women who use other drugs, harm reduction strategies should be discussed. It needs to be emphasized that they should use condoms and not share syringes and needles, if they are using injectable drugs. In this manner, users can reduce their own risk of reinfection and transmission to their sexual partners.[19]

The diagnosis of vertical transmission needs to be confirmed by performing a screening test for HIV-1 and HIV-2 and at least one confirmatory test. In the event of positive results, a new sample should be collected to confirm the positive results from the first sample.[3,4,13]

The cases of 81.1% of the HIV-positive pregnant women were only notified in the third trimester, thus indicating that there were delays in notification. In Brazil, notification is supposed to occur at the time of detection of HIV infection in pregnant women and/or children infected by vertical transmission.[4]

Healthcare professionals need to work towards reducing vertical HIV transmission through providing recommendations for interventions, early identification of women exposed to HIV, implementation of preventive measures and appropriate use of antiretroviral therapy in prenatal care. Controlling AIDS can prove to be a challenge.[8]

The limitations of this study included its cross-sectional design, which did not allow causality to be established. Moreover, the primary source of data was the notification forms and medical records of the pregnant women and children exposed to HIV.

CONCLUSION

This study showed that the rate of vertical transmission in a specialized service is 2%, twice the national average. Risk factors for increased vertical transmission of HIV were: injected drug use, confirmation of HIV infection in prenatal period or childbirth, non-use of antiretroviral drugs during pregnancy, high viral load, reduced CD4 T lymphocytes and presence of associated infections.

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Sources of funding: None
Conflict of interest: None

Date of first submission: June 1, 2016
Last received: June 11, 2016
Accepted: June 14, 2016

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Acoustic radiation force impulse (ARFI) elastography compared with biopsy for evaluating hepatic fibrosis after liver transplantation: a cross-sectional diagnostic study

Elastografia ARFI (*acoustic radiation force impulse*) comparada com biópsia na avaliação de fibrose hepática após transplante: estudo transversal diagnóstico

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KEY WORDS:
Elasticity imaging techniques.
Liver transplantation.
Fibrosis.
Liver cirrhosis.
Ultrasonography.

PALAVRAS-CHAVE:
Técnicas de imagem por elasticidade.
Transplante de fígado.
Fibrose.
Cirrose hepática.
Ultrassonografia.

ABSTRACT

CONTEXT AND OBJECTIVE: Biopsies are used after liver transplantation to evaluate fibrosis. This study aimed to evaluate the elasticity of transplanted livers by means of a non-invasive examination, acoustic radiation force imaging (ARFI) elastography, correlating the results with the histological analysis.

DESIGN AND SETTING: Cross-sectional study in a public university hospital.

METHODS: All patients consecutively operated between 2002 and 2010 with an indication for biopsy were evaluated by means of elastography. The radiologist evaluating ARFI and the pathologist doing anatomopathological examinations were blinded to each other's evaluations.

RESULTS: During the study period, 33 patients were included. The indication for transplantation was cirrhosis due to hepatitis C in 21 cases (63%). Liver biopsies showed absence of fibrosis (F0) in 10 patients, F1 in 11, F2 in 8 and F3 in 4. There were no cases of F4 (cirrhosis). The difference in ARFI values (degree of fibrosis) was 0.26 (95% confidence interval, CI: 0.07-0.52) between the groups F0-F1 and F2-F4 (P = 0.04). An area under the curve of 0.74 (CI: 0.55-0.94) and a cutoff of 1.29 m/s between the groups resulted in the best relationship between sensitivity and specificity. Sensitivity (0.66; CI: 0.50-0.83) was lower than specificity (0.85; CI: 0.72-0.97). There was no significant difference in ARFI between patients with hepatitis C and those with other diseases.

CONCLUSIONS: The values obtained from elastography were not affected by inflammatory reaction or anatomical alterations. A cutoff point of 1.29 m/s separating patients with or without significant fibrosis was identified.

RESUMO

CONTEXTO E OBJETIVO: Biópsias são utilizadas para avaliar fibrose após transplante de fígado. O estudo objetivou avaliar a elasticidade hepática após transplante por meio de um exame não invasivo, a elastografia ARFI (*acoustic radiation force imaging*), correlacionando-a com a análise histológica.

TIPO DE ESTUDO E LOCAL: Estudo transversal em hospital público universitário.

MÉTODOS: Todos os pacientes consecutivamente operados entre 2002 e 2010, com indicação para biópsia, foram avaliados por elastografia. O radiologista avaliando ARFI e o patologista fazendo exames anatomopatológicos estavam cegos para as avaliações um do outro.

RESULTADOS: No período do estudo, 33 pacientes foram incluídos. A indicação para o transplante foi cirrose por hepatite C em 21 (63%). As biópsias mostraram ausência de fibrose (F0) em 10 pacientes, F1 em 11, F2 em 8, F3 em 4 e nenhum caso de F4 (cirrose). A diferença nos valores de ARFI (grau de fibrose) foi de 0,26 (intervalo de confiança, IC, de 95%: 0,07-0,52) entre os grupos F0-F1 e F2-F4 (P = 0,04). A área sob a curva de 0,74 (IC: 0,55-0,94) e o valor de corte de 1,29 m/s entre os grupos resultaram na melhor relação entre sensibilidade e especificidade, de 0,57. A sensibilidade (0,66; IC: 0,50-0,83) foi menor que a especificidade (0,85; IC: 0,72-0,97). Não houve diferença significativa em ARFI entre pacientes com hepatite C e aqueles com outras doenças.

CONCLUSÕES: Os valores obtidos com a elastografia não foram afetados por reação inflamatória ou alterações anatômicas. Foi identificado ponto de corte de 1,29 m/s que separa pacientes com ou sem fibrose significativa.

INTRODUCTION

Liver transplantation is an established form of therapy for treating acute and chronic end-stage hepatic diseases and for some hepatic tumors, with ten-year graft survival greater than 70% at most transplantation centers.[1-4] Nonetheless, histological changes in transplanted livers can occur subclinically and progressively even in asymptomatic patients and without significant laboratory alterations.[3-6]

Liver biopsy is currently the gold standard for histological evaluation of the liver.[7-10] However, it is invasive and poses a risk of complications with morbidity around 0.3 to 0.6% and mortality of 0.05%, besides hospitalization of at least 6-18 hours.[3,4] In order to diagnose these alterations, some transplantation centers recommend routine biopsies at fixed intervals (annually) after liver transplantation, thus called "protocol biopsies".[11] Other centers do not follow this protocol, taking the view that liver biopsy is both risky and invasive.[3,4]

The main histological alterations observed in anatomopathological evaluations on biopsies on transplanted livers involve inflammation and fibrosis.[6] However, the degree of fibrosis may be underestimated in situations of inadequate sampling, given that the volume of the sample evaluated in the biopsy is only 1/50,000 of the organ. There have been reports of discrepancies in both inter and intraobserver histological analyses, at estimated rates of 10 to 30% of the cases.[12]

New noninvasive diagnostic methods, such as serum tests, magnetic resonance imaging and elastography, which have shown significant correlation with the histological test,[13] can be introduced with the objective of reducing the number of biopsies. This has already been happening in relation to patients with chronic hepatopathy. Several noninvasive methods have been proposed for staging hepatic fibrosis. These include indices based on biochemical tests and imaging examinations.[14] Among the biochemical tests, the aspartate aminotransferase (AST) to platelet ratio index (APRI) stands out due to its simplicity and low cost. The APRI was proposed in 2003 by Wai et al. and promising results were reported.[15,16]

Transient hepatic elastography (Fibroscan, Echosens, France) was the first noninvasive diagnostic method for quantifying the degree of hepatic fibrosis, and the first scientific paper on this method was published in 2003.[17] Its use on patients with liver disease is based on the relationship between stiffness and hepatic fibrosis. It measures the elasticity of a volume of hepatic tissue corresponding to a cylinder with a thickness of 1 cm and depth of 2 cm, with results expressed in kilopascals. Different studies have assessed its diagnostic accuracy. Using optimized cutoff points, Castéra et al.[7] found a positive predictive value (PPV) of 95% and a negative predictive value (NPV) of 48% for the presence of significant fibrosis, and PPV of 77% and NPV of 95% for the presence of cirrhosis. The same group also reported concordance of 83% with liver biopsy regarding the diagnosis of significant fibrosis and 90% regarding the diagnosis of cirrhosis.[7]

Another method for quantifying the degree of hepatic fibrosis was presented more recently, in 2009: acoustic radiation force imaging (ARFI) (S2000, Siemens, Germany). In the ARFI elastography method, short-duration pulses are emitted in the region of interest (ROI), thus generating waves with velocities measured in meters per second.[18,19] Fierbinteanu-Braticevici et al. measured the area under the ROC curve of ARFI elastography and found accuracy of 90.2% in predicting fibrosis.[20] Some advantages of ARFI elastography merit special emphasis, including the facts that manual compression is unnecessary and that this elastography is coupled to conventional ultrasound equipment, thus also enabling analysis of other organs.

Elastography and other noninvasive methods have been used over the short term (one to five years) on patients undergoing liver transplantation, in order to determine the degrees of fibrosis.[8,9,11,21] Determination of the degrees of hepatic fibrosis in liver transplant patients is crucial for early detection of fibrosis and for making decisions on the therapeutic approach to be adopted.[1]

OBJECTIVE

The current study aimed to evaluate liver elasticity in patients who had undergone liver transplantation at least one year earlier, by means of ARFI elastography, correlating the results with the histological analysis and determining a cutoff value for ARFI results by comparing patients presenting fibrosis grades 0 and 1 with those presenting grades 2 to 4.

METHODS

Study design, location and ethics

In this cross-sectional observational study, we analyzed patients operated on for liver transplantation in the Department of Gastroenterology, Liver Transplantation and Surgery of the School of Medicine of the University of São Paulo. During the period between April 2012 and March 2015, all patients with an indication for liver biopsy were recruited for ARFI evaluation. The research project was approved by the Ethics Committee for Analysis of Research Projects (CAPPESQ), and the patients signed informed consent forms.

Participants

All the patients who had been consecutively operated for liver transplantation at our institution between 2002 and 2010 and who had a clinical indication for biopsies, and whose transplantation had been performed more than one year before the date of our reassessments, were recruited for participation in this study, in a convenience sample. All of these patients underwent

elastography. Patients who presented post-transplantation vascular and biliary complications were excluded.

Procedures: biopsy, elastography and laboratory tests

The biopsy, elastography and laboratory tests were carried out on the same day, or with not more than 15 days between the procedures. All the ultrasound scans were performed by the same radiologist (JS), and all the anatomopathological exams by the same pathologist (VA). The radiologist and the pathologist were blinded to each other's evaluations and to the patients' laboratory results.

Blood samples were also taken from the patients (not more than 15 days before or after the biopsy and the ARFI examination), to evaluate the following variables: aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets, albumin, direct and indirect total bilirubin, blood glucose, insulin, Homa index, total cholesterol and fractions and triglycerides. The biochemical reference values were defined in accordance with the ranges of the institution's biochemistry laboratory.

The liver biopsies were collected subcutaneously,[3,4] guided by ultrasonography, using needles of 1.2-1.4 mm in diameter. The length of the liver biopsy tissue sample was at least 1.5 mm, with a minimum of 10 port spaces in all cases. The biopsy fragments were immediately fixed in formalin.

The inflammatory activity was graded and the fibrosis was staged in accordance with the criteria of the METAVIR Cooperative Study Group[12] classification and other histological parameters (**Chart 1**), for each liver biopsy. According to the METAVIR classification, patients staged as F0 or F1 were considered to have no fibrosis or minimal fibrosis. Significant fibrosis was defined as stages F2, F3 and F4. Patients classified as F4 were considered to have hepatic cirrhosis. For this study, the patients were divided in two groups: the F0-F1 group and the F2-F3-F4 group, given that patients with fibrosis grade 2 and above may require treatment, depending on the disease etiology.

The patients fasted for six hours prior to the elastography examination. The equipment used on all the patients was the Siemens S2000 with CH41 transducer (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA). Twenty hepatic elasticity acquisitions were performed, consisting of 10 in segment V and 10 in segment VIII, with the patient in dorsal decubitus or in left lateral decubitus. The patients held their breath for 5 seconds for each acquisition. The region of interest (ROI) was established in segments 5 and 8, with distances of 3 to 5 cm from the skin in all patients. The results from the measurement acquisitions were expressed in meters per second.

Statistical analysis

The MS-Excel electronic worksheet (Microsoft Office 2010 version) was used to organize the data, and IBM SPSS (Statistical Package for the Social Sciences), version 22.0, was used for the analysis. A significance level of 5% ($P < 0.05$) was used.

For inferential statistics, the measurements from ARFI elastography were compared between the fibrosis groups using the Mann-Whitney test. The Kruskal-Wallis and Mann-Whitney tests were used on the ARFI elastography measurements and groups were formed according to the fibrosis scores from the different hepatic regions. The ARFI elastography was analyzed via the median and the mean of the replicates. Cutoff values for elastography were investigated using receiver operating characteristic (ROC) curves.

RESULTS

During the study period, 33 patients who had undergone a liver transplant more than one year previously, between 2002 and 2010, were included and subjected to liver biopsy and elastography examinations. The original indication for transplantation had been cirrhosis due to the hepatitis C virus in 21 cases (63%) and other causes in 37% (**Table 1**). Among these 21 patients, 8 were alcohol users. The ARFI elastography was performed successfully in all cases. No complications from the liver biopsy were registered.

Twenty-two of these patients were men. The patients' average age was 55 ± 11 years (mean 49.7; minimum 21; maximum 74). The mean body mass index was 26.2 kg/m^2 (range: 16.3-32.7).

Chart 1. Histological variables analyzed by means of liver biopsy

Fibrosis
Portal fibrosis
Septa
Perisinusoidal fibrosis
Portal and periportal infiltrate
Lobular infiltrate
Steatosis
Balloonization
Sinusoidal dilation

Table 1. Indications for liver transplantation

Hepatitis C	21 patients
Hepatocellular carcinoma	2 patients
Alcohol-induced cirrhosis	2 patients
Fulminant hepatitis	2 patients
Autoimmune hepatitis	2 patients
Budd-Chiari syndrome	1 patient
Hepatitis C and carcinoma	2 patients
Alagille syndrome	1 patient
Total	**33 patients**

The anatomopathological results from the liver biopsies showed absence of fibrosis (stage F0) in 10 patients (out of 33, 30.3%), stage 1 fibrosis (F1) in 11 patients (33.3%), stage 2 fibrosis (F2) in eight patients (24.2%), stage 3 fibrosis (F3) in four patients (12.1%) and no cases of stage 4 fibrosis (F4; cirrhosis). The mean ARFI result was 1.11 ± 0.14 for patients staged as F0; 1.21 + 0.28 for those who were F1; 1.36 + 0.35 for patients in the F2 group; and 1.57 + 0.47 for F3 patients. There was no significant difference between groups for ARFI values (P = 0.10). There were significant associations between the fibrosis classification and the number of septa, portal fibrosis, perisinusoidal fibrosis, centrilobular fibrosis and periportal and portal infiltrate (P < 0.05). However, steatosis observed in the histological examination did not show any correlation with fibrosis stage according to ARFI (P > 0.05).

The fibrosis classification groups were then regrouped: FO-F1 (with 21 of the 33 cases, 63%) and F2-F3-F4 (with 12 cases, 37%). The ARFI value was significantly different between these two subgroups: 1.16 + 0.22 (median 1.12, minimum of 0.91 and maximum of 1.99) versus 1.43 + 0.38 (median of 1.38, minimum 0.84 and maximum 2.22), respectively.

The best cutoff value for ARFI that was able to differentiate F0-F1 from F2-F3-F4 was 1.29 m/s, which presented sensitivity of 0.66 (95% confidence interval, CI: 0.50 to 0.83) and specificity of 0.85 (95% CI: 0.72 to 0.97). The area under the ROC curve was 0.74 (95% CI: 0.55 to 0.94). **Table 2** shows the accuracy of ARFI at the different stages of fibrosis.

The Kruskal-Wallis test demonstrated statistical differences between the two groups, with P = 0.02 for the general degree of fibrosis (**Figure 1**), P = 0.031 for septa and P = 0.027 for centrilobular fibrosis. The cutoff point between the groups F0-F1 and F2-F3 was 1.29 m/s (**Figure 2**).

There was no statistical difference between the values from the ARFI elastography between the patients with hepatitis C and those with other hepatic diseases.

Table 2. Cutoff values for acoustic radiation force impulse (ARFI) elastography differentiating each group of patients according to the degree of fibrosis, evaluated by means of biopsy, with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)

Degreee of fibrosis	> F0	> F1	> F2
Cutoff ARFI value	1.26	1.29	1.42
AU-ROC [95% CI]	0.67 [0.50 to 0.87]	0.74 [0.55 to 0.94]	0.77 [0.5 to 1.00]
Sensitivity [95% CI]	0.43 [0.31 to 0.66]	0.68 [0.50 to 0.83]	0.75 [0.60 to 0.90]
Specificity [95% CI]	0.9 [0.81 to 1]	0.86 [0.72 to 0.97]	0.86 [0.76 to 0.99]
PPV [95% CI]	0.91 [0.76 to 10	0.91 [0.76 to 10]	1
NPV [95% CI]	0.43 [0.21 to 0.64]	0.41 [0.20 to 0.62]	0.38 [0.19 to 0.57]

DISCUSSION

The prospect of a reduction in the number of biopsy procedures performed on operated patients is very important, both for patients and for hospitals, because of the risk of the invasive examination and the cost. Therefore, this study strove to contribute through presenting an alternative to liver biopsy for evaluating post-transplantation liver elasticity.

New noninvasive diagnostic methods have arisen for evaluating the degree of liver fibrosis over recent years: serological tests, elastography and magnetic resonance imaging. Hepatic elastography has been highlighted due to its harmlessness, speed and technical ease of implementation.[13]

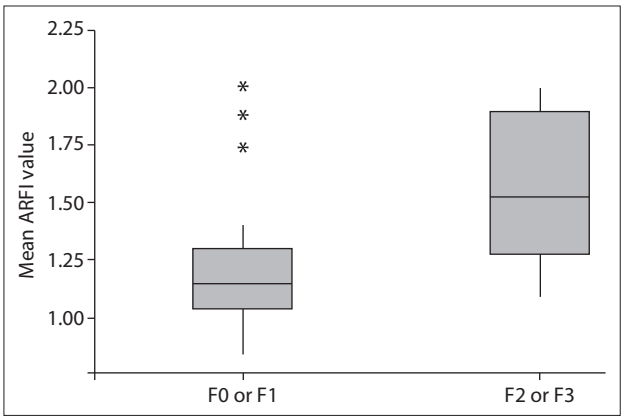

Figure 1. Boxplot of the results from acoustic radiation force impulse (ARFI) elastography regarding the general degree of fibrosis in the two groups of patients, with or without fibrosis.

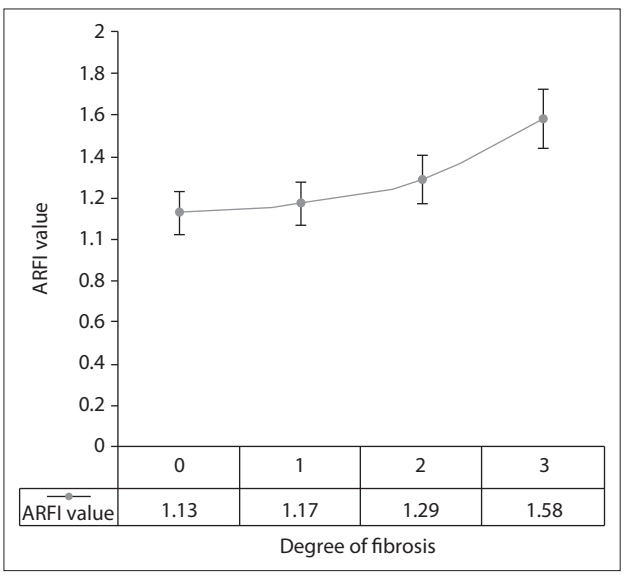

Figure 2. Analysis on the acoustic radiation force impulse (ARFI) values to detect a cutoff point that separates patients with and without fibrosis.

Transient elastography was the first widely disseminated method used for evaluating chronic hepatopathy.[17] Piscaglia et al.[8] demonstrated that transient elastography produced better results than did biochemical tests for quantifying the degree of fibrosis in patients undergoing liver transplantation because of the hepatitis C virus. In 56 patients, accuracy rates greater than 85% were obtained among those with significant fibrosis.[22] The study by Piscaglia et al.[8] contained a description of the importance of future investigations evaluating factors that interfere with hepatic fibrosis, such as hepatic steatosis, perisinusoidal fibrosis and other histological information.

There are few studies on transient elastography performed on transplanted livers, and a meta-analysis only gathered 470 patients.[22] The studies reviewed showed excellent results regarding identification of cirrhosis and good results in major fibrosis cases. However, findings of low levels of fibrosis from transient elastography may not rule out cirrhosis, and in these cases, biopsy is still needed. The major limitation of transient elastography and other noninvasive methods lies in the interpretation of results from intermediate stages of liver fibrosis. Additionally, transient elastography has the disadvantages of only using A and M modes, and the absence of a B mode precludes evaluation of the liver.

ARFI elastography, the subject of the present study, was the first technique to be coupled with conventional ultrasound equipment, and it has the advantage of viewing both the liver and the measurement site. A meta-analysis on more than 3,000 patients demonstrated that it had high accuracy for quantifying the degree of hepatic fibrosis,[23] and that its results were similar to those from transient elastography. However, few studies have used ARFI elastography on transplanted livers.[24]

Crespo et al.[25] examined 87 patients and found that the sensitivity and specificity of ARFI elastography were 76% for F2 and 85% for F4. Wildner et al.[26] used ARFI elastography on 58 patients who underwent transplantation and showed that the velocities were significantly higher in the patients with advanced fibrosis. In the present prospective study, despite the limited number of patients, two primary results can be noted: firstly, ARFI elastography was able to distinguish between livers transplanted in the group with F0-F1 and those in the group with F2-F3, with a statistically significant difference. There was significant correlation between the velocities obtained and the presence of septa and centrilobular fibrosis.

The current case study was on patients who received transplants due to hepatitis C virus or other forms of chronic hepatopathy. In the analysis on the two fibrosis groups, the underlying disease was not taken into consideration. This was in fact one limitation of this study: its analysis of patients with hepatitis C and other liver diseases together. Another limitation was the low number of patients, which serves as a stimulus for further investigations on this subject. The velocities obtained in the various degrees of fibrosis following transplantation were similar to those described in populations of chronic hepatopathy cases that did not undergo transplantation.[10,13]

These preliminary results indicated that the values obtained through ARFI elastography were not affected by conditions that could change these values, such as inflammatory reactions or anatomical alterations. Absence or a low number of patients with F4 was expected, as also found by other authors, due to the good results from antiviral therapies. The differences between biopsy and ARFI results may be due to histological analyses performed in different regions of the liver, heterogeneous liver tissue samples and obese patients. We believe that the following factors could possibly lead to wrong diagnostic conclusions: biopsy samples smaller than 1.5 cm with less than 10 portal spaces; heterogeneous liver tissue, with variable fibrosis density; or obese patients, in which the elastography results are false negatives or false positives.

The second conclusion is that a cutoff value of 1.29 meters per second that separates patients with or without significant fibrosis was identified. This may influence antiviral therapy over the short term, because higher velocities indicated by ARFI mean higher degrees of fibrosis, which require antiviral treatment. The follow-up on fibrosis progression could include this noninvasive method in future post-transplantation protocols.

The goal of ARFI elastography is not to replace liver biopsy in all transplanted livers. Other alterations, such as rejections and vascular or biliary abnormalities, usually require a liver biopsy for diagnosis and follow-up.

This study has demonstrated promising results with regard to differentiation of patients with fibrosis grades 0 and 1 from those with grades 2 to 4, through ARFI elastography. Further studies with larger samples of patients are necessary in order to confirm these results and possibly include ARFI in the protocol for evaluating transplantation patients.

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Sources of funding: None
Conflict of Interest: None

Date of first submission: June 24, 2016
Last received: August 15, 2016
Accepted: August 17, 2016

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Cutoffs and cardiovascular risk factors associated with neck circumference among community-dwelling elderly adults: a cross-sectional study

Pontos de corte e fatores de risco cardiovascular associados com a circunferência do pescoço em idosos da comunidade: um estudo transversal

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KEY WORDS:
Anthropometry.
Blood pressure.
Obesity.
Aged.
Primary health care.

PALAVRAS-CHAVE:
Antropometria.
Pressão sanguínea.
Obesidade.
Idoso.
Atenção primária à saúde.

ABSTRACT

CONTEXT AND OBJECTIVE: In elderly people, measurement of several anthropometric parameters may present complications. Although neck circumference measurements seem to avoid these issues, the cutoffs and cardiovascular risk factors associated with this parameter among elderly people remain unknown. This study was developed to identify the cutoff values and cardiovascular risk factors associated with neck circumference measurements among elderly people.

DESIGN AND SETTING: Cross-sectional study conducted in two community centers for elderly people.

METHODS: 435 elderly adults (371 women and 64 men) were recruited. These volunteers underwent morphological evaluations (body mass index and waist, hip, and neck circumferences) and hemodynamic evaluations (blood pressure values and heart rate). Receiver operating characteristic curve analyses were used to determine the predictive validity of cutoff values for neck circumference, for identifying overweight/obesity. Multivariate analysis was used to identify cardiovascular risk factors associated with large neck circumference.

RESULTS: Cutoff values for neck circumference (men = 40.5 cm and women = 35.7 cm), for detection of obese older adults according to body mass index, were identified. After a second analysis, large neck circumference was shown to be associated with elevated body mass index in men; and elevated body mass index, blood pressure values, prevalence of type 2 diabetes and hypertension in women.

CONCLUSION: The data indicate that neck circumference can be used as a screening tool to identify overweight/obesity in older people. Moreover, large neck circumference values may be associated with cardiovascular risk factors.

RESUMO

CONTEXTO E OBJETIVO: Em idosos, diversas ferramentas antropométricas podem apresentar complicações durante a mensuração. Embora a circunferência do pescoço pareça evitar tais problemas, os pontos de corte e fatores de risco cardiovascular associados a essa ferramenta em idosos permanecem desconhecidos. Este estudo foi desenvolvido para identificar os valores de ponto de corte e fatores de risco cardiovascular associados à circunferência do pescoço em idosos.

DESENHO E LOCAL: Estudo transversal, realizado em dois centros comunitários para idosos.

MÉTODOS: 435 idosos (371 mulheres e 64 homens) foram recrutados. Os voluntários foram submetidos a avaliação morfológica (índice de massa corporal e cintura, quadril, e circunferência do pescoço) e hemodinâmica (valores da pressão arterial e frequência cardíaca). A análise pela curva *receiver operating characteristic* foi usada para determinar o valor preditivo dos valores de ponto de corte da circunferência do pescoço para identificação de sobrepeso/obesidade. Análise multivariada foi usada para identificar os fatores de risco cardiovascular associados com circunferência do pescoço larga.

RESULTADOS: Os valores de corte para circunferência do pescoço (homens = 40,5 cm e mulheres = 35,7 cm) para detectar adultos idosos obesos, de acordo com o índice de massa corporal, foram identificados. Depois da segunda análise, circunferência do pescoço larga foi associada com elevado índice de massa corporal em homens e mulheres e elevados valores de pressão arterial, prevalência de diabetes *mellitus* tipo II e hipertensão em mulheres.

CONCLUSÃO: Os dados indicam que a circunferência do pescoço pode ser utilizada como ferramenta de rastreio para identificar sobrepeso/obesidade em idosos. Ademais, altos valores de circunferência do pescoço podem estar associados com fatores de risco cardiovascular.

INTRODUCTION

Worldwide projections indicate that there will be an exponential increase in the geriatric population over the coming decades.[1] Today, elderly people represent around 15% of the world population, but by 2050, this percentage is expected to double, to reach values near 30%.[1] This phenomenon demands special attention, since aging is associated with increased cardiovascular risk factors (e.g. hypertension and type 2 diabetes), along with the risk of development of sarcopenia and frailty (e.g. decreased muscle power and strength).[2-5]

Epidemiological data from the World Health Organization (WHO) show that, worldwide, more than half a billion adults (i.e. > 18 years old) are overweight or obese.[6] Among elderly people, obesity is one of the most prevalent morbidities, reaching approximately 40% of this population in some countries.[7]

Obesity is a multifactorial condition caused by social, economic, behavioral and biological factors. The prevalence rate of obesity has increased significantly over recent decades, both in developed and in developing countries, thus leading to pandemic status for this morbid condition.[8,9] In Brazil, the prevalence of overweight among adults increased from 43% in 2006 to 52.5% in 2014. Among older adults, the prevalence of overweight and obesity is higher than among younger adults (18-34 years old).[10]

Obesity is associated with several forms of cancer (e.g. esophageal, colon and renal) and contributes towards development of many disorders: metabolic (e.g. glucose intolerance and hyperinsulinemia), hemodynamic (e.g. high blood pressure), endothelial (e.g. increased oxidative stress) and inflammatory.[8,9] Moreover, obesity has been shown to correlate with physiological disorders (e.g. depression and anxiety), muscle weakness (i.e. sarcopenic obesity) and social and economic problems.[8,9,11] Thus, obesity is a public health concern, and continuous monitoring and early detection can prevent the onset of its adverse outcomes.

Since the data and projections indicate that Brazilians are getting older and fatter, continuous monitoring is essential for avoiding these issues associated with obesity among older adults. Regarding the methods used to measure overweight/obesity, neck circumference (NC) has been suggested as a low cost, reliable, non-invasive, easy reproducible and efficient approach for identifying overweight and obese children, adolescents and adults, and cutoff values have been suggested for these populations.[12-21] Moreover, there is some evidence demonstrating that NC is associated with cardiovascular risk factors, such as high waist and hip circumferences, elevated blood pressure values and high total cholesterol and glycemia levels.[12,13,17] However, even though optimal cutoff values for adults have been suggested and have been observed to be associated with cardiovascular risk factors (e.g. elevated blood pressure and insulin resistance),[20,21] there are no data in the literature regarding specific cutoffs for the elderly population.

Therefore, the purpose of this study was to develop cutoff values for identifying overweight/obesity among older adults, and to indicate the cardiovascular risk factors associated with large NC values among women and men.

OBJECTIVE

The aim of this study was to evaluate NC as a screening tool for detecting overweight and obesity in accordance with the body mass index (BMI) classification for the elderly population, as defined by chronology (≥ 60 years old); and secondarily to investigate the cardiovascular risk factors associated with large NC.

METHODS

Design

This study had a cross-sectional design and evaluated a convenience sample. Experiments were developed in the city of Poá, state of São Paulo, Brazil, in 2015.

Subjects

The participants of the present study were recruited voluntarily from two specialized public community health centers for older adults in southeastern Brazil, between February and November 2015. In both centers, they undertook social activities that predominantly involved the physical and cognitive domains. The physical activities comprised a multimodal exercise program that stimulated several physical capabilities (muscle strength, muscle power and cardiorespiratory fitness) within the same exercise session. These sessions lasted approximately 40 minutes and involved low to moderate-intensity physical activities: water aerobics, folk dancing and yoga. Painting was the only activity that predominantly involved the cognitive domain. After registration, these older adults were automatically enrolled in all activities. However, they were not required to participate in or perform activities every day. It is important to mention that neither center was responsible for rehabilitation or for any kind of medical treatment, and that these elderly individuals were functionally and cognitively able to understand and perform all the activities. Moreover, for all participants with clinical diagnoses of diseases (e.g. hypertension or diabetes mellitus type II), their pathological condition was controlled and monitored by their private physician.

These volunteers were recruited according to convenience and were invited orally to participate in this research.

The inclusion criterion was that the subjects needed to be people aged 60 years or over who could perform the study procedures. The exclusion criteria were:

1. morbid obesity, according to the BMI classification (i.e. over 40 kg/m^2); and
2. presence of a disease or condition that could disturb the NC measurement (e.g. goiter).

All subjects provided informed consent before being enrolled in the study procedures. This study was approved by the Research Ethics Committee of the University of Mogi das Cruzes (Universidade de Mogi das Cruzes, UMC), and it was developed in accordance with the Declaration of Helsinki and with Resolution 196/96 of the Brazilian Health Council.

Anthropometric measurements

Weight, height and BMI

A weight scale with a Filizola (Brazil) stadiometer was used to measure body mass (kg) and height (cm). The BMI was determined as follows: body mass index = (kg)/(height [m])^2. A model proposed through the Health, Wellbeing and Aging (Saúde, Bem Estar e Envelhecimento, SABE) study in conjunction with the Pan-American Health Organization (PAHO) study was used to classify BMI.[22] Values ≥ 28 kg/m^2 were considered to represent overweight/obesity for elderly adults.[22]

Circumferences

For all evaluations, i.e. waist circumference (WC), hip circumference (HC) and neck circumference (NC), a flexible and inextensible anthropometric tape (Sanny, Brazil) was used. The subjects remained in the standing position, with head held erect, eyes looking forward, arms relaxed at the side of the body and feet kept together, wearing light clothes. WC was assessed at the midpoint between the last floating rib and the highest point of the iliac crest.[23] HC was evaluated at the highest point of the buttocks.[23] NC was measured just above the cricoid cartilage and perpendicular to the long axis of the neck.[20] If necessary, to facilitate the measurement, the evaluator would possibly require the patient to look up. Starting from the small prominence of the thyroid cartilage, the evaluator applied light pressure using the forefinger and middle finger, moving downwards to find a small space and subsequently the cricoid cartilage in the region demonstrated in **Figure 1**. All subjects were evaluated twice, and the larger measurement was used in the analyses.

Prevalence of morbidities and use of medications

Information regarding prevalence of morbidities (pathological conditions) and use of medications was collected from the medical records of each subject by two researchers and the data were compared. Since both of the community health centers serve a large number of patients, and the medical team (i.e. nurse, physician and physical educator) is of limited size, the pathological conditions and medications used were simply recorded by the head physician and head nurse of each center. A specialist who was not affiliated to and was outside the center then made the diagnosis. In summary, before the participant began the activities in the center, a medical consultation was conducted and the diseases already diagnosed, along with the medications used, had to be informed by the physician. Moreover, over the course of the year, the participants in both centers underwent medical consultations and were asked about symptoms (e.g. pain, polydipsia or polyuria) that are associated with highly prevalent pathological conditions among elderly people (e.g. osteoarthritis or diabetes mellitus type II). Blood pressure and glycemia values were measured and recorded by the nurses on a personal card before all physical activities at any time during the day. It should be noted that the classification of cardiovascular disease (CVD) was based on previous clinical diagnoses of myocardial infarction, stroke (ischemic and hemorrhagic), heart failure (none of the subjects in the present study showed this), arrhythmia and heart valve problems. This personal card was presented by the patient to the physician on the day of the consultation, and, if necessary, the patient was referred to a specialist. If the diagnosis was confirmed, the patient needed to inform the nurse. Regarding the mean number of medications used by the patients (MNM), only the drugs associated with the disease(s) that had been clinically diagnosed were

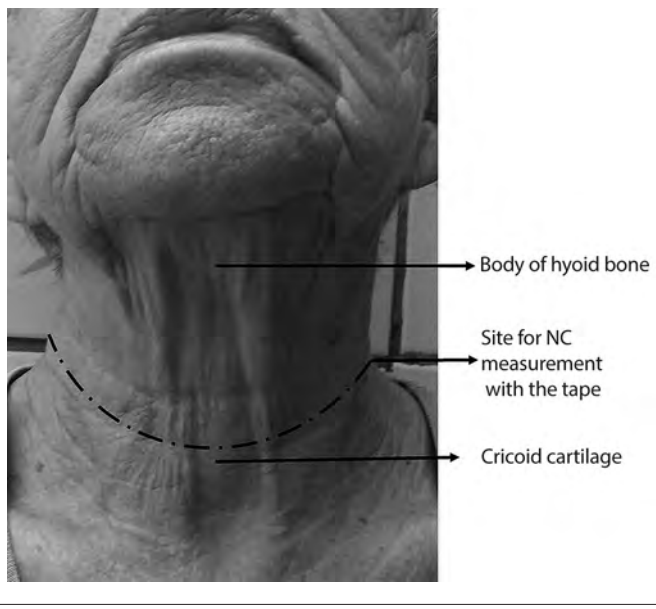

Figure 1. Neck circumference (NC) was measured just above the cricoid cartilage and perpendicular to the long axis of the neck. If necessary, to facilitate the measurement, the evaluator would possibly require the patient to look up. Starting from the small prominence of the thyroid cartilage, the evaluator applied light pressure using the forefinger and middle finger, moving downwards to find a small space and subsequently the cricoid cartilage in the region demonstrated in the photograph. The dashed line represents the point at which the NC should be measured. The cutoff values for NC evaluation were 35.7 cm for women and 40.5 com for men.

quantified. Therefore, over-the-counter medications were not included. Since the medical records were reviewed and updated every six months, the MNM related to the last six months.

Cardiovascular parameters

All cardiovascular parameters were verified with the subjects at rest. The procedures for measuring blood pressure were adapted from the Seventh Joint National Committee for High Blood Pressure (JNC7).[24] In summary, the elderly individual was placed in a sitting position on a comfortable chair for 15 minutes in a dark and quiet room. After this period, a cuff of the correct size was placed approximately at the midpoint of the upper left arm (heart level). An automatic, noninvasive and validated[25] arterial blood pressure monitor (Microlife-BP 3BT0A, Microlife, Widnau, Switzerland) was used to measure systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR). The mean arterial pressure (MAP), double product (DP) and pulse pressure (PP) were evaluated according to the following equations:

$MAP = [SBP + (2 * DBP)]/3$; $DP = SBP * HR$; and
$PP = SBP - DBP$.

The size of the arm cuff was selected after measuring the arm circumference (Sanny, São Paulo, Brazil).

Statistical analyses

Phase one of the statistical analysis was performed to evaluated whether NC could be used as a screening tool for detecting conditions of overweight and obesity in accordance with the BMI classification among elderly women and men. Continuous data (e.g. age) and categorical data (e.g. prevalence) on the characteristics of these elderly adults according to BMI and gender were compared by means of the independent t test and chi-square test (χ^2). Pearson's correlation was performed to analyze the association of NC with age and anthropometric measurements (i.e. BMI, WC, HC and WC/HC). Receiver operating characteristic (ROC) curve analyses were used to determine the predictive validity of NC, and to evaluate optimal cutoff values for identifying overweight/obese older adults in accordance with the BMI classification. Sensitivity and specificity were used to find the optimal cutoff values.

Phase two consisted of investigation of the cardiovascular risk factors associated with higher NC. After the subjects had been categorized dichotomously according to their NC values from phase one, continuous data were compared by means of the independent t-test. The χ^2 test was performed to investigated the association between the dependent categorical variable (i.e. NC) and independent categorical variables (age, BMI, SBP, DBP, MAP, HR, DP, PP, MNM, hypertension [HTN], diabetes mellitus type II [DMTII], arthritis and cardiovascular disease [CVD]). For the categorical determinations, cutoffs for the diagnosis of hypertension (in accordance with JNC7) were used for SBP and DBP, while medians were used for age, MAP, HR, DP, PP and MNM. Independent variables that showed P-values ≤ 0.20 were added sequentially one by one, in increasing P-value order, in the univariate logistic binary analysis. Similarly, variables that showed P-values ≤ 0.05 were added sequentially, one by one, in increasing order of the value of P in the multivariate logistic binary analysis. The fit of the multiple regression model was evaluated by means of the Hosmer-Lemeshow[26] test. All analyses were conducted using the Statistical Package for the Social Sciences software (SPSS; IBM, Chicago, IL, USA), version 20.0.

RESULTS

Firstly, 758 subjects from two specialized public community health centers were invited to participated in the present study. Two hundred and thirty-four of the invited subjects were middle-aged and unable to commit to the present study. Among the remaining 524 older adults, 76 refused to participate, six did not sign the informed consent statement and seven were excluded due to morbid obesity (n = 5) or goiter (n = 2). Therefore, 435 volunteers (371 women [85.2%] and 64 men [14.8%]), of whom 396 were from the first center (Cantinho de Convivência do Idoso da Cidade de Poá) and 39 were from the second center (Instituto Renascer), formed the sample of the present study.

The prevalences of overweight and obesity (after exclusion of the morbidly obese individuals) were 44.8% (women) and 46.6% (men), according to the BMI classification. **Table 1** shows the characteristics of the sample according to BMI and gender.

The anthropometric measurements (i.e. WC, HC, WC/HC and NC) were higher in high-BMI subgroups than in low-BMI subgroups, in all groups (P = 0.000). The prevalences of HTN, DMTII and arthritis were higher in high-BMI subgroups than in low-BMI subgroups among the elderly women, but not among the elderly men. The prevalences of MNM, CVD and osteoporosis did not differ between the subgroups.

Pearson's correlation was performed between NC (dependent variable) and age, weight and anthropometric measurements (e.g. WC, HC and WC/HC) (independent variables). NC was shown to be significantly correlated with age, weight, BMI, WC and WC/HC, in both groups (men and women). However, NC did not show any significant correlation with HC in either group (men: r = 0.20; P = 0.11; women: r = 0.02; P = 0.73). Moreover, Pearson's classification was similar in both groups. Age and WC/HC showed weak correlation coefficients (Age: men: r = -0.15; women: r = -0.12; and WC/HC: men: r = 0.11; women: r = 0.02); while weight (men: r = 0.67; women: r = 0.56), BMI (men: r = 0.55; women: r = 0.47) and WC (men: r = 0.60; women: r = 0.45) showed moderate correlation coefficients.

The receiver operating characteristic (ROC) curve, optimal cutoff and negative and positive likelihood ratio (LR) results are described below. The area under the curve (AUC) showed values

higher than 0.7 in both groups (men = 0.817 and women = 0.819), thus indicating clinical significance. Optimal cutoffs were found both for men (40.5 cm; CI: 0.704-0.929; P < 0.001; sensitivity: 0.864; and specificity: 0.317) and for women (35.7 cm; CI: 0.774-0.863; P < 0.001; sensitivity: 0.821; and specificity: 0.311). The results demonstrated that elderly men (LR+: 2.724; LR-: 0.367) and women (LR+: 2.637; LR-: 0.379) who presented values higher than the optimal cutoff for NC were approximately twice as likely to be overweight and obese according to the BMI classification as were older adults with small NC values.

Because of the results from the first phase, which demonstrated the capacity of NC to screen for overweight and obesity among elderly people of both genders in accordance with their BMI, a second analysis was performed to ascertain the factors associated with large NC. After excluding one volunteer (due to missing data), the sample (n = 434) was allocated to four groups according to NC (i.e. large or small) and gender (i.e. men or women). Weight and BMI were higher in the large-NC subgroup than in the normal-NC subgroup, regardless of gender. Blood pressure measurements at rest did not show similar behavior between the groups. The large-NC subgroup of elderly women showed higher DBP and MAP than did the normal-NC subgroup. Meanwhile, the large-NC subgroup of elderly men showed higher PP than did the normal-NC subgroup. These data are shown in **Table 2**.

A χ^2 test was performed to analyze the association between categorical variables. Among the elderly women, age (0.028),

Table 1. Characteristics of the older adults according to BMI and gender

Variable	Women (n = 371)		P	Men (n = 64)		P
	Normal BMI (n = 198)	High BMI (n = 173)		Normal BMI (n = 42)	High BMI (n = 22)	
Age (years)	68.5 ± 6.3	66.8 ± 4.9	0.004	69.3 ± 5.6	67.7 ± 5.5	0.290
Weight (kg)	59.7 ± 8.2	78.1 ± 11.5	< 0.001	69.9 ± 8.7	86.0 ± 9.0	< 0.001
Height (m)	1.55 ± 0.1	1.56 ± 0.0	0.661	1.67 ± 0.07	1.67 ± 0.07	0.940
BMI (kg/m^2)	24.1 ± 2.7	32.1 ± 3.3	< 0.001	25.0 ± 2.2	30.6 ± 1.8	< 0.001
WC (cm)	88.7 ± 8.4	105.0 ± 12.2	< 0.001	94.4 ± 8.3	107.2 ± 8.3	< 0.001
HC (cm)	101.8 ± 68.4	111.8 ± 7.8	0.056	97.6 ± 5.6	104.0 ± 13.6	0.01
WC/HC	0.90 ± 0.12	0.94 ± 0.10	0.012	0.96 ± 0.07	106 ± 2.69	0.037
NC (cm)	34.7 ± 2.4	38.3 ± 6.2	< 0.001	39.0 ± 2.9	42.5 ± 2.8	< 0.001
MNM	1.2 ± 1.4	1.4 ± 1.3	0.267	1.7 ± 1.5	1.6 ± 1.4	0.850
Hypertension prevalence (%)	48.3	51.7	0.011	59.0	41.0	0.162
DMTII prevalence (%)	41.5	58.5	0.035	70.6	29.4	0.615
Arthritis prevalence (%)	40.0	70.0	< 0.001	45.5	54.5	0.122
CVD prevalence (%)	41.0	59.0	0.102	70.0	30.0	0.751
Osteoporosis prevalence (%)	57.5	42.5	0.308	40.0	60.0	0.209

BMI = body mass index; WC = waist circumference; HC = hip circumference; WC/HC = waist to hip ratio; NC = neck circumference; DMTII = diabetes mellitus type II; CVD = cardiovascular disease; MNM = mean number of medications used by the patients.

Table 2. Characteristics of the older adults according to NC and gender

Variable	P	Women (n = 371)		P	Men (n = 63)		P*
		Normal NC (n = 167)	Large NC (n = 204)		Normal NC (n = 31)	Large NC (n = 32)	
Age (years)	0.007	68.2 ± 5.9	67.2 ± 5.5	0.09	69.7 ± 6.1	68.0 ± 5.0	0.233
Weight (kg)	< 0.001	60.1 ± 9.4	74.9 ± 12.6	< 0.001	67.8 ± 9.2	83.0 ± 8.7	< 0.001
Height (m)	< 0.001	1.54 ± 0.13	1.57 ± 0.12	0.07	1.64 ± 0.80	1.69 ± 0.05	0.003
BMI (kg/m^2)	< 0.001	24.8 ± 3.8	30.2 ± 4.5	< 0.001	25.1 ± 3.3	28.8 ± 2.5	< 0.001
SBP (mmHg)	0.138	132.6 ± 17.1	141.8 ± 91.6	0.200	126.5 ± 2.2	135.6 ± 17.7	0.064
DBP (mmHg)	0.006	75.1 ± 10.4	78.3 ± 10.8	0.005	75.9 ± 14.9	77.3 ± 10.7	0.655
MAP (mmHg)	0.032	94.3 ± 11.0	99.5 ± 32.9	0.052	92.7 ± 15.0	96.7 ± 12.1	0.250
HR (bpm)	0.435	79.5 ± 50.0	76.9 ± 12.5	0.485	74.0 ± 11.0	71.0 ± 12.6	0.327
DP (mmHg.bpm)	0.608	10.517 ± 6.2	10.843 ± 6.0	0.611	9.456 ± 2.5	9.709 ± 2.5	0.693
PP (mmHg)	0.280	57.4 ± 11.9	63.2 ± 89.7	0.414	50.6 ± 16.4	58.2 ± 12.4	0.043
MNM	0.013	1.1 ± 1.3	1.4 ± 1.4	0.067	1.7 ± 1.6	1.6 ± 1.4	0.890

NC = neck circumference; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = heart rate; DP = double product; PP = pulse pressure; MNM = mean number of medications used by the patients.

*P-value refers to the comparison among the Large NC (women and men) and Normal NC (women and men).

BMI (< 0.001), MAP (0.005), HTN (0.001), DMTII (< 0.001) and arthritis (0.041) showed significant P-values to be added to the logistic binary analyses. In turn, the elderly men presented a lower number of associated variables than the elderly older women: BMI (< 0.001), SBP (0.056), MAP (0.055), HTN (0.030) and arthritis (0.023)

Tables 3 and **4** show the results regarding the unadjusted odds ratio (OR), adjusted OR and 95% CI for NC in both groups (women and men, respectively).

After the unadjusted OR analyses, age (P = 0.03), BMI (P < 0.001), MAP (0.005), hypertension (P = 0.001), DMTII (P < 0.001) and arthritis (P = 0.04) were added sequentially, one by one, in increasing P-value order, in the multivariate analysis on the group of elderly women. Likewise, BMI (P < 0.001), SBP (P = 0.06), MAP (P = 0.05), HTN (P = 0.03) and arthritis (P = 0.03) were added in the analysis on the group of elderly men. After the adjusted OR analyses, BMI was still found to be significantly associated with large NC among the elderly women (adjusted OR: 2.246

Table 3. Unadjusted odds ratio (OR), adjusted OR and 95% confidence intervals (CI) for neck circumference (NC) among older women

Variable	Univariate analysis			Multivariate analysis		
	Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age (years)						
≥ 75	-0.704	0.262-0.934	0.030	-0.437	0.296-1.407	0.271
< 75	Ref.			Ref.		
BMI (kg/m²)						
≥ 28	2.284	6.013-16.032	< 0.001	2.246	5.697-15.681	< 0.001
< 28	Ref.			Ref.		
MAP (mmHg)						
≥ 95	0.589	1.189-2.733	0.005	0.524	1.032-2.766	0.037
< 95	Ref.			Ref.		
Hypertension						
Yes	0.720	1.341-3.149	0.001	0.572	1.061-2.958	0.029
No	Ref.			Ref.		
DMTII						
Yes	1.093	1.626-5.476	< 0.001	0.914	1.237-5.026	0.011
No	Ref.			Ref.		
Arthritis						
Yes	0.458	1.018-2.454	0.041	-0.022	0.572-1.673	0.937
No	Ref.			Ref.		

BMI = body mass index; MAP = mean arterial pressure; DMTII = diabetes mellitus type II; CVD = cardiovascular disease; Ref = reference.

Table 4. Unadjusted odds ratio (OR), adjusted OR and 95% confidence intervals (CI) for neck circumference (NC) in older men

Variable	Univariate analysis			Multivariate analysis		
	Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
BMI (kg/m²)						
≥ 28	2.613	3.418-54.437	< 0.001	2.613	3.418-54.437	< 0.001
< 28	Ref.			Ref.		
SBP (mmHg)						
≥ 140	1.138	0.944-10.308	0.062	—	—	—
< 140	Ref.			—	—	—
MAP (mmHg)						
≥ 90	0.933	0.967-7.541	0.058	0.873	0.476-12.040	0.289
< 90	Ref.			Ref.		
Hypertension						
Yes	1.163	1.102-9.292	0.032	0.903	0.684-8.897	0.168
No	Ref.			Ref.		
Arthritis						
Yes	1.736	1.115-28.871	0.037	1.930	0.934-50.787	0.058
No	Ref.					

BMI = body mass index; SBP = systolic blood pressure; MAP = mean arterial pressure; Ref = reference.

[5.697-15.681]) and elderly men (adjusted OR: 2.613 [3.418-54.437]). However, DMTII (adjusted OR: 0.914 [1.237-5.026]), high MAP (adjusted OR: 0.524 [1.032-2.766]) and HTN (adjusted OR: 0.572 [1.061-2.958]) also showed significant results in the group of elderly women.

DISCUSSION

In this study, NC was shown to be a useful screening tool for verifying conditions of overweight/obesity through the BMI among elderly women and men, since AUC showed values higher than 0.7 in both groups. Furthermore, these AUC values were higher in relation to NC than in relation to other parameters commonly used to assess body composition, such as WC/HC (AUC: men = 0.68; and women = 0.62). After identifying the cutoff values for NC (men = 40.5 cm; and women = 35.7 cm) (**Figure 1**), a second analysis was performed to ascertain the cardiovascular risk factors associated with large NC. The data showed that large NC was associated with high BMI in both groups. Moreover, large NC among elderly women was also associated with high MAP and high prevalences of HTN and DMTII.

These data seem to be important, given that some authors have suggested that NC is a low-cost, reliable, noninvasive and easy reproducible tool.[12,13,17] Furthermore, some parameters that are usually used to evaluate obesity (e.g. waist circumference) can be burdensome to use because of the necessity for extensive training of the evaluators and because of measurement site differences, clothing restrictions, religious and social factors, time taken and weather conditions.[14,18,19,27] These factors may preclude or at least decrease the feasibility of using other parameters (WC and HC).[14,18,19,27] On the other hand, these issues seem to be avoided during NC measurement.[14,18,19,27]

Moreover, it is possible to suggest that NC may be a more suitable means for anthropometric measurements among elderly people than other tools, since its evaluation can be performed with the subject in a seated position, with no need to use light clothing (thereby avoiding awkward moments). In addition, the breathing phase does not change the results. Indeed, older adults may present conditions that impair their capacity to remain in an upright standing position, such as frailty, sarcopenia, osteopenia, osteoporosis, arthritis or different kinds of pain or skeletal muscle weakness. Elderly people may have impaired ability to maintain breathing control (e.g. in cases of chronic obstructive pulmonary disease). They may have religious and/or other beliefs regarding clothing, such as the necessity to wear a dress or skirt during measurements, especially among older women.

Studies have been conducted to describe NC cutoff values for factors associated with metabolic syndrome among Brazilian adults.[20,21] However, to our knowledge, our study was the first to ascertain cutoff values for NC in relation to obesity among elderly Brazilians. Thus, because of the lack of studies that aimed to record the association between NC and cardiovascular risk factors among elderly Brazilians, the present discussion is based in both of these studies, which studied samples with a wide age range (i.e. approximately 18-74 years of age).[20,21] Interestingly, both of these studies show cutoff values similar to those of our study.[20,21] Data from Stabe et al. showed that men and women with NC values larger than 40 cm and 36.1 cm, respectively, had higher odds of presenting show insulin resistance and metabolic syndrome than did adults with small NC.[21] Similarly, Baena et al., who studied a sample of 8726 Brazilian adults, showed that men and women with large NC (> 40 cm and > 34.1 cm, respectively) had higher odds of presenting insulin resistance, low HDL, elevated blood pressure and high triglycerides than did the small-NC group.[20]

Regarding the results from correlating NC with cardiovascular risk factors, other studies conducted using Brazilian samples[20,21,28,29] and non-Brazilian samples[12,13,17] corroborate our data. These studies showed that NC is positively associated with fasting triglyceride, glucose, insulin, adiponectin, glycated hemoglobin and blood pressure values, carotid intima-media thickness, uric acid levels and plasminogen activator inhibitor levels (PAI-1), as well as negatively with HDL-cholesterol values.[12,13,17,20,21,28,29]

Interestingly, even though the HTN condition was associated with large NC among elderly women, the hemodynamic measurements made at rest in the present study, except for MAP among elderly women, did not show any association with NC. In both community centers, the elderly individuals underwent constant medical monitoring, since blood pressure was measured every day and abnormalities in these measurements were reported immediately to the head nurse. If these measurements were recurrent, the patients would if necessary be referred to a specialist (i.e. a cardiologist). Taken together with data on the MNM (approximately 1.5), this may indicate that the absence of any association between the factors (hemodynamic measurements at rest and NC) was due to control over the clinical parameters (i.e. blood pressure and heart rate) that are associated with manifestations of the pathological condition (i.e. HTN). However, despite the use of automatic, noninvasive and validated arterial blood pressure monitoring,[25] blood pressure is not a sensitive hemodynamic measurement and better tools, such as ambulatory blood pressure monitoring (ABPM) need to be used to make comparisons with our data and provide better understanding about this association.

Even though the present study was not able to elucidate the mechanisms that can explain the association of NC with diabetes and HTN, evidence in the literature allows inferences

to be made. As mentioned earlier, cross-sectional studies have been showing that NC is associated with factors present in the genesis of DMTII, such as high fasting glucose, insulin and adiponectin, and in the progression of DMTII (i.e. glycated hemoglobin).[12,13,17,28,29] Similarly, increased carotid intima-media thickness, which is a marker of atherosclerosis and, consequently, associated with hypertension, has been shown to have an association with large NC.[29]

Moreover, it has been suggested that NC is a surrogate marker for upper-body subcutaneous fat,[20,21,28,29] which is more lipolytically active than lower body fat,[30,31] due to its association with insulin resistance, impaired glucose uptake, atherosclerosis and endothelial dysfunction. Therefore, higher bioavailability of free fatty acids can be suggested as a common pathway in the relationship between NC and DMTII/HTN.

Some of the limitations of this study include

- the lack of biochemical measurements, which would have had the capacity to lead to better understanding about the association of NC with cardiovascular risk factors among elderly people;
- the limited number of men participating in the research protocol, which may represent bias and limitation on the inferences possible;
- use of data in the medical files to quantify the prevalence of morbidities and drug consumption; and
- lack of cutoffs for abnormal NC.

Thus, a study design comprising large numbers of non-selected samples and follow-up in order to identify individuals who develop major clinical conditions is necessary. Therefore, further studies evaluating larger samples and including biochemical measurements are recommended in order to confirm our findings.

CONCLUSION

Neck circumference is a useful screening tool for detecting overweight/obesity among community-dwelling older adults. Furthermore, it was verified that large NC is associated with increased cardiovascular risk factors.

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Sources of funding: None
Conflict of interest: None

Date of first submission: June 24, 2016
Last received: July 21, 2016
Accepted: September 11, 2016

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DOI: 10.1590/1516-3180.2016.0034150516

Human immunodeficiency virus in institutionalized elderly people

Vírus da imunodeficiência humana em idosos institucionalizados

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KEY WORDS:
Aged.
Health services for the aged.
HIV seroprevalence.
HIV infections.
Homes for the aged.

PALAVRAS CHAVES:
Idoso.
Serviços de saúde para idosos.
Soroprevalência de HIV.
Infecções por HIV.
Instituição de longa permanência para idosos.

ABSTRACT

CONTEXT AND OBJECTIVE: A search in the SciELO and PubMed databases showed few studies on human immunodeficiency virus (HIV) positive individuals in long-term care institutions (LTCIs), thus prompting the present study. The aim of this study was to ascertain whether there were any HIV-positive individuals in LTCIs for the elderly.

DESIGN AND SETTING: Cross-sectional study in which the Hospital Infection Control Committee (HICC) of a 405-bed LTCI was consulted.

METHODS: The medical records of 405 individuals interned in the LTCI who had been tested for HIV infection were requested for analysis of the following variables: [1] age and gender; [2] length of stay at LTCI (months); [3] causes and diagnoses on admission to LTCI according to International Classification of Diseases, 10th edition; [4] date of HIV diagnosis; [5] seropositivity for syphilis and hepatitis B and C viruses; [6] medications used at last prescription in medical file; and [7] mean CD4 lymphocyte count based on: total lymphocyte count/6 and total lymphocyte count x 0.8 x 0.2 or 0.3.

RESULTS: Four men were HIV-positive, with mean age 71.2 ± 8.6 years, LTCI stay 74.2 ± 38.1 months and length of HIV diagnosis 24.5 ± 17 months (confirmed by HICC standard screening). Three had stroke sequelae; one, dementia syndrome; two, seropositivity for syphilis; two, hepatitis B and one, hepatitis C. The main drugs used were lamivudine, zidovudine, lopinavir, ritonavir, levothyroxine, omeprazole, ranitidine, lactulose and risperidone. The estimated CD4 count was 341 ± 237/mm^3.

CONCLUSIONS: HIV-positive individuals are present in LTCIs, diagnosable through serological screening and treatable with antiretroviral drugs.

RESUMO

CONTEXTO E OBJETIVO: Busca nos portais SciELO e PubMed encontrou poucos estudos sobre indivíduos positivos para o vírus da imunodeficiência humana (HIV) em instituições de longa permanência para idosos (ILPIs), fato este que justifica o presente estudo. O objetivo foi verificar se há soropositivos para o HIV em instituições de ILPIs.

TIPO DE ESTUDO E LOCAL: Estudo transversal por consulta à Comissão de Controle de Infecção Hospitalar (CCIH) de ILPI com 405 leitos.

MÉTODOS: Solicitaram-se 405 prontuários de pacientes internados, nos quais se pesquisou sorologia reagente ao HIV para análise de: [1] idade e gênero; [2] período de internação na ILPI (meses); [3] causa(s) e diagnósticos à internação na ILPI pela Classificação Internacional de Doenças, 10ª edição; [4] data do diagnóstico do HIV; [5] soropositividade para sífilis e vírus da hepatite B e C; [6] medicamentos em uso na última prescrição no prontuário; e [7] média de linfócitos CD4 baseada em: número total de linfócitos/6 e número total de linfócitos x 0,8 x 0,2 ou 0,3.

RESULTADOS: Quatro homens eram HIV-positivos. Eles tinham 71,2 ± 8,6 anos de idade; 74,2 ± 38,1 meses na ILPI e 24,5 ± 17 meses de soropositividade (diagnósticos realizados como triagem padrão da CCIH). Havia sequelas de acidente vascular cerebral em 3 e síndrome demencial em 1; sorologias positivas para sífilis em 2, vírus hepatite B em 2 e C em 1. Os principais fármacos utilizados eram: lamivudina, zidovudina, lopinavir, ritonavir, levotiroxina, omeprazol, ranitidina, lactulona e risperidona. O CD4 foi estimado em 341 ± 237/mm^3.

CONCLUSÕES: Há soropositivos para o HIV em ILPIs, passíveis de diagnóstico em triagens sorológicas e de tratamento com antirretrovirais.

INTRODUCTION

Elderly people can be defined as individuals with a chronological age of 60 years or over.[1] This age group is currently growing worldwide and particularly in Brazil.[2] The aging process of this population also creates an increasing need for long-term care.[3] Long-term care institutions (LTCIs) have their own dynamics and provide care for specific subpopulations among the elderly.[4] The question of whether these subpopulations include individuals infected with the human immunodeficiency virus (HIV) arises.

The first case report on acquired immunodeficiency syndrome (AIDS) in Brazil was published in 1980.[5] It involved a retrospective diagnosis on a young bisexual adult living in the state of São Paulo.[5] Cases of AIDS among individuals aged 60 years and older were first reported in 1984, reaching 13,657 cases by mid-2009.[6] This number accounted for 2.5% of all cases of AIDS diagnosed between 1980 and 2009 in Brazil.[6] During this period, the first case of AIDS in an elderly person at the Irmandade da Santa Casa de Misericórdia de São Paulo hospital was reported.[7] Curiosity in relation to this occurrence led us to look more deeply into the topic. Interestingly, we found nearly nothing regarding HIV-positive patients in LTCIs.

It is noteworthy that following the advent of combination antiretroviral therapy and free provision to all HIV-positive Brazilians, the survival of these individuals in Brazil has increased, thus leading to greater numbers of patients aged 50 years or over.[6] Nevertheless, there remains an absence of specific therapeutic guidelines for HIV among the elderly, despite the higher rates of side effects and drug-drug interactions in this group. Moreover, the clinical condition relating to the process of human aging associated with HIV infection remains undefined.[6,8,9]

The questions that can thus be posed are: Is the same demographic process occurring among residents in LTCIs? Are there any HIV-positive LTCI residents requiring diagnosis and specific care? A search conducted in the websites http://www.scielo.br/ and http://www.nlm.nih.gov/ on January 12, 2014, found very little information on HIV-positive LTCI residents.[10,11] This finding prompted the present study, in view of the sparseness of the literature on HIV-positive LTCI residents.

OBJECTIVE

The aim of this study was to ascertain whether there were any HIV-positive individuals in LTCIs for the elderly.

METHODS

Design and setting

This was a cross-sectional study based on medical records, conducted through the Hospital Infection Control Committee (HICC) at a 405-bed LTCI belonging to a philanthropic institution. This LTCI is affiliated to an undergraduate medical course and to medical residency programs in the city of São Paulo. This institution was chosen because of its large number of patients, its academic affiliation and its HICC admission protocol of actively seeking potentially serious diseases among residents that would pose a possible risk of contamination to healthcare professionals who come into contact with these individuals.

Surveillance swab specimens were collected to test for *Klebsiella pneumoniae* carbapenemase-producing bacteria and serological tests for syphilis, HIV and hepatitis B and C viruses were performed. New admissions were also assessed with regard to active tuberculosis, scabies, pediculosis and diarrhea-related diseases.

The medical records of the HIV-positive residents were requested for analysis of the following variables:

1. age and gender;
2. length of stay at the LTCI in months;
3. causes and diagnoses on admission to the LTCI according to the International Classification of Diseases, 10th edition;[12]
4. date of HIV-positive diagnosis;
5. seropositivity for syphilis and hepatitis B and C viruses;
6. number and classes of medications in use at last prescription in the medical file, and presence of potentially inappropriate medications for elderly patients based on the Portuguese versions of two active drug lists;[13,14] and
7. estimated mean CD4 lymphocyte count based on the formulas: total lymphocyte count/6 and total lymphocyte count x 0.8 x 0.2 or 0.3.[15]

The present study was submitted to the institution's Ethics Committee for Research on Humans on January 28, 2014, and was approved on March 6, 2014. The study has been registered as approved on the Brazil Platform (http://aplicacao.saude.gov.br/plataformabrasil) under CAAE 26867214.4.0000.5478.

RESULTS

Four of the residents tested HIV-positive, i.e. approximately 1.0% of the total number of residents at the LTCI studied (total of 405 residents). All of these four individuals were men and their mean age was 71.2 ± 8.6 years (**Table 1**). Their mean length of stay at the LTCI was 74.2 ± 38.1 months and the mean length of time for which they had had an HIV-positive diagnosis (reached through standard HICC screening) was 24.5 ± 17.0 months. Two of them were found to be seropositive for syphilis, two for hepatitis B and one for hepatitis C. The estimated mean CD4 count was 341.1 ± 237.4/mm^3.

Regarding underlying diseases, sequelae of stroke were present in three of these residents, while prostate cancer and

dementia syndrome were found in one of them. The main drugs used were lamivudine, zidovudine, lopinavir, ritonavir, levothyroxine, omeprazole, ranitidine, lactulose and risperidone (**Table 2**). The mean number of medications taken was 10.5 ± 2.8 drugs per HIV-positive patient (range: 7-12 drugs per HIV-positive patient). These four patients were taking an average of 5.3 ± 1.5 antiretroviral drugs (all of them after they received the HIV diagnosis) and 5.3 ± 1.0 other drugs. The presence of potentially inappropriate medications for elderly individuals, based on the Portuguese versions of two active drug lists,[13,14] was 0.7 ± 0.5 potentially inappropriate medications/patient (antihistamines and doxazosin).

DISCUSSION

Cases of AIDS among the elderly have been reported in Brazil over the last three decades. The proportion of elderly patients among all HIV-positive cases reported has been rising sharply due to the survival of carriers using antiretroviral therapy and the aging of the population.[2,6-9] Consultation of the Brazilian literature revealed studies on various aspects of elderly patients with AIDS or who were HIV-positive, although HIV infection among LTCI residents in Brazil has not been fully investigated.[3-9,16-23] Disparities in the definition of elderly among these published papers is also evident. Some of them used the age criterion of ≥ 50 years,[9,16,18,20,21] while others adopted ≥ 60 years.[3,4,6,7,17,20,23] The present study sample comprised residents ≥ 60 years of age.

One notable finding was that approximately 1.0% of the residents in the LTCI studied here were HIV-positive, which was higher than the previously estimated rates of 18.78 and 10.80 cases/100,000 males (1998 and 2010 respectively).[15,20] The greater concentration of elderly patients with greater severity of physical and/or mental conditions in LTCIs, in comparison with the general elderly population, partially explains this discrepancy.[2,24] The size of the present sample (four cases/405 beds) may also have contributed to this difference in rates. It should be noted, however, that these data were obtained through an active search using the HICC protocol of the LTCI studied, thus increasing the likelihood of detecting oligosymptomatic or asymptomatic cases. This explains the finding of an 81-year-old HIV-positive patient, an age group rarely reported.[6,17,23]

Previous studies have reported a predominance of males among elderly HIV-positive individuals.[6,7,9,18,20] This phenomenon can be correlated with the lower survival rate observed among female elderly HIV-positive individuals.[17] These findings may explain the result of only male cases in the present study, i.e. women do not survive long enough to be placed into LTCIs. Presuming that HIV infection preceded admission to the LTCI in the present study, the mean survival of these patients (74.2 ± 38.1 months or 6.2 ± 3.2 years) was longer than that reported in another study (3.4-4.6 years).[16] This finding is also related to the fact that HIV infection was actively detected in these elderly individuals by applying the HICC screening protocol, rather than being diagnosed as a result of symptoms suggestive of AIDS. Given that 50.0% of HIV-positive elderly individuals survive no longer than six months after the first opportunist infection,[17] it is clear that early detection was possible in these cases, thus changing the course of the syndrome and the survival of the infected residents at the LTCI analyzed.

The association of seropositivity for syphilis and/or hepatitis B and C viruses in the present study suggests that the HIV

Table 1. Human immunodeficiency virus-positive long-term care institution residents: general data, serological results, length of long-term care institution stay and lymphocyte count

Age (years)	Ge	HIV Ser	Lues	HCV	HBV	Stay in months	Months HIV(+)	Lymphocytes mm³	F1[11]	F2[11]	F3[11]	F1-3[11]
60	M	R	R	R	R	120	119	1057	176.2	169.1	253.7	199.6
72	M	R	R	NR	NR	30	7	819	136.5	131.0	196.6	154.7
81	M	R	NR	R	NR	61	23	3595	599.2	575.2	862.8	679.0
72	M	R	NR	NR	NR	86	50	1752	292.0	280.3	420.5	330.9
Mn 71.25						74.25	49.75	1805.75	301.0	288.9	433.4	341.1
SD 8.617						38.1434	49.46	1256.796	209.5	201.1	301.6	237.4

Mn = mean; SD = standard deviation; Ge = gender; M = male; Ser = serology; R = reactive; NR = non-reactive; HIV = human immunodeficiency virus; Lues = syphilis; HCV = hepatitis C virus; HBV = hepatitis B virus; CD4 = T4 lymphocytes; F1[11] = estimated mean CD4 lymphocyte count calculation using formula 1; F2[11] = estimated mean CD4 lymphocyte count calculation using formula 2; F3[11] = estimated mean CD4 lymphocyte count calculation using formula 3; F1-3[11] = average.

Table 2. Human immunodeficiency virus-positive long-term care institution residents: age, underlying diseases and medications use

Age (years)	Stroke sequelae	Dementia	Delirium	BCP	UTI	Neoplasm	Alcoholism	Anemia	Herpes zoster	Statin	Ezetimibe	Fibrate	Antipsychotics	Levothyroxine	Salicylate	ARVs
60	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes
72	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes
81	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes
72	Yes	No	No	No	Yes	No	No	No	No	Yes	No	No	No	Yes	Yes	Yes

BCP = pneumonia; UTI = urinary tract infection; ARVs = antiretroviral drugs.

infection had been transmitted sexually. This finding has also been reported in other studies, and it has most notably occurred through heterosexual exposure.[6,16-18,20,23]

The estimated mean CD4 count (341.1 ± 237.4/mm^3) mirrored what had previously been observed in 72.9% of HIV-infected individuals ≥ 60 years of age (≤ 350/mm^3).[6] Interestingly, the highest estimated mean CD4 count (679.0/mm^3) in the present sample was found in an octogenarian patient. This elderly patient had had a short stay at the LTCI and presented few comorbidities (seropositivity for hepatitis C virus, stroke sequelae and Herpes zoster). This finding leads to speculation that the HIV infection in this age group indicates an active and/or slower-than-usual pattern of aging. It is also notable that the individual with the lowest estimated CD4 count (154.7/mm^3) in this sample had had the shortest stay at the LTCI studied and presented a clinical picture of dementia syndrome with several other possible etiologies for his dementia overlapping with HIV (seropositivity for syphilis, alcoholism and hypothyroidism). Moreover, it can be seen that if the LTCI had not had active screening for HIV and syphilis-infected individuals, this would have implied a greater risk of contamination posed for the healthcare professionals at these facilities, with only partial treatment of the underlying causes of dementia, and the possibility that neurological infections might be overlooked.

The finding of stroke sequelae in three out of the four HIV-positive patients points towards two interpretations: chance (due to the small sample) or a clinical correlation warranting attention. Recent discussion has centered on whether HIV represents an independent risk factor for stroke.[25-28] Some studies in the literature have investigated the association between HIV and stroke among children and young adults during the era preceding antiretroviral therapy and also between HIV and the risk of cerebrovascular events among individuals using these drugs.[25-28] However, Hasse et al.[29] reported a hazard ratio for stroke of 17.7, in a multivariable analysis on elderly HIV-positive individuals in Switzerland (confidence interval of 7.06 to 44.5), thus justifying attention to this clinical finding in the present study.

In the literature consulted, we did not find any studies reporting the association of HIV with prostate cancer that was seen in one patient of the present study. Nonetheless, the growing incidence of lethal solid tumors in individuals with HIV infection controlled by means of antiretroviral drugs has raised concerns.[30,31]

Pharmacokinetic and pharmacodynamic characteristics are known to be changed through the aging process,[32,33] and polypharmacy is an additional contributory factor.[34-37] Prescribing drugs for the elderly, with or without HIV, therefore remains a constant clinical challenge, given the high risks of drug-to-drug interactions, side effects and potentially inappropriate medications in this age group.[13,14,32-36]

Metabolic changes and cardiovascular diseases associated with the use of antiretroviral therapy are known, and these call for heightened vigilance among elderly patients. Despite the lack of specific consensus, use of statins and ezetimibe would have been justified in the cases of the present study because of the history of neurovascular events in three of the four patients, and also because of the presence of hypothyroidism in two patients and the need to take risperidone in another.[8,38,39]

The low presence of potentially inappropriate medications per patient was due to the regular checking for potentially inappropriate medications in prescriptions that was conducted by the LTCI. It is important to point out that neither of the two lists of potentially inappropriate medications indicates any antiretroviral drugs as potentially inappropriate for use among elderly patients.[13,14]

CONCLUSION

HIV patients can be found in LTCIs: they are diagnosable through serological screening and treatable with antiretroviral drugs.

Specific investigation and treatment protocols for use among elderly individuals need to be developed in order to aid in the detection and therapeutic control of HIV.

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Sources of funding: None
Conflict of interest: None

Date of first submission: July 21, 2015
Last received: April 27, 2016
Accepted: May 15, 2016

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DOI: 10.1590/1516-3180.2015.0222110716

Targeting stroke risk and improving outcomes in patients with atrial fibrillation in Latin America

Identificando o risco de acidente vascular cerebral e melhorando desfechos em pacientes com fibrilação atrial na América Latina

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KEY WORDS:
Stroke.
Atrial fibrillation.
Anticoagulants.
Warfarin.
Risk factors.

PALAVRAS-CHAVE:
Acidente vascular cerebral.
Fibrilação atrial.
Anticoagulantes.
Varfarina.
Fatores de risco.

ABSTRACT

CONTEXT AND OBJECTIVE: To examine stroke risk factors, including atrial fibrillation, management and prevention, and stroke outcomes across Latin America.

DESIGN AND SETTING: Narrative review conducted at Piedmont Heart Institute, United States.

METHODS: The PubMed, Embase and Cochrane databases were searched for stroke AND "Latin America" AND epidemiology (between January 2009 and March 2015). Further studies in the SciELO, World Health Organization and Pan-American Health Organization databases were used to address specific points.

RESULTS: Countries categorized as low or middle-income nations by the World Bank, which includes most of Latin America, account for two-thirds of all strokes. Globally, fewer than half of patients (median treatment level: 43.9%) with atrial fibrillation receive adequate anticoagulation to reduce stroke risk, which correlates with data from Latin America, where 46% of outpatients did not receive guideline-compliant anticoagulation, ranging from 41.8% in Brazil to 54.8% in Colombia.

CONCLUSIONS: Atrial fibrillation-related stroke carries a heavy burden. Non-vitamin K antagonist oral anti-coagulants provide options for reducing the risk of atrial fibrillation-related stroke. However, cost-effectiveness comparisons with warfarin are warranted before observational health-economics study results can be applied clinically. Initiatives to remedy inequalities and improve access to care across Latin America should accompany risk factor modification and guideline-based prevention.

RESUMO

CONTEXTO E OBJETIVO: Examinar os fatores de risco para acidente vascular cerebral (derrame), incluindo fibrilação atrial, manejo e prevenção, e desfechos do derrame na América Latina.

TIPO DE ESTUDO E LOCAL: Revisão narrativa da literatura, realizada no Instituto do Coração Piedmont, Estados Unidos.

MÉTODOS: Os termos "derrame" E "América Latina" E epidemiologia (entre janeiro de 2009 e março de 2015) foram buscados nas bases de dados PubMed, Embase e Cochrane. Estudos adicionais nas bases de SciELO, Organização Mundial da Saúde e Organização Pan-Americana de Saúde foram utilizados para discutir pontos específicos.

RESULTADOS: Os países classificados como de baixa ou média renda pelo Banco Mundial, que incluem a maior parte da América Latina, representam dois terços de todos os derrames. Mundialmente, menos da metade dos pacientes (nível de tratamento mediano: 43,9%) com fibrilação atrial recebe anticoagulação adequada para reduzir o risco de derrame, o que correlaciona com os dados da América Latina, onde 46% dos pacientes ambulatoriais não receberam anticoagulação conforme as diretrizes, variando de 41,8% no Brasil a 54,8% na Colômbia.

CONCLUSÕES: Derrames associados à fibrilação atrial impõem um ônus significativo. Anticoagulantes orais antagônicos sem vitamina K oferecem opções de redução do risco de derrames associados a fibrilação atrial. No entanto, comparações do custo-benefício com varfarina são justificáveis antes da aplicação clínica de resultados dos estudos observacionais relativos à economia da saúde. Iniciativas para solucionar diferenças e melhorar o acesso aos cuidados médicos na América Latina devem acompanhar a modificação dos fatores de risco e a prevenção baseada em orientações.

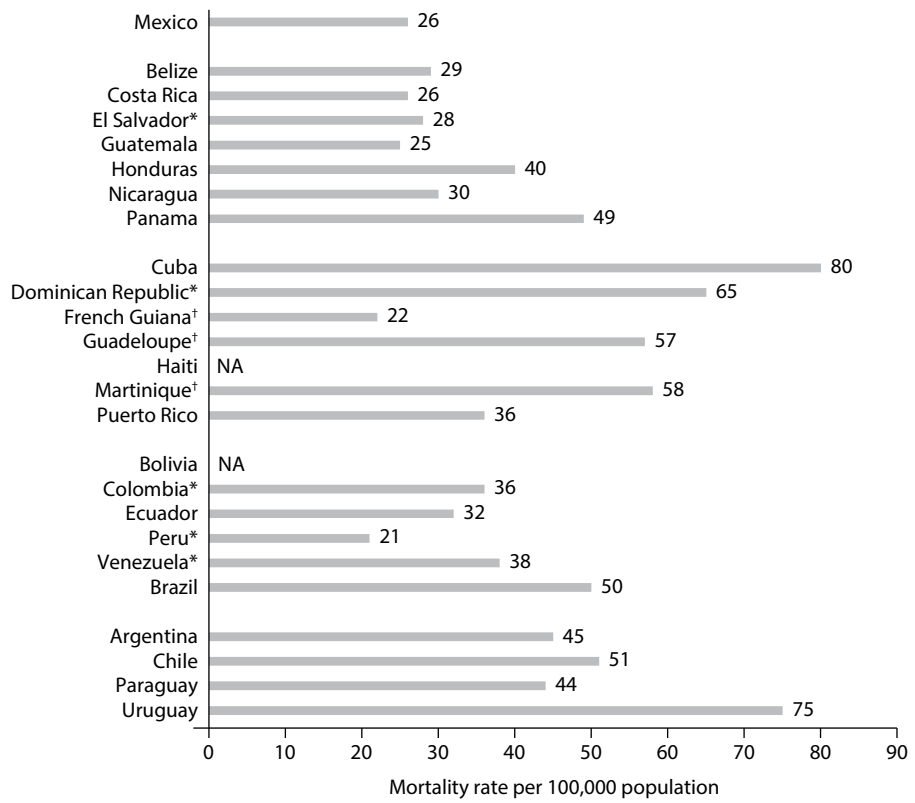
INTRODUCTION

Stroke is a serious challenge in Latin America and throughout the world. The Global Burden of Disease (GBD) study estimated that in 2013 there were approximately 26 million stroke survivors worldwide, 71% of whom had experienced ischemic strokes.[1] In the same year, 10.3 million people experienced new strokes (67% consisting of ischemic stroke) and 6.5 million people died from stroke (51% consisting of ischemic stroke).[1] Two-thirds of all strokes occur in low and middle-income countries,[2,3] as categorized by the World Bank, which include most of Latin America.[3-5] Continuing studies will help to clarify the complexities of stroke epidemiology.[6-9]

According to the most recent figures available from the Pan-American Health Organization (PAHO) for the Americas region, cardiovascular diseases accounted for 1.6 million deaths in 2012, of which 22% were due to cerebrovascular diseases (ahead of heart failure and hypertension, each with 9% of the total).[10] A similar pattern was observed throughout the region, with some variations. For example, 31% of cardiovascular deaths in Brazil were attributed to cerebrovascular diseases.[10] The GBD investigators noted that age-standardized stroke incidence, mortality, prevalence and stroke-related disability declined from 1990 to 2013.[1] However, over the same period, the absolute number of people affected by stroke increased considerably across the globe, suggesting that the worldwide stroke burden continues to increase due to population growth and aging.[1]

Although most of the burden of stroke is borne by low- and middle-income countries, stroke incidence rates have fallen concomitantly with reductions in risk factors associated with stroke therapies in high-income countries.[11] For instance, people in the United States had fewer strokes, and were less likely to die after strokes, in 2011 than in 1987.[12] PAHO/World Health Organization (WHO) age-adjusted estimates for cerebrovascular mortality by country in 2013 (except years as indicated) are shown in **Figure 1**.[10] The GBD 2013 survey demonstrated that stroke was among the ten leading causes of disability-adjusted life-years (DALYs) in the majority of countries in Latin America and the Latin Caribbean, and was one of the five leading causes in most of them.[11]

Stroke prevalence in Latin America per 1,000 population based on door-to-door surveys ranges from 1.7 among rural Bolivians to 7.7 among urban Mexicans.[12-14] In the PISCIS (Proyecto Investigación de Stroke en Chile: Iquique Stroke) study among a predominantly Hispano-Mestizo population, the age-adjusted incidence of first-ever stroke was 1.40 per 1,000 (95% confidence interval, 1.24, 1.56).[15] Among individuals aged



*Data from 2012; †Data from 2011; NA = no data available.

Figure 1. Stroke mortality (per 100,000 population per year) in Latin America by country, 2013.[10]

> 60 years, the crude prevalence of stroke ranges from 18.2 per 1,000 in Mexico to 46.7 per 1,000 in Colombia,[13] in line with the observed worldwide trend for increased stroke risk with increasing age.

The leading risk factors for ischemic stroke worldwide are hypertension, smoking, sedentary lifestyle, diabetes and atrial fibrillation.[13,16] Although detected less easily than the other risk factors, atrial fibrillation is responsible for 20% of ischemic strokes,[16] and the one-year mortality risk for Latin American patients with atrial fibrillation is almost twice that found in high-income countries.[17] Although data on the prevalence of atrial fibrillation in Latin America are limited, a substantial number of people are believed to have arrhythmia. A recent study of atrial fibrillation-related disease and mortality in adults aged > 40 years estimated atrial fibrillation prevalence in the seven countries surveyed as follows: Argentina, 1.95%; Brazil, 1.44%; Chile, 1.68%; Colombia, 1.59%; Mexico, 1.58%; Peru, 1.55%; and Venezuela, 1.47%.[18] Atrial fibrillation is more common with increasing age: 75% of individuals with atrial fibrillation are aged ≥ 60 years.[18] Further, many cases of atrial fibrillation are not detected, and there is a clear need to improve the diagnosing of atrial fibrillation so as to reduce stroke risk in Latin American countries.

OBJECTIVES

Stroke is common but has been incompletely characterized across Latin America. An English-language literature review was conducted to identify the incidence and prevalence of stroke, the approaches to its management and prevention and patient outcomes across a range of countries in Latin America and the Caribbean, with particular attention to the association between stroke and nonvalvular atrial fibrillation, which is an important and underdiagnosed risk factor.

METHODS

Information for this narrative review was obtained through a systematic search of the literature to identify published English language scientific papers relating to the search terms. The search terms used were stroke AND "Latin America" AND epidemiology, covering the period from January 2009 to March 2015. The primary search was performed using MEDLINE (via PubMed), Embase (via ProQuest Dialog) and the Cochrane Library. The database search strategy and results are shown in **Table 1**. Additional searches were conducted in SciELO and in the WHO and PAHO databases to address specific points regarding epidemiology, risk factors and disease management. Reference lists from studies identified through the electronic search were searched manually for further sources. Because the overall yield from PubMed searches was sparse, the authors expanded on the search results, by making further individual searches of relevant publications from January 2000 to March 2015. A flow diagram of the literature search and disposition of the initial structured search is shown in **Figure 2**. The results from the pivotal trials that demonstrated the efficacy and safety of four non-vitamin K antagonist oral anticoagulants that have been indicated for reducing the risk of stroke in patients with atrial fibrillation are summarized in **Table 2**.[19-23]

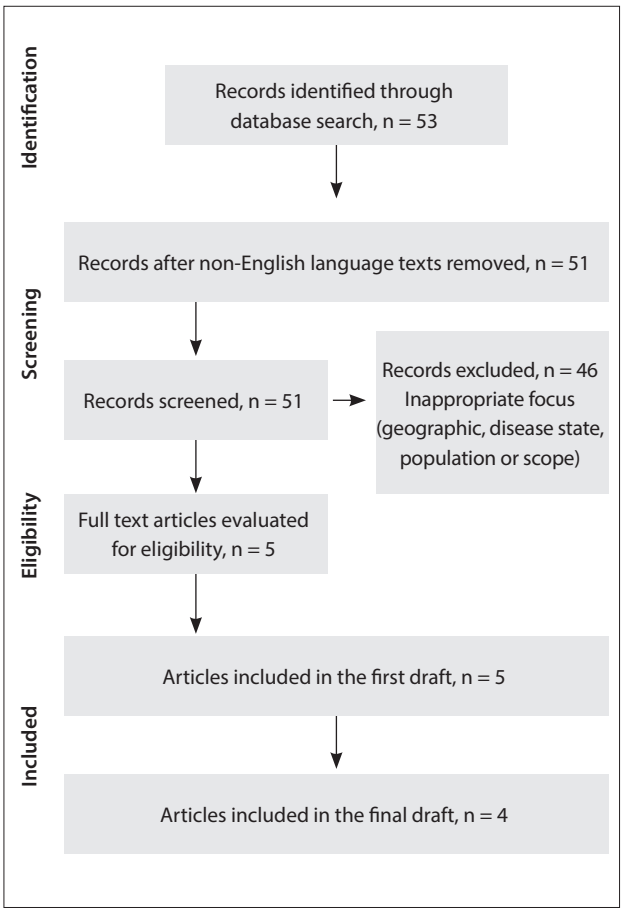


Figure 2. Flow diagram of literature search and disposition.

Table 1. Database search strategy and results

Electronic search	Database	Search terms*	Filters	Results
PubMed	MEDLINE	Stroke AND "Latin America" AND Epidemiology	Published: January 1, 2009, to March 31, 2015	Articles retrieved: 53† Identified for full text review: 5 Articles included: 4
ProQuest dialog	Embase (Excerpta Medica Database)			
Cochrane systematic reviews/ clinical trials database	Cochrane Library			

*Search terms were included as MeSH terms when searching MEDLINE and as Emtree terms when searching Embase. In querying the Cochrane library, the search was performed against the title, abstract and key words in the clinical trials and systematic reviews databases; †Excluding cross-database duplicates.

RESULTS

Stroke in Latin America

The populations of Latin America encompass wide ethnic, socioeconomic and geographic variations, and direct comparisons may be misleading. Many factors confound assessments of epidemiology, prevention and treatment. In 1990, the authors of the first global and regional comparative assessment of mortality and DALYs attributable to 10 major risk factors cautioned that different methods of epidemiological assessment for various risks limited the comparability of results.[24] However, with the development of a common framework and methods, subsequent surveys have afforded opportunities to reassess the evidence for exposure and effect sizes for a much broader set of risk factors.[11]

According to WHO, the estimated stroke mortality per 100,000 population in 2008 was 11.3 for Latin Americans aged ≤ 60 years, compared with 301.3 for those aged 61-79 years.[25] International differences in case-fatality rates and the proportions of patients who have died or remain dependent six months after a stroke have been attributed to differences in acute care, including access to stroke units and computed tomography scans, and in aspirin use on discharge.[6]

Stroke-associated costs are substantial. National expenditure for ischemic stroke management in 2008 was US$ 326.9 and 239.9 million in Brazil and Argentina, respectively.[26,27] The mean per-patient cost of hospitalization for ischemic stroke was $1,902 in Brazil versus $3,888 in Argentina for a similar mean duration of hospital stay: 13.3 and 13.0 days, respectively.[26,27] The personal financial burden can be heavy for Latin Americans, many of whom incur high out-of-pocket healthcare costs.[28]

Health transitions

As the global threat of communicable diseases recedes, chronic and non-communicable conditions are taking their place.[13,29] For Brazil overall, this shift occurred in the 1960s, but analysis confined to the major cities shows that cerebrovascular mortality rates began to exceed mortality from other cardiovascular conditions, such as rheumatic heart disease and syphilitic aortic disease, as early as the mid-1940s.[30] The GBD study in 2013 found that the leading risk factors threatening global health were those underlying non-communicable diseases, including stroke: high blood pressure, smoking, diet, obesity, elevated blood glucose, dyslipidemia, air pollution, and alcohol over-consumption.[13] Furthermore, Latin America is undergoing a transition in which, although deaths from chronic diseases now exceed deaths from infections and malnutrition for most of the region, residents of underserved regions still remain at risk of infections and malnutrition, which are associated with an elevated risk of stroke.[3,6,13] Hypertension is acknowledged to be the leading risk factor for stroke in Latin America,[2,11] but because hypertension and other preventable risk factors are amply covered in the literature, the

Table 2. Non-vitamin K antagonist oral anticoagulants: key findings of pivotal randomized controlled trials

RCT Anticoagulant Patients (N)	Treatments	Study design	Follow-up	SSE %/year (HR [95% CI except as noted]); P versus comparator	Major bleeding %/year (HR [95% CI]); P versus comparator
ARISTOTLE[19] Apixaban (18,201)	**5 mg** BID (2.5 mg BID for selected patients) versus warfarin*	DB, DD, NI	1.8 year median	**5 mg:** 1.27 versus 1.60 (0.79 [0.66, 0.95]); P < 0.001 for NI; P = 0.01 for superiority	**5 mg:** 2.13 versus 3.09 (0.69 [0.60, 0.80]); P < 0.001
AVERROES[20] Apixaban (5,599)	**5 mg** BID (2.5 mg BID for selected patients) versus aspirin 81-324 mg/day	DB, superiority	1.1 year mean (terminated early)	**5 mg:** 1.6 versus 3.7 (0.45 [0.32, 0.62]); P < 0.001	**5 mg:** 1.4 versus 1.2 (1.13 [0.74, 1.75]); P = 0.57
ENGAGE-AF TIMI 48[21] Edoxaban (21,105)	**High-dose 60 mg**/day (or reduction to 30 mg/day) or **low-dose 30 mg**/day (or reduction to 15 mg/day) versus warfarin	DB, DD, NI	2.8 year median	**60 mg:** 1.18 versus 1.50 (0.79 [97.5% CI, 0.63, 0.99]); P < 0.001 for NI **30 mg:** 1.61 versus 1.50 (1.07 [97.5% CI, 0.87, 1.31]); P = 0.005 for NI	**60 mg:** 2.75 versus 3.43 (0.80 [0.71, 0.91]); P < 0.001 **30 mg:** 1.61 versus 3.43 (0.47 [0.41, 0.55]); P < 0.001
RE-LY[22] Dabigatran (18,113)	**110 mg** BID or **150 mg** BID versus warfarin	SB, OL warfarin, NI	2.0 year median	**110 mg:** 1.53 versus 1.69 (RR, 0.91 [0.74, 1.11]); P < 0.001 for NI **150 mg:** 1.11 versus 1.69 (RR, 0.66 [0.53, 0.82]); P < 0.001 for NI; P < 0.001 for superiority	**110 mg:** 2.71 versus 3.36 (RR, 1.16 [1.00, 1.34]); P = 0.052 **150 mg:** 3.11 versus 3.36 (RR, 0.93 [0.81, 1.07]); P = 0.31
ROCKET-AF[23] Rivaroxaban (14,264)	**20 mg**/day (or reduction to 15 mg/day) versus warfarin	DB, DD, NI	1.9 year median	**20 mg:** 1.7 versus 2.2 (0.79 [0.66, 0.96]); P < 0.001 for NI	**20 mg:** 14.9 versus 14.5 (1.03 [0.96, 1.11]); P < 0.44

Warfarin dose adjusted to target INR 2.0-3.0.

BID = twice daily; CI = confidence interval; DB = double-blind; DD = double-dummy; HR = hazard ratio; INR = international normalized ratio; NI = non-inferiority; OL = open-label; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SSE = stroke or systemic embolism.

present review focused on atrial fibrillation, a less easily diagnosed but significant and treatable cause of ischemic stroke.

Poverty: a global risk factor for stroke

The Latin American/Caribbean region, like many others, has considerable economic inequality and a widening income gap.[6,29] Stroke prevalence rates are higher in poorer areas than in more affluent areas. In a 2010 survey of low-income residents in São Paulo aged > 35 years, 5.4% self-reported prior stroke. The age-adjusted prevalence rates for men and women were 4.6% and 6.5%, respectively, i.e. higher than those reported in many other countries.[31] Another study on low-income residents aged > 65 years in São Paulo found higher prevalence of coronary heart disease, left bundle-branch block and atrial fibrillation, consistent with the burden of stroke mortality in Brazil.[32] However, this disparity is not limited to urban areas, given that a 2011 survey of residents aged > 35 years in *ribeirinha* communities compared with urban residents of the same municipality found higher crude prevalence of stroke in rural areas (6.3 versus 3.7%, respectively) after adjustment for sex and age.[33] Despite trends showing declining stroke mortality rates across Brazil consistent with the worldwide trend, stroke mortality rates remain high among low-income Brazilians and have not dramatically decreased over the last three decades. Reductions in stroke mortality over the last 20 years were greatest in the two wealthiest regions and least in the poorest regions.[34]

The burden of stroke risk factors, and in particular, hypertension, has been characterized as a partial consequence of social determinants, including socioeconomic inequality and perceived discrimination. These are structural factors underlying global health inequalities that exceed the expected influence of access to health services.[30,35,36] Efforts to modify risk factors and alleviate the burden of stroke could be aided by economic and social improvements, including implementation of cost-effective public health policies. Enhanced surveillance efforts in outlier regions where there is a high stroke burden, particularly at low- and middle-income levels, could help to clarify factors implicated in the disproportionate stroke burden and guide interventions with specific goals.[6]

Atrial fibrillation

The principal mechanism for stroke in patients with atrial fibrillation is embolization of stasis-induced thrombi in the left atrial appendage. The risk of stroke in patients with atrial fibrillation increases with age and other risk factors, including hypertension, diabetes, heart failure and previous stroke.[16,37] Strokes associated with atrial fibrillation are generally more severe, cause greater disability and are associated with worse outcomes than are strokes in patients without atrial fibrillation.[37] In a survey of seven countries in Latin America, more than half of the patients with atrial fibrillation were receiving medical treatment, but a significant proportion of the 60% treated as outpatients were not receiving appropriate anticoagulant therapy, despite having a high stroke risk.[18] Moreover, the proportion of patients with atrial fibrillation receiving treatment within the national healthcare system decreased with increasing age across all countries. Cost and lack of health infrastructure are major barriers to care, and suboptimal care is associated with poor outcomes.[1,3,6] The Mexican PREMIER registry investigators urged secondary prevention to modify stroke risk factors, including atrial fibrillation.[38]

Guidelines and management initiatives

Patients with atrial fibrillation are an important target for efforts to reduce the risk of stroke through anticoagulant therapy. Vitamin K antagonists, such as warfarin, phenprocoumon and acenocoumarol, are widely prescribed in Latin America. Compared with no therapy, vitamin K antagonists reduce the risk of stroke by 62-68% and the rate of death by 26-33%.[37] For every 1,000 patients adequately treated with warfarin, 31 ischemic strokes are prevented each year.[39]

Globally, fewer than half of patients with atrial fibrillation receive adequate anticoagulation to reduce the risk of embolic stroke.[40] The Acute Decompensated Heart Failure National Registry (ADHERE), which enrolled patients with decompensated heart failure and either new-onset or a history of atrial fibrillation in 10 countries across Latin America/Asia-Pacific, found that prophylactic anticoagulation was underused, with significant differences in use among the participating countries.[41] Many physicians may overestimate bleeding risk and underestimate the benefits of stroke prevention measures.[40,41] The investigators noted misuse of anticoagulant therapy, with greater warfarin use among patients with low stroke risk, according to a validated screening tool, and little warfarin use among high-risk patients in greatest need of anticoagulation.[40] The Latin American Society of Cerebrovascular Diseases advises warfarin for patients with a moderate-to-high risk of stroke, as recommended by the European Society of Cardiology 2010 guidelines.[42,43] However, the well-known complexities of warfarin therapy may hinder its use. Warfarin requires frequent monitoring of anticoagulant effect, dose adjustments and close attention to diet. Difficulties of access to monitoring, including distance and cost, may help explain why physicians hesitate to prescribe warfarin for patients with limited resources.

After the Iberoamerican Society of Neurology declared stroke a catastrophic disease in 2004,[44] medical specialists organized to improve the quality of care. Public health programs promoting national stroke days and other efforts to raise awareness have been established throughout Latin America.[6] Several countries have participated in the WHO STEPwise approach to Surveillance (STEPS) stroke program to standardize stroke data, estimate the

resources necessary for preventing stroke and measure the effects of public health efforts.[6,45]

Since 2006, the Chilean Ministry of Health national guidelines have guaranteed a minimum level of care for every patient with ischemic stroke, with assurance of rapid neurological assessment, computed tomography scans, hospitalization, neurorehabilitation and secondary prevention.[6] At a Cuban stroke center, a 10-component fast-track approach doubled hospital admission rates and halved case-fatality rates in the region from 1990 to 2003.[46] Many hospitals have established stroke units, which increase the likelihood of good outcomes, although stroke units are yet to be adopted as national health care policy by any regional government.[6] Practices at a comprehensive care center in Brazil changed following a retrospective study showing that adequate oral anticoagulation for patients with atrial fibrillation could have prevented half of all strokes.[47] However, another survey at a tertiary care clinic in São Paulo showed that only 55% of patients with atrial fibrillation and high stroke risk received dose-adjusted warfarin.[48] In a Mexican cohort, fewer than half of patients with nonvalvular atrial fibrillation and cerebral infarction were discharged with an oral anticoagulant; patients who lived in rural areas or had functional impairment on discharge were least likely to be prescribed warfarin.[49]

In October 2015, in support of the WHO 25/25 goal of achieving a 25% decrease in premature mortality due to non-communicable diseases by 2025, representatives of government institutions, scientific and professional societies, academic institutions and health policy bodies across Latin America issued a unified call for action regarding prevention and treatment of stroke in the Americas.[50] The Declaration of Santiago de Chile (Scaling up Stroke Prevention and Treatment in the Americas) urged regional authorities to allocate financial and human resources commensurate with local and regional stroke burdens.[50] It stressed the need to prioritize strategies within national and regional institutions to achieve organized systems of stroke care and emphasized the importance of primary and secondary prevention, including pharmacological management of treatable risk factors by means of antihypertensives, traditional and newer anticoagulants in patients with atrial fibrillation, lipid control therapies and antiplatelet therapy.[50]

Non-vitamin K antagonists for stroke prevention in nonvalvular atrial fibrillation

Treatment with newer oral anticoagulants, which are given as fixed doses, do not require monitoring, have predictable clinical effects and have better safety profiles than vitamin K antagonists. They may improve preventive care for patients with nonvalvular atrial fibrillation who are at risk of stroke, in regions with limited access to medical resources. Non-vitamin K antagonist oral anticoagulants were approved for reducing the risk of stroke in patients with nonvalvular atrial fibrillation after large international trials demonstrated their efficacy and safety versus warfarin (**Table 2**).[19-23] The agents that have been approved are dabigatran, rivaroxaban and apixaban. Edoxaban, recently approved in the United States, may soon be approved in Latin America. Latin American tertiary centers contributed approximately 20% of the participants in the clinical trials.[19-23]

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study compared dabigatran (150 mg or 110 mg twice daily) with adjusted-dose warfarin in more than 18,000 patients with nonvalvular atrial fibrillation who were at moderate-to-high risk of stroke or systemic embolism, including 1,134 patients from Latin American tertiary centers.[22] The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study on more than 14,000 patients with nonvalvular atrial fibrillation included 1,878 patients from Latin America in the intention-to-treat population.[23] The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial assessed the efficacy and safety of apixaban (5 mg twice daily; 2.5 mg for selected patients) in more than 18,000 patients with nonvalvular atrial fibrillation and ≥ 1 additional risk factor for stroke, including 3,468 patients from Latin America.[19] The AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study, a comparison of apixaban with aspirin (81-324 mg daily), included 5,599 patients, of whom 1,185 were from Latin America.[20] In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial, there were more than 21,000 patients with nonvalvular atrial fibrillation, including 2,661 from Latin America.[23] In the pivotal trials, primary efficacy and safety findings were consistent across subgroups, including those in Latin America and other geographic regions worldwide.[19-23]

Non-vitamin K antagonist oral anticoagulants are easier to use than warfarin, are at least as effective and are associated with lower rates of intracranial hemorrhage.[19-23] Acquisition costs for these drugs are higher than for warfarin, but a cost-benefit review of treatment for atrial fibrillation, based on observational studies, suggested that the overall cost of therapy may be lower because, in contrast to warfarin, dose adjustment and routine monitoring of the anticoagulant effect are not required, and the risk of complications from therapy over the long term may be lower.[51] However, cost-effectiveness comparisons of non-vitamin K antagonist agents versus warfarin are warranted before the results can be directly applied to the real-world setting.[51]

Observational studies and registries have begun assessing the impact, safety and efficacy of non-vitamin K antagonist oral

anticoagulants for reducing stroke risk in cases of nonvalvular atrial fibrillation in routine clinical practice around the world. GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation, NCT01428765) is a multinational, prospective registry designed to characterize the treatment of patients newly diagnosed with nonvalvular atrial fibrillation who are at risk of stroke and are receiving treatment with warfarin, aspirin or non-vitamin K antagonist oral anticoagulants. XANTUS-EL (Xarelto for Prevention of Stroke in Patients with Nonvalvular Atrial Fibrillation, Eastern Europe, Middle East, Africa and Latin America, NCT01800006) is evaluating the real-world use of rivaroxaban. The PINNACLE (Practice Innovation and Clinical Excellence) registry and research alliance (an outpatient cardiology registry) is calculating performance measurements for outpatient management of several cardiovascular conditions, including atrial fibrillation, in the United States and other countries. These registries will provide important real-world information on anticoagulant prescribing patterns and outcomes.

DISCUSSION

Shifts in risk factors, economic and social influences and health effects in Latin America have exposed stroke and its consequences as a serious public health problem, which was described as catastrophic a decade ago. Studies currently in progress will build a base of evidence for management and prevention of stroke across Latin America. Today, stroke mortality in the region remains higher than in the developed world, but stroke mortality rates in Latin America have declined, especially in wealthier regions, and this trend could continue if countries were to gain control over a number of modifiable cardiovascular risk factors while implementing public health measures to continue with improvement to social and economic conditions. Patients with nonvalvular atrial fibrillation are an important population to target in efforts to reduce the burden of stroke across the region. Anticoagulant therapy, appropriately used and monitored, lowers stroke risk among patients with nonvalvular atrial fibrillation by at least two-thirds and mortality by around one-third.[37] However, anticoagulation is underused owing at least in part to the well-known limitations of vitamin K antagonists. Non-vitamin K antagonist oral anticoagulants may have advantages over vitamin K antagonists, and could play an important role in reducing the risk of stroke among Latin American patients with nonvalvular atrial fibrillation.

CONCLUSIONS

This narrative review draws on the current literature, including systematic reviews by several investigators, and thus does not report original findings or any results from systematic analysis. Nonetheless, the consensus from this review of the literature indicates that greater awareness and further studies, resources and actions are needed to reduce the heavy and growing burden of stroke in Latin America.

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Acknowledgements: Professional medical writing was provided by Rosemary Perkins and Nicole Draghi, PhD, and editorial assistance was provided by Sandi Lusk, at Caudex

Sources of funding: Bristol-Myers Squibb Company and Pfizer Inc. funded editorial services

Conflicts of interest: Dr. Scazzuso declares that there were no conflicts of interest. Dr. Stambler has served on speakers' bureaus for Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, and Janssen Pharmaceuticals; has consulted for Janssen; and has received support for publications from Pfizer and Bristol-Myers Squibb

Date of first submission: November 2, 2015
Last received: July 8, 2016
Accepted: July 11, 2016

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DOI: 10.1590/1516-3180.2016.024227092016

"EMMA Study: a Brazilian community-based cohort study of stroke mortality and morbidity"

"Estudo EMMA: estudo coorte brasileiro baseado na comunidade sobre mortalidade e morbidade por acidente vascular cerebral"

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KEY WORDS:
Stroke.
Public health surveillance.
Cohort studies.
Risk factors.
Mortality.

PALAVRAS-CHAVE:
Acidente vascular cerebral.
Vigilância em saúde pública.
Estudos coortes.
Fatores de risco.
Mortalidade.

ABSTRACT

CONTEXT AND OBJECTIVE: Stroke has a high burden of disability and mortality. The aim here was to evaluate epidemiology, risk factors and prognosis for stroke in the EMMA Study (Study of Stroke Mortality and Morbidity).

DESIGN AND SETTINGS: Prospective community-based cohort carried out in Hospital Universitário, University of São Paulo, 2006-2014.

METHODS: Stroke data based on fatal and non-fatal events were assessed, including sociodemographic data, mortality and predictors, which were evaluated by means of logistic regression and survival analyses.

RESULTS: Stroke subtype was better defined in the hospital setting than in the local community. In the hospital phase, around 70% were first events and the ischemic subtype. Among cerebrovascular risk factors, the frequency of alcohol intake was higher in hemorrhagic stroke (HS) than in ischemic stroke (IS) cases (35.4% versus 12.3%, P < 0.001). Low education was associated with higher risk of death, particularly after six months among IS cases (odds ratio, OR, 4.31; 95% confidence interval, CI, 1.34-13.91). The risk of death due to hemorrhagic stroke was greater than for ischemic stroke and reached its maximum 10 days after the event (OR: 3.31; 95% CI: 1.55-7.05). Four-year survival analysis on 665 cases of first stroke (82.6% ischemic and 17.4% hemorrhagic) showed an overall survival rate of 48%. At four years, the highest risks of death were in relation to ischemic stroke and illiteracy (hazard ratio, HR: 1.83; 95% CI: 1.26-2.68) and diabetes (HR: 1.45; 95% CI: 1.07-1.97). Major depression presented worse one-year survival (HR: 4.60; 95% CI: 1.36-15.55).

CONCLUSION: Over the long term, the EMMA database will provide additional information for planning resources destined for the public healthcare system.

RESUMO

CONTEXTO E OBJETIVO: O acidente vascular cerebral (AVC) tem alta carga de incapacidade e mortalidade. Objetivou-se avaliar a epidemiologia, fatores de risco e prognóstico do AVC no Estudo EMMA (Estudo da Mortalidade e Morbidade do AVC).

TIPO DE ESTUDO E LOCAL: Estudo longitudinal prospectivo de base comunitária conduzido em hospital universitário.

MÉTODOS: Dados sobre AVC baseados em eventos fatais e não fatais foram avaliados, incluindo dados sociodemográficos, mortalidade e preditores, por meio de regressão logística e análises de sobrevida.

RESULTADOS: O subtipo de AVC foi melhor definido no ambiente hospitalar do que na comunidade local. Na fase hospitalar, cerca de 70% eram eventos primários e do subtipo isquêmico. Entre os fatores de risco cerebrovascular, a frequência de ingestão de álcool foi mais alta no AVC hemorrágico comparado com o isquêmico (35,4% *versus* 12,3%, P < 0,001). O risco de morte depois de AVC hemorrágico foi maior que o do AVC isquêmico e este gradiente foi máximo aos 10 dias após o evento (razão das chances, 3,31; intervalo de confiança (IC) de 95%: 1,55-7,05). Análise de sobrevivência em 4 anos com 665 casos de AVC primário (82,6% AVC isquêmico e 17,4% AVC hemorrágico) demonstrou taxa de sobrevida global de 48%. Aos 4 anos, maiores riscos de morte foram para casos de AVC isquêmico e pacientes analfabetos (*hazard ratio*, HR: 1,83; 95% IC: 1,26-2,68) ou com diabetes (HR:1,45; IC 95%: 1,07-1,97). Casos com depressão maior apresentaram pior sobrevida de 1 ano (HR: 4,60; IC 95%: 1,36-15,55).

CONCLUSÃO: Em longo prazo, dados do EMMA fornecerão informações adicionais para planejamento de recursos destinados ao sistema de saúde público.

INTRODUCTION

More than half of the global burden relating to cardiovascular disease (CVD) is concentrated in low and middle-income countries like Brazil.[1] Although age-standardized rates of stroke mortality have declined over the last two decades, updated information from the Global Burden of Disease (GBD) study covering 1990-2013 has shown that the absolute numbers of stroke cases have been increasing for both stroke subtypes, to reach around 10 million incident cases of stroke, 6.5 million deaths due to stroke and almost 26 million stroke survivors.[1] Moreover, a rise in the absolute number of disability-adjusted life years (DALYs), mainly due to ischemic stroke (IS), which corresponded to 70% of all stroke cases, was observed over the same period. Lower incidences of IS for both sexes were observed in 2013, compared with 1990. However, higher incidence rates of IS among men than among women were still observed in 2013. Over the same period, no statistical differences in hemorrhagic stroke (HS) according to sex were noticed.[2]

In a global comparison, the stroke burden remains unequally distributed in developing countries.[1] Particularly, stroke mortality rates in Brazil are the highest in Latin America.[3-6] Brazilian data show that CVDs have ranked highest among mortality rates since the early 1960s and account for the highest proportion of hospitalizations. Although mortality rates should be interpreted with caution because of improvements in national statistics and the aging of the Brazilian population over recent decades, age-adjusted mortality rates relating to CVDs were seen to decline by around 20% from 2000 to 2011. Nonetheless, an increase in the overall number of CVD deaths was still reported (DATASUS, the data processing system of the Brazilian Ministry of Health). In 2011, CVDs were responsible for 31% of mortality and cerebrovascular diseases for 30% in this country. Similarly to global trends, CVD mortality rates in Brazil have been influenced by race, sex and other socioeconomic status (SES) characteristics. A greater decline in CVD mortality rates has also been observed among women than among men since 1996. Particularly, stroke mortality has declined by 3.6% and 3.3% per year among women and men, respectively.[7] In addition, stroke mortality based on death certificate notifications is slightly higher among blacks than among mixed-race and white people.[7] Data from the city of São Paulo (1996-2011) also followed the same trend in comparisons of both gender and family income. A greater decline in the stroke mortality rate was seen in relation to coronary heart disease (CHD) rates. The decrease in mortality was greater among women than among men and was inversely related to income, particularly for men.[8]

In addition to mortality data, the National Health Survey (PNS), which was a Brazilian community-based epidemiological survey with a nationally representative sample, provided estimates relating to around 2,231,000 stroke cases in 2013, of which 568,000 cases presented severe disabilities. The point prevalences were 1.6% and 1.4% for men and women, respectively. The prevalences of post-stroke disability were 29.5% for men and 21.5% for women. Although stroke prevalence rates were especially higher among older individuals without formal education who were urban dwellers than among individuals with high SES, the degree of stroke disability according to SES was not determined.[9]

Similarly to other data published worldwide, most research in developing countries, including in Brazil, has focused on the epidemiology of and therapeutic advances in CHDs rather than cerebrovascular diseases.[5] Despite the undoubted importance of evaluating stroke epidemiology from a broad perspective, including prognostic factors and long-term mortality, there is still a lack of consistent data from developing countries.[10] and the majority are from developed countries.[10-13] Most previous stroke surveillance surveys in Brazil have been based on community and population-based studies restricted to one year at most.[14,15] In fact, few authors have assessed long-term stroke survival or post-stroke disability, or even prognostic risk factors among stroke survivors in Brazil.[16-18] One of these long-term stroke cohorts is the Study of Stroke Mortality and Morbidity in Adults (EMMA Study), which is an ongoing stroke surveillance survey in which the main objectives are to report on headline mortality rates and to monitor disability and prognostic risk factors among survivors living in a low-income area of the city of Sao Paulo, Brazil.[17,19-21]

OBJECTIVE

Here, we describe this Brazilian initiative, focusing on concepts and the main findings regarding stroke burden, including mortality and prognostic risk factors among stroke survivors living in a low-income area who were enrolled in the EMMA cohort between 2006 and 2014.

METHODS

Design, ethics and setting

This is an ongoing prospective community-based stroke cohort study conducted at the Hospital Universitário, University of São Paulo (Universidade de São Paulo, USP).

The institutional review board of USP's university hospital approved the main study, and also ancillary studies linked to the EMMA cohort.

Population

We evaluated stroke distribution and mortality within all three settings of the WHO STEPS stroke surveillance approach, in a low-income population living in the Butantan area. This area comprises six districts on the western side of São Paulo, with an estimated population of 424,377 (2009), of whom only 12%

are over 60 years of age. Among these six districts, the proportion of households with a family income less than or equal to five monthly minimum wages (2000, National Census data) ranges from 13.1% to 40.8%. This range is narrower than in other districts of this city (6.4-60.3%). Cardiovascular diseases account for 40% of all deaths in Butantan and São Paulo, and stroke mortality represents one quarter of all vascular deaths. The proportion of violent deaths during the last 10 years was slightly lower in the Butantan area (4.8%) than in the city overall (5.9%).

In Butantan, there are 16 primary care facilities, seven with an emergency room. The only hospital in the area is the university hospital (Hospital Universitário) of the University of Sao Paulo (USP), which is a community hospital with 260 beds in which STEP 1 was implemented.[19] This hospital supports emergencies from primary care units and paramedic ambulances and it is responsible for 80% of the hospitalizations of people living in this location. The center for neurological referral from this community facility is Hospital das Clinicas, which is a tertiary-care hospital located 8 km away. The primary care units are affiliated to the University, which also manages both hospitals.

EMMA registry in the different settings

WHO STEPS stroke approach within the EMMA cohort

The data collection for the EMMA study was initially based on the WHO manual Stepwise Approach to Surveillance.[22] The methodology for case ascertainment data and management of the entire STEPwise method is described elsewhere.[19]

In brief, STEP 1 (hospital phase), which is still ongoing, was started at USP's university hospital among patients who had neurological symptoms, fulfilled the initial criteria and agreed to participate in EMMA. The main study enrolled its first participant in April 2006 and its last one in September 2014. In this phase, we described the main objectives of the WHO project and some preliminary data, comprising evaluation of hospitalized events and including sociodemographic data (i.e. name, gender, age, race, income, educational level and occupation), acute stroke information regarding stroke recurrence, date and time of onset of stroke symptoms, hospitalization, history of traditional risk factors associated, medical treatment, neurological functionality (modified Rankin scale) and discharge status.[19]

For STEP 2 (fatal events in the community), which began in November 2006 and ended in 2007, the WHO methodology for cerebrovascular disease was applied in order to investigate cases that evolved to death through application of questionnaires that had previously been set up by WHO plus additional information relating to local realities.[19] Mortality data was obtained from the city of São Paulo's health statistics system (PRO-AIM, "Programa de Aprimoramento das Informações de Mortalidade", i.e. the program for improving mortality information). The objective was to identify the set of characteristics that might make it possible to quantify and qualify deaths that occurred within the university hospital's catchment area. In this approach, information on reported deaths was collected according to health areas determined by the Municipal Health Department of the city of São Paulo, taking into account the respective area covered by each primary care unit. From this information, a protocol for action towards this disease was recommended.

STEP 3 (non-fatal events in the community) started in February 2008 and finished in May 2008. The community area was previously delimited through a public family healthcare program at one primary care unit within the university hospital's catchment area (at Jardim São Jorge). A potential total number of 4,725 subjects older than 35 years of age was estimated for this first part. Trained interviewers administered the screening instrument, asking each family member to answer symptom questions and to perform simple physical tasks.[23,24] All participants who had been screened positive for events suggestive of stroke in the past were invited to answer an individual questionnaire that asked for information similar to that of the STEP 1 questionnaire. All of these individuals were classified according to their clinical diagnosis and their clinical and tomographic diagnoses of stroke. In relation to this last item, the stroke diagnoses of a subset of the patients were validated by a neurologist.[23,24]

Additional actions within the EMMA cohort

In addition to the STEPS stroke approach, we implemented other tools to investigate short and long-term mortality and the prognostic risk factors associated with survival, over the course of the follow-up on the EMMA cohort.[17,20,21,25-30] An extension of the EMMA protocol, which was developed in collaboration with this researcher's time spent within the main study, was also implemented in a municipality of the Amazon region, in northern Brazil.[31]

Mortality and prognosis

Vital status was investigated periodically by means of a hot-pursuit strategy using telephone contacts and medical registries during the follow-up. Particularly with regard to the main cohort at USP's university hospital in São Paulo, we double-checked all the mortality data through collaboration with the municipal statistics system (PRO-AIM), the data analysis system of the state of São Paulo (Fundação Sistema Estadual de Análise de Dados, SEADE) and the Brazilian Ministry of Health offices, every year. The reported causes of death on death certificates were transformed into medical codes in accordance with the Tenth Revision of the International Classification of Diseases (ICD-10).[31] Ultimately, mortality was categorized as all-cause,

cerebrovascular or cardiovascular. Here, we report data from previous EMMA publications based on all-cause mortality.

In the EMMA study, the mortality analyses included evaluation of case-fatality rates at 10, 28 and 180 days and survival analyses one year after the acute event, with exploration of some prognostic risk factors.[17,20,21] Short-term mortality (10 and 28-day case-fatality rates) was compared with other stroke registries in other Brazilian cities located in the northeastern region (João Pessoa and Natal).[26]

Regarding prognosis over the course of the follow-up, we implemented an extended evaluation of cognitive impairment, using a specific validated questionnaire (Modified Telephone Interview for Cognitive Status, TICS-M) on a subsample of EMMA survivors, three months after the index event.[27] In addition, post-stroke depression (PSD) after the acute phase and its influence on one-year survival was evaluated among stroke survivors, who answered a questionnaire on depression, the Patient Health Questionnaire (PHQ-9), by means of telephone interviews conducted one to three months after the acute event.[28]

Furthermore, we assessed an experimental open-case series to ascertain the effect of transcranial direct current stimulation (tDCS). This is a novel treatment that may improve clinical outcomes from PSD, which is traditionally refractory to pharmacotherapy, among stroke patients with aphasia during the first year after their stroke.[29]

Multicenter evaluation

An extended evaluation based on the original EMMA protocol (19) was also developed in the city of Coari, located in the Brazilian Amazon region. In this municipality, cerebrovascular prevalences were compared between the urban zone and rural riverbank areas of the municipality, between May and October 2011.[30]

Stroke ascertainment

We ascertained all consecutive cases of potential acute stroke events in the hospital, including first-ever and recurrent events. All patients older than 18 years of age were eligible for STEP 1. The WHO definition of stroke was used, i.e. "a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), of presumed vascular origin."[22] Histories of stroke were based on information from patients, caregivers or hospital records. When it was not possible to obtain information, the item was coded as "incomplete data". Stroke diagnoses were validated by a medical practitioner and supported by non-contrasted computed tomography (CT) scans. We used the codes of chapter I of ICD-10 to categorize stroke according to the following subtypes: ill-defined or unspecified stroke (ICD-10:I64), intracerebral hemorrhage (ICD-10:I61), cerebral infarction (ICD-10:I63), late effects of cerebrovascular diseases (ICD-10:I69) and subarachnoid hemorrhage (ICD-10:I60). All suspected stroke cases were also categorized as previous stroke (recurrent incidence of stroke) or no previous stroke (first-ever incidence of stroke), through access to medical records.

All data collection was performed by trained interviewers and medical researchers in accordance with the instructions in the STEPS stroke manual. Quality control was assured through cross-checking the information, which was done by three medical coordinators of the EMMA study.

Statistics

The main baseline findings were reported as absolute and relative frequencies[19-21,25,26] or as prevalence rates[23] for categorical variables; and as parametric or nonparametric test results, in accordance with the distribution of continuous variables in each subsample that had been evaluated in previous publications.[19-21,23-30]

In the EMMA study, the mortality analyses included evaluation of case-fatality rates at 10, 28 and 180 days, and at one year, calculated by means of the chi-square test and logistic regression, using the odds ratio (OR) and 95% confidence interval (95% CI).[25,26] One year after the index event, survival analyses were performed by means of Kaplan-Meier survival curves and Cox regression models, using the hazard ratio (HR) and 95% CI, to investigate predictors for long-term mortality, such as educational level, gender and depression.[17,20,21] Further details on the statistical analyses in each previous publication are summarized in **Table 1**.

RESULTS

Previous publications from the EMMA study are summarized in **Table 1.**

Main findings from STEPS within the EMMA study

The first published data from EMMA study reported on 682 stroke cases out of 1,023 cases of cerebrovascular disease (66.6%). The participants were over 18 years of age and their acute stroke event was confirmed through medical diagnosis and CT within the first 24-48 hours, upon hospital admission. All of them were attended at the university hospital's emergency care sector and were enrolled in EMMA (STEP 1) between April 2006 and May 2009.[19]

During the surveillance of fatal events within the community (STEP 2), 256 deaths due to stroke were identified over a 12-month follow-up period. The primary cause of death (causa mortis) according to stroke subtype showed that 30.5% of the deaths were due to IS, 26.6% were due to HS and 43% had an unspecified form of stroke as the primary cause.[19]

The initial screening of non-fatal stroke cases in the community (STEP 3) included 4,446 individuals living in the reference area of USP's university hospital, near to the Jardim São Jorge primary

Table 1. Executive summary of previous publications from the Study of Stroke Mortality and Morbidity in Adults (EMMA Study), 2006-2014

Study	Objectives	Methodology	Main findings and conclusions
Goulart et al., 2010[19]	To evaluate stroke epidemiology based on WHO STEPS stroke surveillance in São Paulo, Brazil: STEP 1: hospitalized fatal and non-fatal events STEP 2: fatal events in the community STEP 3: stroke survivors in the community.	Design/population: cross-sectional evaluation based on the WHO Stepwise Approach to Stroke Surveillance: STEP 1: hospital-based data comprising fatal and nonfatal stroke cases. STEP 2: stroke-related mortality data in the community using WHO questionnaires. STEP 3: questionnaire determining stroke prevalence, applied door-to-door within a family-health program in the neighborhood. Exclusion criteria: people who did not belong to the reference area. Statistics: frequencies, prevalence (95% CI), case-fatality rates according to CBV.	STEP 1: 682 CBV cases ≥ 18 years: 472 incident cases, presented with CBV (84.3% with IS and 85.2% with first-ever stroke) from April 2006 to May 2009. STEP 2: 256 deaths from stroke were identified during 2006–2007. 44% of the deaths were unspecified stroke, 1/3 were IS, and 1/4 were HS. STEP 3: 577 subjects ≥ 35 years were screened at home, and 243 cases of stroke survival were diagnosed via a questionnaire, validated by a board-certified neurologist.
Abe et al., 2010[24]	To validate a questionnaire for evaluating individuals with stroke symptoms in the EMMA study, São Paulo, Brazil.	Design/population: cross-sectional evaluation in a sample from all households in the coverage area of a primary healthcare unit in Butantan. Household members ≥ 35 years answered a stroke symptom questionnaire addressing limb weakness, facial weakness, speech problems, sensory disorders and impaired vision and 36 participants were randomly selected for a complete neurological examination (gold standard). Exclusion criteria: people who did not belong to the reference area and were not able to give responses to survey. Statistics: frequencies, sensitivity, specificity, PPV, NPV, positive and negative LH.	Questionnaire properties: sensitivity 72.2%, specificity 94.4%, PPV 92.9% and NPV 77.3%. LR+ was 12.9, LR- was 0.29. Limb weakness was the most sensitive symptom, and speech problems were the most specific. The stroke symptom questionnaire is a useful tool and can be applied by trained interviewers with the aim of identifying community-dwelling stroke patients, through the structure of the Family Health Program.
Abe et al., 2011[23]	To verify the prevalence of stroke in a deprived neighborhood in São Paulo, Brazil and compared it with other surveys worldwide.	Design/population: cross-sectional evaluation using questionnaire with six questions concerning limb and facial weakness, articulation, sensory disturbances, impaired vision and past diagnosis of stroke was completed door-to-door in a well-defined area of 15,000 people. Questionnaires were considered positive when a participant answered two or more questions about stroke symptoms or when the presence of stroke was confirmed by a physician, or when at least three questions had positive findings, even if not confirmed by a doctor. Exclusion criteria: people who did not belong to the reference area and were not able to give responses to survey. Statistics: prevalence rates (95% CI).	A total of 243 people initially screened positive for stroke. Age-adjusted prevalence rate for men was 4.6% (95% CI: 3.5-5.7). For women, the prevalence rate was 6.5% (95% CI: 5.5-7.5); when considering only one question, the rate was 4.8% (95% CI: 3.9-5.7). Most commonly reported symptoms were limb weakness and sensory disorders.
Goulart et al., 2012[25]	To identify case-fatality rates up to one year in a community hospital in São Paulo, Brazil.	Design/population: cross-sectional evaluation of all patients with first-ever stroke seeking acute care at the hospital's emergency ward between April 2006 and December 2008, to verify early and late case fatality according to stroke subtype. We used years of formal education as a surrogate for socioeconomic status. Exclusion criteria: people who did not belong to the reference area; those who did not receive first acute treatment at the community hospital; and cases of recurrent stroke. Statistics: frequencies, case-fatality rates and OR from 10 days to 1 year.	Out of 430 first-ever stroke events, 365 (84.9%) were IS. After 1 year, we reported 108 deaths (86 of IS; 22 of HS). Age-adjusted case-fatality rates for IS and HS were: 6.0% versus 19.8% at 10 days, 10.6% versus 22.1% at 28 days, 17.6% versus 29.1% at 6 months and 21.0% versus 31.5% at 1 years. Low education was a predictor of death at 6 months (OR: 4.31; 95% CI: 1.34-13.91) and 1 years (OR: 4.21; 95% CI: 1.45-12.28) particularly in IS cases.

Continues...

Table 1. Continuation

Study	Objectives	Methodology	Main findings and conclusions
Fernandes et al., 2012[21]	To evaluate the functional dependence of stroke survivors in the EMMA study.	Design/population: cross-sectional evaluation of ischemic stroke individuals who survived after acute phase (after 28 days) in subsample from EMMA using the modified Rankin scale at 28 days and 6 months. Exclusion criteria: people who did not belong to the reference area; those who did not receive first acute treatment at the community hospital; HS; and recurrent stroke. Statistics: frequencies, case-fatality rates and OR from 10 days to 1 year.	Among 355 survivors from first-ever IS (mean age: 67.9 years), 40% had some functional dependence at 28 days and 34.4% had some functional dependence at 6 months. Most predictors of physical dependence were identified at 28 days, and these comprised low education (OR: 3.7; 95% CI: 1.60-8.54) and anatomical stroke location (total anterior circulation infarct; OR: 16.9; 95% CI: 2.93-97.49).
Fernandes et al., 2012[26]	To evaluate early stroke case-fatality rates in three hospitals in three distinct cities located in two macroregions of Brazil.	Design/population: cross-sectional evaluation of 10 and 28-day case-fatalities in stroke registries in São Paulo, João Pessoa and Natal. Exclusion criteria: people who did not belong to the reference area; those who did not receive first acute treatment at the hospitals; and cases of recurrent stroke. Statistics: frequencies and case-fatality rates at 10 days, 28 days and 6 months after acute event.	Out of 962 first-ever events (mean age: 68.1 years; 53% men), 83.6% were classified as IS and 16.4% as HS. Overall, the case-fatality rates and 95% CI for HS were higher than for IS, both at 10 days [12.3%; (95% CI: 7.2-17.4) versus 7.0% (95% CI: 5.3-8.8) and at 28 days (19.8%; 95% CI: 13.6-26.0 versus 11.1%; (95% CI: 8.9-13.3)].
Barros et al., 2013[27]	To evaluate the distribution of stroke hospital admissions (weekdays or weekend) and their respective prognosis based on a sample from the EMMA study.	Design/population: prospective evaluation of all consecutive stroke cases between April 2006 and December 2008, with subsequent 1-year follow-up. Exclusion criteria: people who did not belong to the reference area; those who did not receive first acute treatment at the community hospital; and cases of recurrent stroke. Statistics: frequencies, case-fatality rates and OR from 10 and 28 days after acute event.	Out of 430 first-ever stroke cases in people ≥ 35 years old, no associations between frequencies of hospital admissions due to IS and HS and the specific day of the week on which the admission occurred were found. However, 10 and 28-day case-fatality rates were higher in HS cases admitted at the weekend. It was found that HS admitted on weekends had a worse survival rate (50%) than those admitted during weekdays (25.6%; P log-rank = 0.03). Multivariate HR was 2.49 [95% CI: 1.10-5.81; P trend = 0.03] for risk of death at the weekend compared with weekdays for HS cases, but no difference in survival was observed for IS cases.
Goulart et al., 2013[17]	To identify prognostic factors associated with long-term stroke survival among IS and HS first-ever stroke cases in the EMMA study.	Design/population: prospective evaluation on consecutive IS and HS stroke cases in a community hospital in São Paulo, Brazil. Cardiovascular risk factors and sociodemographic characteristics (age, gender, race and educational level) were evaluated as prognostic factors. Exclusion criteria: people who did not belong to the reference area; those who did not receive first acute treatment at the community hospital; and cases of recurrent stroke. Statistics: Kaplan-Meier survival and crude and multiple Cox proportional hazard models (with HR) were performed.	Among 665 first-ever stroke cases, we found a lower survival rate among HS cases than among IS cases at the end of 4 years of follow-up (52% versus 44%; P = 0.04). The risk of death was highest among people with IS and without formal education (HR: 1.83; 95% CI: 1.26-2.68) and with diabetes (HR: 1.45; 95% CI: 1.07-1.97). Age had equal influence on the high risk of poor survival, regardless of stroke subtype. In addition, HS, low education and diabetes were significant independent predictors of poor long-term survival.
Fernandes et al., 2014[31]	To determine the CBV prevalence in a town in the Brazilian Amazon region, comparing urban versus rural population in the same municipality.	Design/population: cross-sectional evaluation of CBV to calculate prevalence rates among 6,216 residents ≥ 35 y old in the town of Coari, Amazonas, using a screening questionnaire, the Stroke Symptom Questionnaire. CBV prevalence rates (PRs) from the door-to-door survey were calculated according to the location of the home. Exclusion criteria: people who did not belong to the reference area and were not able to give responses to survey. Statistics: prevalence rates (95% CI).	There were 4,897 respondents in the urban area and 1,028 in the rural area. The crude prevalence of stroke was 6.3% in the rural area and 3.7% in the urban area, regardless of age and sex. Among stroke cases, people in the rural area were those with less access to medical care in comparison with the urban area (32.1% versus 52.5%; P = 0.01), and there was a positive association between the rural area and no medical care (PR: 1.33; 95% CI: 1.03-1.71), independently of age, sex, education and functional impairment.

Continues...

Table 1. Continuation

Study	Objectives	Methodology	Main findings and conclusions
Baccaro et al., 2015[28]	To examine the psychometric properties of the Brazilian version of the Modified Telephone Interview for Cognitive Status (TICS-M) for cognitive impairment in a post-stroke subsample from the EMMA study.	Design/population: validation study. Original version of the TICS-M was translated and adapted into Brazilian-Portuguese language, and applied to 30 non-clinical subjects. After that, two trained researchers applied TICS-M to 61/73 EMMA participants who completed the follow-up: (i) personal interview 6 months after stroke; (ii) telephone interview 1 week after the first evaluation; and (iii) telephone interview 2 weeks after the first evaluation. Exclusion criteria: aphasia or other clinical conditions that made the interview impossible. Statistics: Reliability (test-retest) using Pearson's correlation, ICC and Cronbach's alpha coefficient. ROC analysis using the MMSE was used as a comparison. Structural validity of TICS-M was assessed through PCA in relation to 103 individuals (30 non-clinical and 73 stroke patients).	Reliability and ICC ranged from 0.87 to 0.97 across the evaluations. Cronbach's alpha was 0.96. PCA analysis extracted three meaningful domains: working memory, recall memory and orientation. Best cutoff point for screen cognitive impairment was 14 out of 15 (91.5% sensitivity; 71.4% specificity). The area under the curve was 0.89.
de Mello et al., 2016[29]	To evaluate the influence of major depression disorder (MDD) on long-term survival in a subsample of EMMA participants.	Design/population: prospective evaluation of IS and HS cases. The Patient Health Questionnaire (PHQ-9) for MDD was applied 30 days after index event and periodically during 1-year follow-up. All participants were able to answer telephone interview. Exclusion criteria: aphasia or other clinical conditions that made the interview impossible. Statistics: Kaplan-Meier survival and crude and multiple Cox proportional hazard models.	Among 164 (85.9%) subjects with IS and 27 (14.1%) with HS, overall incidence of MDD was 25.1% during 1 year of follow-up, regardless of stroke subtype or recurrence. The peak rate of MDD was more than 1 month post-acute event. Post-stroke MDD was associated with lower survival after 1 year of follow-up (85.4% with MDD versus 96.5% without MDD; log-rank P = 0 .006). A higher and independent risk of all-cause mortality among those who developed MDD compared with participants without MDD was also detected (HR: 4.60; 95% CI: 1.36-15.55; P = 0 .01).
Valiengo et al., 2016[30]	To evaluate the safety and efficacy of tDCS for patients with post-stroke depression (PSD) and with aphasia post-stroke.	Design/population: open-label study on PSD depression diagnosed by means of Aphasic Depression Questionnaire (SADQ) and the Aphasic Depression Rating Scale (ADRS), to evaluate the severity of PSD in four first-ever stroke cases from October 2012 to August 2014. Diagnoses of PSD and aphasia were confirmed by a psychiatrist and a speech-language pathologist, respectively. All eligible individuals (subsample from EMMA) received 10 sessions (once a day) of bilateral tDCS to the dorsolateral prefrontal cortex (DLPFC) and two additional sessions after two and four weeks (total of 12 sessions). Exclusion criteria: non-confirmed PSD and aphasia. Statistics: patients' scores from the ADRS and SADQ were subjected to one-way analysis of variance (ANOVA) with time (baseline, week 2, week 4, week 6) as the within-subject factors. Post-hoc comparisons were carried out using Bonferroni test. Additionally, the partial Eta squared (pη2) was calculated for each ANOVA.	Among the four females evaluated, all exhibited improvement in depression after tDCS [decreases in SADQ (47.5%) and in ADRS (65.7%)]. This improvement was maintained four weeks after the treatment. In this preliminary open-label study conducted on four PSD patients with aphasia, bilateral tDCS over the DLPFC was shown to induce a substantial mood improvement; tDCS was safe and well tolerated by every patient.

CBV = cerebrovascular disease; WHO = World Health Organization; IS = ischemic stroke; HS = hemorrhagic stroke; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value; OR = odds ratio; HR = hazard ratio; ICC = Cronbach's intraclass correlation coefficient; ROC = receiver operating characteristic curve; PCA = principal-component analysis; tDCS = transcranial direct current stimulation.

care unit, which is located in the western area of the city of São Paulo. Among these individuals, 618 (13.7%) were not found, 204 (4.5%) refused to participate in the study and 13 (0.29%) were incapable of answering the questions. In total, 3,661 individuals (81.4%) answered a familial screening questionnaire, and 582 of them were identified as having screened neurologically positive, based on additional information relating to their treatment, disability and neurological recovery after stroke. A total of 577 subjects answered the final questionnaire, of whom 243 were screened positive for stroke, based on a questionnaire, and were validated by a board-certified neurologist.[23,24] The age-adjusted prevalence rate for men was 4.6% (95% CI: 3.5-5.7). For women, the prevalence rate was 6.5% (95% CI: 5.5-7.5) and, when considering only one question, the rate was 4.8% (95% CI: 3.9-5.7). The most commonly reported symptoms were limb weakness and sensory disturbances. Hypertension and heart disease were very frequent conditions associated with previous stroke.[23]

In all settings, most of the participants were white and married, and had low education (1-7 years). We observed that most of the subjects in STEP 1 and 2 were older (mean ages: 66 and 74 years, respectively) than those who participated in STEP 3 (50.7% of subjects were of ages ranging from 45 to 64 years). Regarding the respondents' gender, we observed that in STEP 3, more females participated in the study (59.4% in STEP 3, 49.2% in STEP 2 and 45.3% in STEP 1).

Short and long-term mortality during extended follow-up

Regarding the mortality rates from the hospital registry, we evaluated case-fatality rates from ten days to one year among all consecutive patients with first-ever stroke who sought acute care at the USP university hospital's emergency service and were enrolled in the EMMA study between April 2006 and December 2008. Among 430 first-ever stroke events, 365 (84.9%) were IS and 65 (15.1%) were HS.[25] Among cerebrovascular risk factors, the frequency of alcohol intake was higher in hemorrhagic stroke (HS) than in ischemic stroke (IS) cases (35.4% versus 12.3%, $P < 0.001$). After one year, we found that 108 deaths had occurred (86 cases of IS and 22 of HS). The age-adjusted case fatality rates for IS and HS were 6.0% versus 19.8% at 10 days, 10.6% versus 22.1% at 28 days, 17.6% versus 29.1% at six months, and 21.0% versus 31.5% at one year. Illiteracy or no formal education was a predictor for death at six months (OR: 4.31; 95% CI: 1.34-13.91) and one year (OR: 4.21; 95% CI: 1.45-12.28) among patients with ischemic stroke. It was also a predictor at six months (OR: 3.19; 95% CI: 1.17-8.70) and one year (OR: 3.30; 95% CI: 1.30-8.45) for all stroke patients. Other variables, including previous cardiovascular risk factors and acute medical care, did not change this association to a statistically significant degree. In conclusion, case fatality, particularly up to six months, was higher in cases of hemorrhagic stroke, and lack of formal education, particularly among IS cases, was associated with increased stroke mortality.[25]

Our early case-fatality rates were also compared with other stroke registries located in general hospitals in the northeastern region of Brazil (cities of João Pessoa and Natal).[26] Out of 962 first-ever events recorded in three centers, the proportions of ischemic-to-hemorrhagic cases were maintained at 5:1, as we previously observed in our single-center analysis at USP's university hospital, where the EMMA study was set up.[25]

Additional long-term mortality data, including survival analyses from April 2006 to December 2010, were used to evaluate 665 first-ever stroke cases, of which 545 (82.6%) were IS and 116 (17.4%) were HS during the four-year follow-up. We found an overall survival rate of 48% (mean survival of 40 months). Again, we confirmed that lack of formal education and diabetes were independent predictors of poor survival, particularly among IS subjects during long term-follow-up[15] (**Table 1**).

Cognitive impairment

Cognitive status three months after acute stroke was evaluated during the follow-up as an additional action relating to post-stroke disabilities. In this context, we previously adapted and validated the Brazilian version of the TICS-M for cognitive impairment among post-stroke patients, in a subset of EMMA participants, using the Mini-Mental State Examination (MMSE) as the comparison.[28] We found that cognitive impairment was present in 22.9% of the individuals, post-stroke. The test-retest reliability and intraclass correlation from TICS-M were found to be good, with coefficients ranging from 0.87 to 0.97 across the evaluations. Principal-component analysis extracted three meaningful domains: working memory, recall memory and orientation. The best cutoff point for screening for cognitive impairment was 14 out of 15 (91.5% sensitivity and 71.4% specificity), based on MMSE as the comparison. The area under the curve was 0.89 and, in the end, we concluded that the Brazilian version of the TICS-M was a reliable, stable and homogeneous instrument for screening for cognitive impairment among stroke patients.[28]

Post-stroke depression

In a subsample of 191 EMMA participants who reported their depressive status using PHQ-9, one to three months after the acute event, we found that 164 (85.9%) had suffered IS and 27 (14.1%), HS. Among these, the overall incidence of major depression disorder was 25.1% during the one-year follow-up, regardless of stroke subtype. The peak rate of major depression subsequent to the acute event was more than one month afterwards. We observed that there was a lower survival rate among individuals who developed post-stroke major depression disorder than

among those who did not develop this condition, after one year of follow-up (85.4% versus 96.5%; log rank P = 0.006). After multiple analysis, we found that there continued to be higher risk of all-cause mortality among those who developed major depression disorder than among participants without major depression disorder (HR: 4.60; 95% CI: 1.36-15.55; P = 0.01), thus suggesting that incident major depression disorder is a potential marker for poor prognosis, one year after stroke.[29]

tDCS in post-stroke depression (PSD) and aphasia

The sample comprised four females (mean age: 48 years) with aphasia after stroke who developed the onset of post-stroke depression after the index event (mean time elapsed: six months). The treatment was well tolerated by all these patients and no adverse effects were observed. For the Aphasic Depression Rating Scale (ADRS), the main effects of time reached significance: post-comparisons showed significant reductions in the patients' scores only at week 6 (5.5), in comparison with baseline (16; P < 0.001), week 2 (12.75; P < 0.01) and week 4 (11.75; P < 0.02). For the Aphasic Depression Questionnaire (SADQ), the significant main effects of time were reductions of patients' scores from baseline (56.25) to week 2 (38.5; P < 0.001), week 4 (35.5; P < 0.001) and week 6 (29.75; P < 0.0001).[30]

Extended EMMA initiative

In the area studied in Coari, 6,216 residents over 35 years of age were interviewed using a screening questionnaire, the Stroke Symptom Questionnaire. From this door-to-door surveillance, cerebrovascular prevalence rates (PR) were calculated according to the location of the home.[31] The total numbers of respondents were 4,897 in the urban area and 1,028 in the rural area. The crude prevalence rate (PR) of stroke was 6.3% in the rural area and 3.7% in the urban area, regardless of age and sex. As expected, lower levels of medical care were observed in the rural area than in the urban area (32.1 versus 52.5%, P = 0.01). There was a positive association between living in the rural area and no medical care for stroke (PR: 1.33; 95% CI: 1.03–1.71), regardless of SES.[31]

DISCUSSION

Since 2006, unified data provided through the EMMA study have demonstrated trends regarding stroke surveillance in three spheres of investigation (hospital, official mortality data and community sources).[19,23] The data have also shown potential risk factors and disability and mortality statistics based on case-fatality and survival rates in this low-income population over the course of four-year follow-up.[17,20,21,25,26]

At first view, the demographic characteristics among the EMMA participants were similar in the three STEPS, except for age and sex. In the community (STEP 3), we found younger survivors and more females than in other settings.[19] As expected, information on stroke subtype was better defined in the hospital setting (STEP 1) than in the community (STEP 3).[19] Among the cases included in the hospital phase, about 70% were confirmed as first-ever stroke and ischemic subtype (ratio of hemorrhagic-to-ischemic cases of 1:6) during the period 2006-2009.[25] We noticed that there was a slight increase in the proportions of hemorrhagic-to-ischemic cases. to 1:4, by adding one year of follow-up (2006-2010).[17] In addition to aging, regular alcohol consumption was closely associated with intracerebral hemorrhage.

Comparisons across epidemiological studies on stroke worldwide are difficult because of divergences of methodology, especially regarding the study sample (hospital or community or population-based data), the criteria used for ascertaining cases and the stroke subtype enrolled. Nevertheless, the EMMA study, which used a stroke cohort based on a low-income community on the western side of the city of São Paulo, had results that were in accordance with those from most population-based studies.[32] In addition, the extension of the EMMA study to a community in the Brazilian Amazon region confirmed that the prevalence of stroke in rural areas is higher than in urban areas.[31]

A systematic review conducted on 56 population-based studies, including Brazilian data,[14] which reported stroke incidence and case-fatality from 1970 to 2008 in low to middle-income countries, found that the proportion of ischemic stroke ranged from 54% to 85% and that the proportion of intracerebral hemorrhage ranged from 14% to 27% over the period from 2000 to 2008.[32] As expected, hemorrhagic cases were more commonly detected in low-income countries.[32] Although we found a slight increase in the proportion of incident cases of HS, compared with IS, over a four-year period, our rates were similar to those reported in developed countries.[32] Regarding mortality, our case-fatality rate over a one-year period was 25% (ratio of ischemic to hemorrhagic stroke cases of 1:4). As expected, the risk of death due to HS was greater than the risk due to IS and this gradient reached its maximum at 10 days (OR: 3.31; 95% CI: 1.55-7.05). Low education was the main sociodemographic factor associated with higher risk of death, particularly among those with ischemic stroke. The influence of lack of education on mortality was markedly higher at 10 days.[25]

Our case rates for IS (85%) and HS (15%) were similar to those reported in other Brazilian studies.[14,33] However, they differed from those reported in other countries in Latin America, such as Chile (72% for IS and 28% for HS)[33] and were much more divergent from data from southern African (Mozambique), from where the highest rate of HS (46%) versus IS (56%) was reported.[34]

A comparison of our findings with those from two other Brazilian population-based studies showed that our study had a

lower one-year overall case fatality rate than the rate reported in Matão (22.7% versus 30.9%)[14] and a lower 180-day lethality rate than the rate in Joinville (overall stroke rate: 19.5% versus 25%; ischemic stroke rate: 17.6% versus 19%; and hemorrhagic stroke rate: 29.1% versus 49%).[33]

Overall, life expectancy within the first four years after stroke was about 50% in the EMMA study. Our cumulative survival rate for hemorrhagic stroke was 44%.[18] The main determinants of poor survival up to four years were hemorrhagic stroke and lack of education for ischemic cases. Moreover, we found that diabetes was an independent predictor of all-cause mortality in a long-term follow-up on our study data.[18]

Regarding functionality, there was a slight decrease in the hospital phase of EMMA, from 40% at 28 days to 34% at six months after the acute event, particularly among individuals of low education level with IS.[21] Reinforcing these findings, in EMMA STEP 3 (community level), the referral rate for rehabilitation services was roughly 25% for all participants within the community who were identified as presenting a previous history of stroke.[23]

Overall, our statistics revealed similar proportions for incident cases of ischemic and hemorrhagic stroke cases in comparison with developed countries. On the other hand, we continue to be behind developed countries in terms of decreasing the mortality rates. The case-fatality rates remain high and the survival rates remain poor in our setting. There is also a high degree of dysfunctionality among stroke survivors, particularly those with low SES, which is much more similar to the stroke pattern in developing countries.[1] These findings reaffirm the trends recently reported by GBD in 2013, regarding the significant burden of stroke concentrated in developing countries. The impact on mortality rates, DALYs and years lived with disability (YLDs) that comes mainly from hemorrhagic stroke was shown to be significantly higher in developing than in developed countries. During the period from 1990 to 2013, the proportional contributions of deaths due to HS and IS increased by 1.8% and 2.2% in developing countries, respectively. Meanwhile, in developed countries, these rates decreased by 0.73% for HS and by 1.45% for IS.[1]

The EMMA study has some strengths. Although our cohort was not a population-based study, we based our data on a community area with low SES, located in a developing country. This may have contributed towards filling the gap in the information on stroke epidemiology. We developed an extended evaluation that included epidemiology, mortality and predictors associated with poor prognosis among individuals who survived the acute phase of the cerebrovascular event. We implemented a standard protocol in order to follow up our participants by means of telephone contacts and thus update the following data: vital status; functional disability; non-fatal outcomes such as hospitalization; recurrence of stroke or other CVD outcomes (heart failure and myocardial infarction); progression of depression; and cognition. All of these data will be available in the near future for prospective analysis.

The information acquired over the course of the follow-up was all double-checked by the medical researcher responsible, based on the patient's medical records and additional examinations such as CT, echocardiography and electrocardiogram for the main study. The mortality information was all confirmed through official death certificates provided by the local health statistics departments at all centers involved in the stroke surveillance. Thus, mortality specified as due to cerebrovascular or cardiovascular causes will be available for survival analyses.

Other than the EMMA cohort, only a few Brazilian studies have reported on the big picture of stroke epidemiology, including long-term follow-up with its admixture of outcomes.[16,18,35]

Finally, the contribution of the EMMA cohort related to knowledge of stroke epidemiology in hospital and community settings, thereby enabling comparisons across developing countries that have applied the WHO methodology for stroke surveillance.[36-38]

Our main limitations related mainly to the initial data collection, which lacked acute neurological evaluation for quantifying stroke severity in most cases. We implemented the NIH Stroke Scale (NIHSS) from the outset of the study, but less than 10% of the cohort presented trustworthy data. In addition, we implemented some protocols to investigate post-stroke depression and cognitive impairment/dementia after 2010.

CONCLUSIONS

Data provided by the EMMA cohort study have depicted stroke surveillance in three spheres of investigation (hospital, official mortality data and community sources). The foremost findings of high rates of post-stroke disability and mortality and poor long-term survival have mainly been influenced by low education levels so far, up to the four-year follow-up.

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Acknowledgements: We are grateful for all the time spent by researchers and physicians linked to the EMMA (Estudo de Mortalidade e Morbidade do Acidente Vascular Cerebral) cohort, as well as by collaborators within the Program for Improvement of Mortality Information in the Municipality of São Paulo (Programa de Aprimoramento das Informações de Mortalidade no Município de São Paulo, PRO-AIM), the healthcare data analysis system of the State of São Paulo (Fundação Sistema Estadual de Análise de Dados, SEADE) and the Brazilian Ministry of Health; as well as to hospital administrators for their help in collecting and analyzing the data for this Brazilian initiative relating to stroke surveillance

Sources of funding: This study was funded by the Brazilian National Research Council (CNPq) under number 47219/2004-0, and the Research Support Foundation of the State of São Paulo (FAPESP), under numbers 2010/20562-5, 2011/023-360, 2011/17568-4, 2011/22872-4 and 2015/17321-0
Conflicts of interest: None declared

Date of first submission: September 13, 2016
Last received: September 13, 2016
Accepted: September 27, 2016

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Statins for aortic valve stenosis

This is the abstract of a Cochrane Review published in the Cochrane Database of Systematic Reviews 2016, issue 9, art. no.: CD009571. DOI: 10.1002/14651858.CD009571.pub2.

Luciana Thiago, Selma Rumiko Tsuji, Jonathan Nyong, Maria Eduarda dos Santos Puga, Aécio Flávio Teixeira de Góis, Cristiane Rufino Macedo, Orsine Valente, Álvaro Nagib Atallah

The independent commentary was written by Marcio Miname

ABSTRACT

BACKGROUND: Aortic valve stenosis is the most common type of valvular heart disease in the USA and Europe. Aortic valve stenosis is considered similar to atherosclerotic disease. Some studies have evaluated statins for aortic valve stenosis.

OBJECTIVES: To evaluate the effectiveness and safety of statins in aortic valve stenosis.

METHODS:

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS - IBECS, Web of Science and CINAHL Plus. These databases were searched from their inception to 24 November 2015. We also searched trials in registers for ongoing trials. We used no language restrictions.

Selection criteria: Randomized controlled clinical trials (RCTs) comparing statins alone or in association with other systemic drugs to reduce cholesterol levels versus placebo or usual care.

Data collection and analysis: Primary outcomes were severity of aortic valve stenosis (evaluated by echocardiographic criteria: mean pressure gradient, valve area and aortic jet velocity), freedom from valve replacement and death from cardiovascular cause. Secondary outcomes were hospitalization for any reason, overall mortality, adverse events and patient quality of life.

Two review authors independently selected trials for inclusion, extracted data and assessed the risk of bias. The GRADE methodology was employed to assess the quality of result findings and the GRADE profiler (GRADEPRO) was used to import data from Review Manager 5.3 to create a 'Summary of findings' table.

MAIN RESULTS: We included four RCTs with 2360 participants comparing statins (1185 participants) with placebo (1175 participants). We found low-quality evidence for our primary outcome of severity of aortic valve stenosis, evaluated by mean pressure gradient (mean difference (MD) -0.54, 95% confidence interval (CI) -1.88 to 0.80; participants = 1935; studies = 2), valve area (MD -0.07, 95% CI -0.28 to 0.14; participants = 127; studies = 2), and aortic jet velocity (MD -0.06, 95% CI -0.26 to 0.14; participants = 155; study = 1). Moderate-quality evidence showed no effect on freedom from valve replacement with statins (risk ratio (RR) 0.93, 95% CI 0.81 to 1.06; participants = 2360; studies = 4), and no effect on muscle pain as an adverse event (RR 0.91, 95% CI 0.75 to 1.09; participants = 2204; studies = 3; moderate-quality evidence). Low- and very low-quality evidence showed uncertainty around the effect of statins on death from cardiovascular cause (RR 0.80, 95% CI 0.56 to 1.15; participants = 2297; studies = 3; low-quality evidence) and hospitalization for any reason (RR 0.84, 95% CI 0.39 to 1.84; participants = 155; study = 1; very low-quality evidence). None of the four included studies reported on overall mortality and patient quality of life.

AUTHORS CONCLUSIONS: Result findings showed uncertainty surrounding the effect of statins for aortic valve stenosis. The quality of evidence from the reported outcomes ranged from moderate to very low. These results give support to European and USA guidelines (2012 and 2014, respectively) that so far there is no clinical treatment option for aortic valve stenosis.

The full text of this review (English), the abstract (English and Polish) and the plain language summary (English and Polish) are available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009571.pub2/full

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1. Thiago L, Tsuji SR, Nyong J, et al. Statins for aortic valve stenosis. Cochrane Database Syst Rev. 2016;9:CD009571. [Epub ahead of print]

COMMENTS

Life expectancy of the populations of Brazil and other countries around the world has increased over recent decades. Aging of the population increases the prevalence of aortic stenosis due to fibrotic calcification of valves. The risk factors for development of this etiology of aortic stenosis are the same factors that contribute towards accelerating atherosclerotic disease: dyslipidemia, systemic arterial hypertension, diabetes mellitus and smoking.[1] The classic model showing a strong association between hypercholesterolemia and aortic stenosis is homozygous familial hypercholesterolemia.[2] In this disease, in which patients present very high levels of LDL-cholesterol, aortic stenosis or supravalvular stenosis progresses very fast and is an important cause of morbidity and mortality among these patients. Treatment of dyslipidemia possibly also has the benefit of attenuating or slowing down the progression of aortic stenosis due to fibrotic calcification, given the similarity of the lesion to atherosclerotic disease.

This systematic review of randomized controlled clinical trials evaluated the efficacy and safety of statins on patients with aortic stenosis.[3] Only four clinical trials met the selection criteria and could be included. Overall, the quality of evidence was low to moderate and did not show any beneficial effect from statins on the development of aortic stenosis. This review demonstrates that, given the limitations of these studies regarding sample size and length of follow-up, the role of statins on the evolution of aortic stenosis may still be a field for research. It is in fact possible that statins will not modify the evolution of severe aortic stenosis because the mechanical and hemodynamic changes have already become established. On the other hand, they may play a role in preventing progression in patients with mild to moderate aortic stenosis caused by fibrotic calcification. A study on this profile of aortic stenosis, with adequate sample size and long follow-up may demonstrate some benefit from statins among patients with aortic stenosis. Thus, there are still some questions to be answered regarding this topic. However, it should be noted that many of the patients with aortic stenosis who would be candidates for inclusion in this type of study might already be candidates for statin treatment for prevention of coronary artery disease, given the similarity of the risk factors between these two entities.

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Immediate versus delayed treatment for recently symptomatic carotid artery stenosis

This is the abstract of a Cochrane Review published in the Cochrane Database of Systematic Reviews 2016, issue 9, art. no.: CD011401. DOI: 10.1002/14651858.CD011401.pub2

Vladimir Vasconcelos, Nicolle Cassola, Edina Mariko Koga da Silva, José Carlos Costa Baptista-Silva

The independent commentary was written by Nilo Mitsuru Izukawa

ABSTRACT

BACKGROUND: The timing of surgery for recently symptomatic carotid artery stenosis remains controversial. Early cerebral revascularization may prevent a disabling or fatal ischemic recurrence, but it may also increase the risk of hemorrhagic transformation, or of dislodging a thrombus. This review examined the randomized controlled evidence that addressed whether the increased risk of recurrent events outweighed the increased benefit of an earlier intervention.

OBJECTIVES: To assess the risks and benefits of performing very early cerebral revascularization (within two days) compared with delayed treatment (after two days) for people with recently symptomatic carotid artery stenosis.

METHODS:

Search methods: We searched the Cochrane Stroke Group Trials Register in January 2016, the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2016, issue 1), MEDLINE (1948 to 26 January 2016), EMBASE (1974 to 26 January 2016), LILACS (1982 to 26 January 2016), and trial registers (from inception to 26 January 2016). We also handsearched conference proceedings and journals, and searched reference lists. There were no language restrictions. We contacted colleagues and pharmaceutical companies to identify further studies and unpublished trials

Selection criteria: All completed, truly randomized trials (RCT) that compared very early cerebral revascularization (within two days) with delayed treatment (after two days) for people with recently symptomatic carotid artery stenosis.

Data collection and analysis: We independently selected trials for inclusion according to the above criteria, assessed risk of bias for each trial, and performed data extraction. We utilized an intention-to-treat analysis strategy.

MAIN RESULTS: We identified one RCT that involved 40 participants, and addressed the timing of surgery for people with recently symptomatic carotid artery stenosis. It compared very early surgery with surgery performed after 14 days of the last symptomatic event. The overall quality of the evidence was very low, due to the small number of participants from only one trial, and missing outcome data. We found no statistically significant difference between the effects of very early or delayed surgery in reducing the combined risk of stroke and death within 30 days of surgery (risk ratio (RR) 3.32; confidence interval (CI) 0.38 to 29.23; very low-quality evidence), or the combined risk of perioperative death and stroke (RR 0.47; CI 0.14 to 1.58; very low-quality evidence). To date, no results are available to confirm the optimal timing for surgery.

AUTHORS CONCLUSIONS: There is currently no high-quality evidence available to support either very early or delayed cerebral revascularization after a recent ischemic stroke. Hence, further randomized trials to identify which patients should undergo very urgent revascularization are needed. Future studies should stratify participants by age group, sex, grade of ischemia, and degree of stenosis. Currently, there is one ongoing RCT that is examining the timing of cerebral revascularization.

The full text of this review (English), the abstract (English and Polish) and the plain language summary (English and Polish) are available from: http://onlinelibrary.wiley.com/wol1/doi/10.1002/14651858.CD011401.pub2/abstract

REFERENCE

1. Vasconcelos V, Cassola N, da Silva EM, Baptista-Silva JC. Immediate versus delayed treatment for recently symptomatic carotid artery stenosis. Cochrane Database Syst Rev. 2016;9:CD011401. [Epub ahead of print]

COMMENTS

The authors of this study attempted to answer the question of the best time to indicate revascularization (surgery or angioplasty) in patients presenting neurological events caused by carotid stenosis. To achieve this, they undertook an extensive and systematic bibliographical search, following standard procedures, but only found one study that fulfilled the criteria. This study involved 40 patients and was unable to demonstrate any superiority of early revascularization over late revascularization. This emphasizes that further studies on this topic are needed.

Nilo Mitsuru Izukawa, MD, PhD. Head of the Medical Section of Vascular Surgery, Instituto Dante Pazzanese de Cardiologia, São Paulo (SP), Brazil.

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- Hurt AC, Hardie K, Wilson NJ, et al. Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza. N Engl J Med. 2011;365(26):2541-2.

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- Miller WI, Achernabb JC, Fluck CE. The adrenal cortex and its disorder. In: Sperling M. Pediatric endocrinology. 3rd ed. Elsevier Health Sciences; 2008. p. 444-511.

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Images must have good resolution (minimum of 300 DPI) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint documents. If photographs are inserted in a

Microsoft Word file, the images should also be sent separately. Graphs must be prepared in Microsoft Excel (do not send them in image formats) and must be accompanied by the tables of data from which they have been generated. The number of illustrations must not exceed the total number of pages minus one.

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 legend or title sentence should be short but comprehensible without depending on reading the article.

All the figures and tables should be cited in the text.

São Paulo Medical Journal/Evidence for Health Care is for now published in black-and-white in its printed version. Photographs, photomicrographs, bar and line graphs and any image to be published must be prepared considering that there will be no color differentiation (any color information will be discarded). Shades of gray and printing patterns (dots, stripes and others) should be used instead, with good contrast.

Original articles

Clinical trials, cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies, and systematic reviews with or without meta-analysis, are considered to be original articles.

The São Paulo Medical Journal/Evidence for Health Care 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, from 2008 onwards, manuscripts on clinical trials have been accepted for publication only if they have received an identification number from one of the clinical trial registers that have been validated in accordance with the criteria established by WHO and ICMJE. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal/Evidence for Health Care. The addresses for these registers are available from the ICMJE website (http://www.icmje.org). The identification number should be declared at the end of the abstract.

Authors will be required to comply with the guidelines for writing each type of original article, as follows:

1. Observational articles: STROBE Statement;[5,6]
2. Clinical trials: CONSORT Statement;[2]
3. Accuracy studies on diagnostic tests: STARD Statement;[7,8]
4. Systematic reviews of the literature and meta-analyses: PRISMA[4]

The São Paulo Medical Journal takes the view that these guidelines not only aid in writing and organizing the content of articles in a standardized manner, thereby improving their quality and facilitating reading and assessment, but also these guidelines help to avoid situations in which important information on the methodology of studies remains outside of the manuscript.

As a partner institution of the Cochrane Collaboration and the Brazilian Cochrane Center, the *Associação Paulista de Medicina* considers that production of articles in accordance with these guidelines also aids in future production of systematic reviews of the literature and meta-analyses. Thus, articles submitted for publication that are not in accordance with these norms may be returned to their authors for adjustment before the peer review process begins.

Original articles must be structured so as to contain the following parts: Introduction, Objective, Methods, Results, Discussion and Conclusion. The text must not exceed 5,000 words (excluding tables, figures and references), from the introduction to the end of the conclusion, and must include a structured abstract with a maximum of 250 words.[9] "Structured abstract" means that the abstract must contain the following items: Context and objective, Design and setting, Method, Results and Conclusion.

The structure of the document should follow the format laid out below:

1) *Title and abstract*: the study design and/or the way participants were allocated to interventions, for example "randomized" or "retrospective" study, should be mentioned in the title and in the abstract. The abstract should provide a summary of what was done and what was found.
2) *Introduction:* specify the reasons for carrying out the study, describing the present state of knowledge of the topic. Describe the scientific background and "the state of the art". Do not include here any results or conclusions from the study. Use the last paragraph to specify the principal question of the study, and the principal hypothesis tested, if there is one. Do not include discussions about the literature in the introduction; the introduction section should be short.
3) *Objective:* describe briefly what the main objective or question of the study was. Clearly describe the pre-specified hypotheses.
4) *Methods*

4.1) *Type of study*: describe the design of the study and specify, if appropriate, the type of randomization (the way in which draws were conducted), the blinding (how this was ensured), the diagnostic test standards (gold standard or range of normal values) and the time direction (retrospective or prospective). For example: "randomized clinical trial", "double-blind placebo-controlled clinical trial", "cross-sectional accuracy study", "retrospective cohort study", "cross-sectional prevalence study" or "systematic review of clinical trials".

4.2) *Sample, participants or patients*: describe the eligibility criteria for participants (inclusion and exclusion criteria) and the sources and procedures for selection or recruitment. In case-control studies, describe the rationale for distributing the subjects as cases and controls, and the matching criteria. The numbers of patients at the beginning and end of

the study (after exclusions) must be made clear. A flow diagram showing the initial recruitment, the exclusions and the final sample of patients included should be produced and inserted in the article.

4.3) *Setting:* indicate the place where the study was carried out, including the type of healthcare provided (i.e. whether primary or tertiary; and whether in a private or in a public hospital). Avoid stating the name of the institution where the study was developed (for blinding purposes in the peer review). Only the type of institution should be made clear, for example: "public university hospital" or "private clinic".

4.4) *Procedures (*intervention, diagnostic test or exposure): describe the principal characteristics of any intervention, including the method, the timing and the duration of its administration or of data collection. Describe the differences in interventions administered to each group (if the study is controlled). Detail the procedures in such a way that other researchers will be able to repeat them in other localities.

4.5) *Main measurements, variables and outcome*: state what the primary and secondary outcomes analyzed in the study are. Describe the method of measuring the primary result, in the way in which it was planned before data collection. For each variable of interest, detail the assessment methods. If the hypothesis of the study was formulated during or after data collection (and not before), this needs to be declared. Describe the methods used to enhance the quality of measurements (for example, multiple observers, training, etc.) and to avoid bias. Explain how quantitative variables were handled in the analyses.

4.6) *Sample size and statistical analysis*: describe the sample size calculation method, or the study period in the event that patients were consecutively admitted over a period. Readers need to understand why a given number of patients was used. The planned statistical analysis, the statistical tests used and their significance levels, along with any *post hoc* analyses, should be presented in this section. Describe the methods used to control for confounding factors and variables, and explain how missing data and cases lost from the follow-up were dealt with.

4.7) *Randomization*: describe the method used to implement the random allocation sequence (for example, sealed envelopes containing random sequences of numbers or software for generating random numbers). If appropriate, report that the study used "quasi-randomization".[12] In addition, describe who generated the random sequence, who assigned the participants to each group (in the case of controlled trials) and who recruited the participants.

5) *Results:* describe the main findings. If possible, these should be accompanied by their 95% confidence intervals and the exact level of statistical significance (it is not enough to write "$P < 0.05$": the exact P value should be supplied). For comparative studies, the confidence interval must be stated for the differences between the groups.

5.1) *Participant flow diagram*: describe the flow of participants through each stage of the study (inclusions and exclusions) and the follow-up period, and the number of participants completing the study (or lost from the follow-up). Use a flow diagram to demonstrate the numbers of patients, from the initial recruitment to the end of the study, and the reasons for exclusions. If there was any "intention-to-treat" analysis, describe it.

5.2) *Deviations*: if there was any deviation from the protocol, away from what was initially planned, describe it and the reasons for it.

5.3) *Adverse events*: describe any side effect, adverse event or complication.

6) *Discussion:* provide an interpretation of the results, taking into account the study hypotheses and conclusions. Emphasize the new and important factors encountered in the study, which will form part of the conclusion. Do not repeat data presented in the introduction or results in detail. Mention any limitations of the findings that should be noted and any possible implications for future research. Describe any potential bias. Report any relevant findings from other studies: it is important to review the recent literature to seek new evidence that may have been published, which needs to be discussed. State whether the findings can be generalized to populations (i.e. whether the findings have external validity). It is recommended that the last two paragraphs should contain implications for practice and for further research.

7) *Conclusions:* specify only the conclusions that can be sustained by the results, together with their clinical significance (avoiding excessive generalization). Draw conclusions based on the objectives and hypotheses of the study. The same emphasis should be placed on studies with positive and negative results.

Systematic reviews with or without meta-analyses should comply with the same publication norms established for original articles, and be produced in accordance with PRISMA[4] and the Cochrane Collaboration's systematic review Handbook.[13] The text should not exceed 5,000 words (excluding tables, figures and references)

Short communications, case reports or case series

Short communications and case reports must be limited to 3,000 words (from the introduction to the end of the conclusion). 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 thus: Introduction, Objective, Methods, Results, Discussion and Conclusion, like in original articles.

Individual case reports should contain: Introduction, Case Report, Discussion and Conclusion. Reports on case series constitute observational studies and these should be structured in accordance with the norms of the STROBE Statement.[5]

Both short communications and case reports must be submitted with abstracts and key words. The abstracts in short communications should be structured with: Context and objective, Design and setting, Methods, Results and Conclusion, like in original articles. The abstracts in case reports and case series should contain: Context, Case Report (with a description of the case and a pertinent discussion) and Conclusion.

The São Paulo Medical Journal/Evidence for Health Care is interested in publishing rare or instructive case reports, accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[14] The results from the systematic search of the main databases — Medline (via PubMed), Embase, Lilacs and Cochrane Library — should be presented in a table with the search strategy for each database and the number of articles obtained.

Narrative reviews

Narrative reviews may be accepted by the São Paulo Medical Journal/Evidence for Health Care and should be structured with: Introduction, Objectives, Methods, Results, Discussion and Conclusions. The abstract must be structured with: Context and objective, Design and setting, Methods, Results and Conclusions, like in original articles. The manuscript must comply with the norms of the Vancouver style[1] and must include a systematic search in the main databases: Medline, Embase, Lilacs and Cochrane Library. The search strategy for each database and the number of articles obtained from each database should be presented in a table. 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 use for Medline, LILACS and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, search strategy must be performed, at the same time, with English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms. 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).

Letters to the editor

Letters to the editor may address articles published in the São Paulo Medical Journal/Evidence for Health Care publication or may deal with health issues of interest. Case reports must not be submitted as letters. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

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