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Improving the transparency and integrity of scientific reports on health. New instructions for authors!

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Healthcare practice should be based on the best available evidence, coming from rigorous research methodologies.[1] Improvement of practice, going from doing no harm to incorporation of new technologies in public assistance, therefore requires access to robust scientific evidence, through the availability of good and complete research reports. However, what we see today is that access to high-quality evidence is somewhat hampered by poor reporting.

More than 80% of clinical trials and observational studies published today fail to report one or more important feature of their methodology or results.[2] Inconsistent, biased, incomplete and inaccurate reports are published in the medical literature every day.[3,4] However, we have resources to fight this battle: just as we have clinical guidelines for practice, we also have reporting guidelines to help authors to write and publish better research reports. These are the articles that systematic reviewers use to synthetize the evidence and inform practice.

Reporting guidelines have existed for more than 20 years now. However, adherence to them by authors, peer reviewers and journals has been modest and slow.[2,5-7] The São Paulo Medical Journal has taken a step forward in the direction of improving transparency, quality and integrity of scientific reporting within the field of health research, in this issue. We are now publishing new Instructions for Authors in which we emphasize the need to adhere to reporting guidelines, and we will require all authors to submit complete reports.

In this new version of the São Paulo Medical Journal Instructions for Authors, we have taken into consideration the main reporting guidelines and principles of good reporting that are available. There is at least one reporting guideline for each main study design type, and they are all available through the EQUATOR Network website (http://www.equator-network.org).

The EQUATOR (Enhancing the Quality and Transparency of Health Research) Network is an international initiative that has been promoting the use of reporting guidelines since 2008. The UK EQUATOR Centre curates and maintains a very large and searchable database of reporting guidelines, provides toolkits for writing and organizes many training initiatives. It thus makes available a large amount of material to support author within the mission of better reporting.[5,8] These instructions are very useful for everyone really interested in developing skills in clinical research.

Good reporting encompasses research reports that are clear and transparent, and that empower reproducibility. Clarity means being unambiguous and not allowing more than one interpretation. This is an essential feature within health research reporting, in which any misinterpretation can potentially prove fatal. Transparency means reporting everything, even bad news or methods that failed, which is broadly supported through efforts to encourage registration of clinical trials and systematic reviews prior to study commencement. Reproducibility requires details: again, reporting everything that was done and found, so that other researchers can repeat experiments. These are all essential features of scientific reporting.[9]

In our new Instructions for Authors, we have also considered the latest revision of the Recommendations by the International Committee of Medical Journal Editors (ICMJE), released in December 2018.[10] In this latest revision, sensitive issues like authorship, plagiarism (and self-plagiarism), conflicts of interest and other matters are now addressed more explicitly by the Committee.[11] Many of these issues are problems that our staff have been dealing with for a long time. Our new Instructions for Authors clearly set out what authors need to know about our submission

requirements, what they should expect from the Journal and also what the Journal expects from them. As the late Douglas Altman said, "Readers should not have to infer what was probably done, they should be told explicitly".[12]

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The pace of reduction of cardiovascular mortality in Brazil (1990 to 2017) is slowing down

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The risk of death due to cardiovascular diseases, coronary heart disease (CHD) and stroke in Brazil has been declining since the 1980s.[1] Two analyses relating to CHD and stroke mortality trends have revealed that the downward trend has continued to decline over the most recent years.[2-3] In contrast, in the United States, there are indications of stagnation of cardiovascular death rates.[4]

Since the 2000s, the coverage of the Brazilian national mortality surveillance system has increased, and the quality of death certification has improved. This has yielded a higher proportion of accurate diagnoses. Thus, for example, there are now fewer cases of mortality due to "heart failure" (a garbage code) and more of CHD; and fewer cases of mortality due to "hypertension" (also a garbage code) and more of stroke.[5]

I hypothesized that this improvement in quality ought to alter the real trend of mortality due to CHD and stroke. To verify this possibility, I used information from the Global Burden of Disease study, which corrects these two phenomena (i.e. increased coverage plus improved quality) through new data.[6] To analyze differences in trends from 1990 to 2017, the annual percentage change (APC) was calculated by applying the Joinpoint regression software.[7]

Figure 1 shows that the reductions in age-adjusted mortality rates for men (A) and women (B) have been declining over the course of this period, which comprises almost three decades. However, visually, it is not possible to conclude whether the rates have flattened or have continued to fall over the last five years (2013-17). **Table 1** shows the APCs according to sex and type of disease. For all cardiovascular diseases, the decline has been maintained for men, but not for women. Indeed, the flattening of the cardiovascular disease rate trend is due to the trend observed for stroke mortality, but not for CHD. The reductions in deaths due to CHD have occurred among both men and women. However, the year-on-year decrease in CHD has become progressively smaller over the last few years, compared with the situation when these observations began.

This "almost stagnated" pattern of mortality rates for stroke and all cardiovascular diseases, but not for coronary heart disease, should serve to alert epidemiologists to the need to continue studying the determinants of cardiovascular diseases.

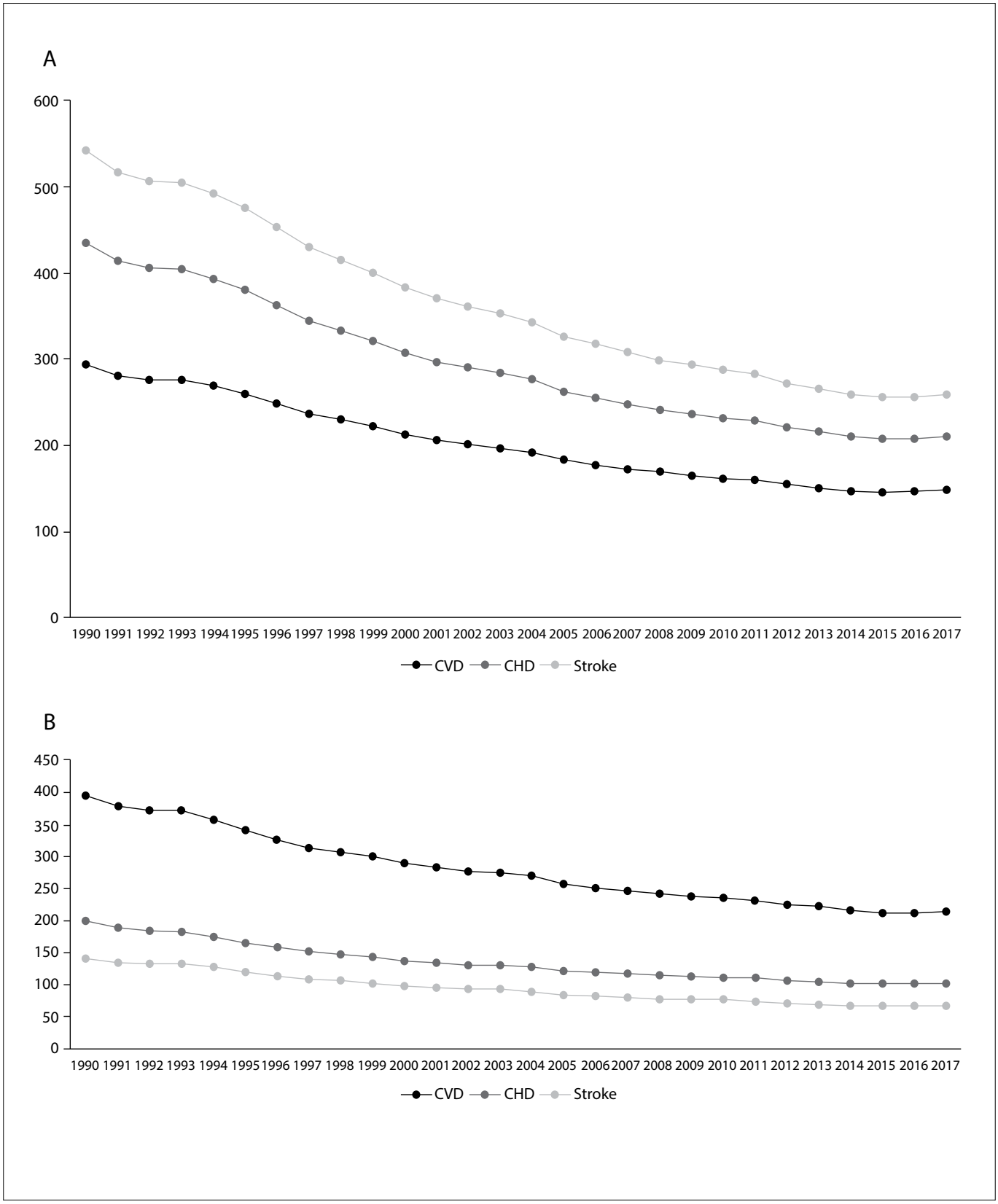

Figure 1. Age-adjusted death rates due to cardiovascular diseases (CVD), coronary heart disease (CHD) and stroke among men (A) and women (B) in Brazil from 1990 to 2017.[5]

Table 1. Annual percentage change (APC) (and 95% confidence interval) of the age-adjusted death rates among men and women in Brazil from 1990 to 2017

	Period		APC (95% confidence interval)
Men			
Cardiovascular diseases	1990	1994	-1.8 (-2.6 to 0.9)
	1994	1998	-4.0 (-5.4 to -2.7)
	1998	2007	-3.1 (-3.3 to -2.8)
	2007	2015	-2.2 (-2.6 to -1.8)
	2015	2017	0.9 (-1.8 to 3.8)
Coronary heart disease	1990	1994	-2.6 (-3.8 to -1.4)
	1994	2000	-4.4 (-5.3 to -3.6)
	2000	2009	-3.2 (-3.7 to -2.8)
	2009	2017	-1.9 (-2.3 to -1.5)
Stroke	1990	1994	-1.8 (-2.8 to 0.8)
	1994	1998	-4.7 (-6.2 to -3.2)
	1998	2008	-3.3 (-3.6 to -3.1)
	2008	2015	-2.8 (-3.3 to -2.2)
	2015	2017	1.2 (-2.0 to 4.4)
Women			
Cardiovascular diseases	1990	1994	-2.1 (-3.0 to -1.3)
	1994	1997	-4.5 (-7.1 to -1.8)
	1997	2007	-2.3 (-2.6 to -2.1)
	2007	2015	-1.9 (-2.2 to -1.5)
	2015	2017	0.4 (-2.4 to 3.2)
Coronary heart disease	1990	1994	-3.1 (-4.1 to -2.0)
	1994	1997	-5.1 (-8.2 to 1.8)
	1997	2007	-2.5 (-2.8 to -2.2)
	2007	2017	-1.6 (-1.8 to -1.3)
Stroke	1990	1994	-2.1 (-3.2 to -1.1)
	1994	1997	-5.4 (-8.4 to 2.2)
	1997	2015	-2.7 (-2.8 to -2.6)
	2015	2017	0.9 (-2.4 to 4.3)

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Translation to Brazilian Portuguese, cultural adaptation and psychometric properties of 8-item Arthritis Self-Efficacy Scale (ASES-8)

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KEY WORDS:
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Arthritis, rheumatoid.
Surveys and questionnaires.

ABSTRACT

BACKGROUND: Self-efficacy refers to one's belief in one's ability to organize, perform actions and face challenges in order to achieve goals and motivation. High self-efficacy improves disease coping and adherence to treatment among patients with rheumatoid arthritis. The objective of this study was to translate, culturally adapt and test the reproducibility of the 8-item Arthritis Self-Efficacy Scale (ASES-8) questionnaire for use in Brazil.

DESIGN AND SETTING: Validation study conducted in university outpatient clinics.

METHODS: The questionnaire was translated into Brazilian Portuguese and then back-translated into English. The final version in Portuguese was tested on 30 patients with rheumatoid arthritis and was shown to be understandable and culturally adapted. A further 32 patients with rheumatoid arthritis were evaluated three times using the questionnaire. On the first occasion, two evaluators applied the questionnaire to check inter-evaluator reproducibility. After 15 days, one of the evaluators reassessed the patients to verify intra-evaluator reproducibility. At the first assessment, to test the construct validity of ASES-8, the Numerical Pain Scale, Health Assessment Questionnaire, Beck Depression Inventory and Short Form-36 questionnaire were also applied to all the patients.

RESULTS: The inter and intra-evaluator correlation coefficients for ASES-8 were high. Cronbach's alpha was higher than 0.90 for the questionnaire, indicating excellent internal consistency. There were moderate correlations between ASES-8 and most of the instruments tested, indicating good construct validity.

CONCLUSION: ASES-8 was translated and adapted to the Portuguese language for Brazil. This instrument is valid, reproducible and reliable for evaluating self-efficacy among patients with rheumatoid arthritis.

INTRODUCTION

Self-efficacy refers to a person's beliefs in their ability to organize, perform actions and face challenges in order to achieve aims and motivation.[1,2] It is not a matter of possessing certain capacities but is a belief that one has them or that one can acquire them through personal efforts (outcome expectancy). The strength of individuals' self-efficacy has an effect on how much effort and perseverance they will apply to achieve an aim.[3]

Rheumatoid arthritis is a chronic autoimmune inflammatory disease characterized by pain and destruction of synovial joints that may lead to disability.[4] Epidemiological studies have estimated that the prevalence of rheumatoid arthritis in the adult population is 1%. It affects women three times as much as men and its incidence is highest among people aged between 35 and 65 years.[5]

Several studies have found that among patients with rheumatoid arthritis, greater self-efficacy is a predictor for healthy behaviors, such as physical activity, healthy eating and strategies for dealing with pain.[6-9] Greater self-efficacy has also been correlated with lower daily pain, better emotional states, less stiffness, better functional capacity, better physical and mental wellbeing, less depression and better adherence to medication and other health recommendations.[10] It has also been associated with better health outcomes, including physical activity recommendations for rheumatoid arthritis patients.[6,7,11] In a recent review of the literature, negative correlations were found between self-efficacy and disability, pain, fatigue and duration of disease.[12] Studies have also suggested that self-efficacy is associated with the health outcomes of people with rheumatoid arthritis. In these studies, it was observed that the higher the self-efficacy was (which can be changed through educational programs), the higher the association that the patients had with better health status.[13-15]

The 8-item Arthritis Self-Efficacy Scale (ASES-8) was created as part of a development process on a set of health assessment tools for the Spanish language. ASES-8 is derived from the full version of the Arthritis Self-Efficacy Scale (ASES), which has a total of 20 items divided into three subsets. ASES-8 features two items from the ASES pain subscale, four items from the ASES other symptoms subscale and two new items relating to prevention of pain and fatigue that interfere with daily activities. Thus, it contains a total of eight items without a subscale. The responses to each of the items range from 1 (very uncertain) to 10 (very certain), such that higher scores indicate higher confidence or self-efficacy. The final score is the mean of the scores from the eight items.[10]

The original scale, in Spanish, was published in 1995.[16] The English version of ASES-8 refers to both rheumatoid arthritis and fibromyalgia in each item.[17] The German version was translated from the English version and was tested on both rheumatoid arthritis and fibromyalgia patients; in this German version, the term rheumatoid arthritis was replaced by fibromyalgia.[18] ASES-8 has been shown to have good reliability, validity and adaptability, even when translated into several languages, such as English, German and Chinese.[10,17,19]

OBJECTIVE

To translate, culturally adapt and test the reproducibility and construct validity of the ASES-8 questionnaire for use in Brazil, among patients with rheumatoid arthritis.

METHODS

This validation study was conducted in two stages among a total of 62 patients. Firstly, the translated version of the questionnaire (used for translation and cultural adaptation) was administered to 30 patients to test their understanding of the tool. In the second stage, 32 patients were included to test the reproducibility and construct validity.

The sample size was determined as at least 30 patients for each phase, in accordance with the guidelines of Beaton et al.[20] and Guillemin et al.,[21,22] which have been used in other published studies to test the cultural validation and reproducibility of other questionnaires.

Ethical considerations

This validation study was approved by our institution's Ethics Committee (no. 907.062; date: December 9, 2014), and all participants gave their written approval before the evaluations were done.

Translation and cultural adaptation

Two English speakers who were Brazilian natives translated ASES-8 from English to Brazilian Portuguese as indicated by Beaton et al.[20] and Guillemin et al.[21,22] These two translators were English teachers. A committee composed of a rheumatologist and two physiotherapists reviewed the translation in order to reach an agreement on the Brazilian Portuguese version. This approved version was then translated back into English by two other English teachers who were natives of English-speaking countries and had no knowledge of the original questionnaire. This back-translated version was then compared with the original questionnaire to ensure that it was semantically equivalent.

This Brazilian Portuguese version of ASES-8 (which was considered to be the test version) was then applied to 30 patients aged between 18 and 60 years who were selected from the outpatient clinic. All of these patients had presented rheumatoid arthritis (classified in accordance with the criteria of the American College of Rheumatology) for at least one year[23] and had been undergoing treatment while in a stable condition for at least three months.

Patients with associated rheumatic, neurological or musculoskeletal diseases, patients who were unable to understand the Portuguese language and patients whose medication dose or treatment had been changed were excluded from this study. To assess cultural equivalence, the understanding level of the patients was measured through a yes/no answer to the question, "Do you understand what is being asked?" All items that were not understood by at least 20% of the respondents would be reviewed by the specialist committee and the revised version of the questionnaire would be retested on 30 patients.

Reproducibility

After the Brazilian Portuguese version of ASES-8 had been tested and its semantic and cultural equivalence had been verified, a new group composed of 32 patients was selected with the same inclusion and exclusion criteria. These patients were evaluated three times, on two occasions. On the first occasion, two evaluators applied the questionnaire in separate interviews on the same day to verify inter-observer reproducibility. On the second occasion, between 7 and 15 days later, one of the evaluators reapplied ASES-8 in a single interview with the intention of verifying intra-observer reproducibility. The internal consistency was also evaluated.

Construct validity

The construct validity was tested during the first interviews through simultaneous application of the following questionnaires: Numerical Pain Scale (NPS),[24] Health Assessment Questionnaire (HAQ),[25] Beck Depression Inventory (BDI)[26] and Short-Form Health Survey (SF-36).[27] The NPS evaluates pain through a numerical scale, on which patients quantify their degree of pain on a line from 0 to 10 centimeters, such that 0 represents absence of pain and 10 represents an unbearable pain.[24]

The HAQ evaluates the functional capacity of patients with rheumatoid arthritis using a total of 20 questions, from which the score is obtained by adding together the highest grades of each subscale. The scores range from 0 to 3, and the higher the resultant value is, the lower the functional capacity of the patient is.[25] The BDI evaluates the depressive state of the patient through 21 questions regarding how the individual felt in the last week. Each question has at least four possible answers (0 to 3). The result is obtained by summing the values of each question and is categorized thus: 0 to 13, no depression; 14 to 19, mild depression; 20 to 28, moderate depression; and 29 to 63, severe depression.[26] The Short Form-36 (SF-36) evaluates the patient's quality of life. It is divided into eight domains with 36 questions in total. The scores range from 0 (worst) to 100 (best), and the higher the score is, the better the patient's quality of life is.[27] All of these instruments had previously been validated for use in Brazilian Portuguese. These instruments were chosen because the ASES-8 items correlate with the patient's emotional state, pain and functional ability. To assess the versions of ASES-8 that were previously validated for use in German and Chinese, similar methods were used.[18,19]

Statistical analysis

Descriptive analyses were used to demonstrate the data averages and standard deviations. Interclass correlation coefficients (ICCs) and Bland-Altman analyses were used to assess the inter and intra-observer reproducibility. Internal consistency was assessed using the Cronbach's alpha test. Spearman's correlation test was used to investigate the construct validity. Analyses were performed with assistance from the Statistical Package for the Social Sciences (SPSS) software, version 17.0 (Chicago, IL, USA).

RESULTS

A total of 94 patients were invited to take part to the study, but 32 of them were not included because of the presence of exclusion criteria, thus leaving a total of 62 patients. Thirty patients were included in the cultural adaptation phase and 32 in the reproducibility and construct validity phase. There was no patient loss during the application of the study.

In the cultural adaptation phase, every question of the questionnaire was understood by more than 80% of the participants, and no item required review by the committee experts (**Appendix 1**). **Table 1** shows the demographic and clinical data of the patients who participated in the reproducibility and construct validity phase.

Table 2 indicates that there were strong correlations between the results obtained in the intra and inter-observer assessments, with an ICC of 0.954 in the intra-observer assessment and an ICC of 0.972 in the inter-observer assessment (95% confidence interval). None of the patients changed their medication in the interval between the testing and retesting of the questionnaire. **Table 2** also shows that the Cronbach's alpha was higher than 0.90, thus indicating that the questionnaire had good internal consistency.

Figure 1 illustrates the strong intra and inter-observer correlations of the questionnaire through Bland-Altman plots, which show that the average difference was always close to zero. **Table 3** indicates the correlation between ASES-8 and the other instruments, i.e. the HAQ, BDI, SF-36 and NPS. Moderate correlations were found between ASES-8 and the other instruments except for NPS, which did not show any statistically significant correlation with ASES-8.

DISCUSSION

Self-efficacy, which can be altered through educational programs, is related to a specific behavioral characteristic and is strongly associated with health improvement and reduction in healthcare costs, thereby playing a key role in patients' adaptation to chronic disease.[10,29] Self-efficacy can potentially explain the discrepancy

Table 1. Clinical and demographic characteristics of the patients in the reproducibility and construct validity phase

Variables	Total (n = 32)
Gender (n, %)	
Female	26 (81.3%)
Male	6 (18.7%)
Age (years)	53.8 (± 8.2)
Education (years)	7.2 (± 4.3)
Length of time with illness (years)	13.1 (± 6.9)
Employment situation (%)	
Employed	13 (40.3%)
Unemployed	7 (21.9%)
Retired	12 (37.5%)
Steinbrocker functional classification[28] (%)	
1	10 (31.3%)
2	21 (65.6%)
3	1 (3.1%)
4	0 (0%)

Data are presented as average ± standard deviation or as percentage (%); n = number of patients.

Table 2. Inter and intra-evaluator reproducibility and internal consistency of the 8-item Arthritis Self-Efficacy Scale (ASES-8)

	A1 Mean ± SD	A2 Mean ± SD	R1 Mean ± SD	ICC A1 vs. A2	ICC A1 vs. R1	Cronbach's alpha
ASES-8	5.93±2.19	5.73±2.23	5.94±2.04	0.954	0.972	0.985

A1 = evaluator 1; A2 = evaluator 2; R1 = re-evaluation of evaluator 1; ICC = interclass correlation coefficient; A1 versus A2 = inter-rater evaluation; A1 versus R1 = intra-rater evaluation; SD = standard deviation; vs. = versus.

between possessing a skill and the ability to perform a task using that skill. Belief in self-efficacy predicts motivation levels, opinion standards, moods, emotional reactions and attitudes. Therefore, it is important to measure self-efficacy among patients with chronic disease.[30]

An increasing number of questionnaires are used to evaluate self-efficacy among patients with chronic conditions, and these questionnaires include ASES-8. A recent review of the literature indicated that ASES-8 provides high reproducibility, validity and responsiveness, thus making it highly recommended for evaluation of self-efficacy among patients with rheumatoid arthritis.[10]

There are two possible ways to make a questionnaire viable in a specific language: create a questionnaire for a particular ethnic group or translate and validate a questionnaire previously developed for use in another language. This second option, besides being less expensive in terms of time and resources, enables comparison of data collected in different countries.

ASES-8 includes a total of 8 items without any subscale, and higher scores equate to higher confidence or self-efficacy.[16] The advantage of the ASES-8 questionnaire is that it specifically evaluates self-efficacy among rheumatoid arthritis patients, through focusing on the essential issues and characteristics of these patients, unlike the broader focus of general self-efficacy questionnaires, such as the General Self-Efficacy Scale (GSES).[31]

We followed the validation process described by Beaton et al.[20] and Guillemin et al.[21,22] and obtained results with high internal consistency (Cronbach's alpha of 0.985). Because rheumatoid arthritis is a chronic disease, we chose a two-week test-retest interval because we believed that over this period, there would be no significant changes in the disease state, and sufficient time would have elapsed for the patient to have forgotten the content of the first interview. None of the patients changed their medication during the test-retest interval. The intra and inter-observer ICC values were high (0.972 and 0.954, respectively).

To assess the construct validity, we compared the Portuguese version of ASES-8 with the NPS, HAQ, BDI and SF-36. Moderate correlations were found between ASES-8 and the HAQ and BDI tests and between ASES-8 and the majority of the SF-36 domains. However, comparison between ASES-8 and the NPS did not show any significant correlation. One reason for this might be that NPS assesses pain in an overall manner and at the current time, rather than in a way that specifically addresses the daily routine activities of rheumatoid arthritis patients, as is done in the three questions involving pain in the ASES-8 questionnaire. According to Barlow et al. and Mueller et al., these findings also can be explained by the fact that some people with rheumatoid arthritis feel that they have highly effective coping mechanisms, in relation to pain, regardless of the intensity of the pain. Conversely, some individuals with

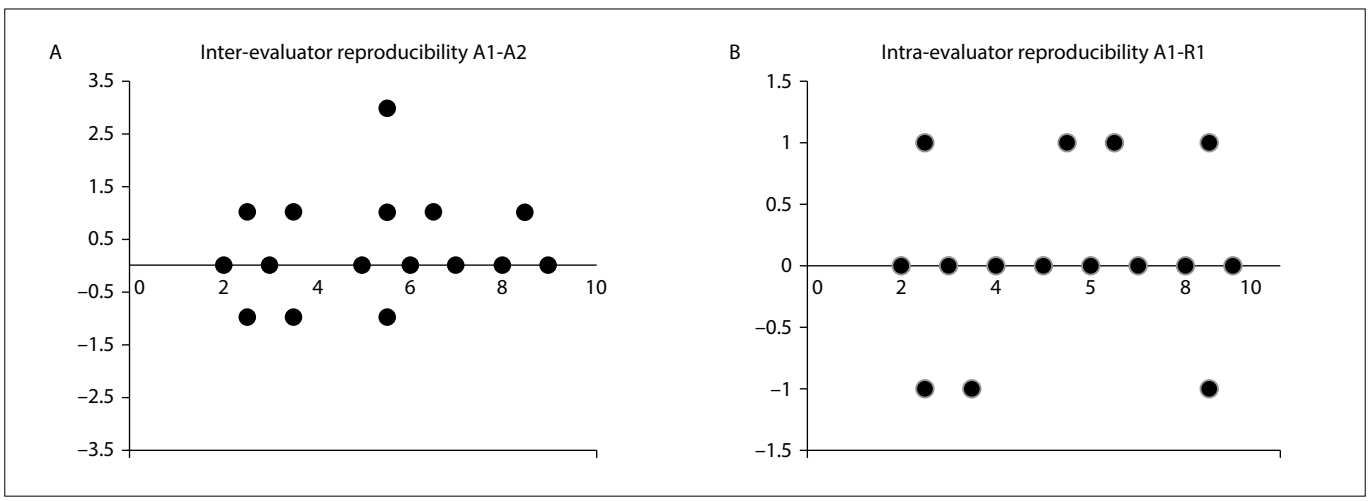

Figure 1. Bland-Altman reproducibility graphs: (A) inter-evaluator reproducibility; (B) intra-evaluator reproducibility.

Table 3. Spearman correlations between ASES-8 and NPS, HAQ, BDI and SF-36, to assess construct validity

ASES-8	NPS	HAQ	BDI	SF36 PF	SF36 PRF	SF36 BP	SF36 GHP	SF36 VIT	SF36 SRF	SF36 ERF	SF36 MH
r	- 0.278	- 0.437	- 0.562	0.545	0.321	0.427	0.473	0.445	0.435	0.376	0.558
P	0.12	0.01	0.001	0.001	0.04	0.01	0.006	0.01	0.01	0.03	0.001

Data are presented as r = correlation coefficient and P = significance; ASES-8 = 8-item Arthritis Self-Efficacy scale; HAQ = Health Assessment Questionnaire; BDI = Beck Depression Inventory; NPS = numerical pain scale; SF-36 = Short Form-36; PF = physical functioning; PRF = physical role functioning; BP = bodily pain; GHP = general health perception, VIT = vitality; SRF = social role functioning; ERF = emotional role functioning; MH = mental health.

relatively low levels of pain may feel that they have little control over this symptom. Another explanation is the fact that patients with rheumatoid arthritis can increase their pain control through medication, thereby reversing the influence of pain on self-efficacy.[17,18] Another factor that may explain the lack of correlation is that the behavior of the pain correlates not only with the intensity of the pain but also, in a major way, with the patient's emotional state.

One limitation of our study was the low number of male patients, which can be explained by the higher prevalence of rheumatoid arthritis among women. However, this limitation will not prevent use of ASES-8 among men, given that it was developed to be applied to both genders. Another limitation was that we did not analyze criterion validity during the study.

CONCLUSION

The 8-item Arthritis Self-Efficacy Scale (ASES-8) questionnaire was translated and adapted for use in Brazilian Portuguese. This questionnaire is a valid, reproducible and reliable instrument for evaluating self-efficacy among patients with rheumatoid arthritis.

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Appendix 1

ASES-8

1. Quanta certeza você tem que é capaz de diminuir um pouco a sua dor?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

2. Quanta certeza você tem que é capaz de evitar que a dor da artrite interfira em seu sono?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

3. Quanta certeza você tem que é capaz de não deixar que a dor da artrite ou fibromialgia interfira nas coisas que você tem vontade de fazer?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

4. Quanta certeza você tem que é capaz de controlar suas atividades para continuar ativo e não agravar sua artrite?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

5. Quanta certeza você tem que é capaz de impedir que o cansaço causado pela artrite ou fibromialgia interfira nas coisas que você tem vontade de fazer?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

6. Quanta certeza você tem que é capaz de fazer alguma coisa que o faça sentir-se melhor quando estiver se sentindo deprimido?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

7. Quando comparado a outras pessoas com o mesmo quadro de artrite que o seu, quanta certeza você tem que é capaz de administrar a dor da artrite durante suas tarefas diárias?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

8. Quanta certeza você tem que é capaz de lidar com a frustração da artrite?

Nenhuma certeza 1 2 3 4 5 6 7 8 9 10 Muita certeza

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Secondhand smoking, knowledge/attitudes and socioeconomic status among married Bangladeshi women: a cross-sectional study

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KEY WORDS:
Tobacco smoke pollution.
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Attitude.
Bangladesh.

ABSTRACT

BACKGROUND: There is a paucity of research on knowledge/attitudes regarding the dangers of exposure to secondhand smoking (SHS) among women. The relationship between exposure to SHS, socioeconomic status (SES) and knowledge/attitudes regarding the risks of SHS has often been ignored. We therefore aimed to examine (1) whether SES and exposure to SHS were independently associated with knowledge/attitudes regarding the risks of SHS; and (2) whether women with low SES and exposure to SHS were uniquely disadvantaged in terms of deficient knowledge and more dismissive attitudes towards the risks of SHS.

DESIGN AND SETTING: Cross-sectional study in the Rajshahi district, Bangladesh.

METHODS: A total of 541 women were interviewed. Knowledge of and attitudes towards the risks of SHS were the outcomes of interest.

RESULTS: A majority of the respondents were exposed to SHS at home (49.0%). Only 20.1% had higher levels of knowledge, and only 37.3% had non-dismissive attitudes towards the risks of SHS. Participants in the low SES group and those exposed to SHS had lower odds of higher knowledge and their attitudes towards the risks of SHS were more dismissive. Regarding deficient levels of knowledge and scores indicating more dismissive attitudes, women in the low SES group and who were exposed to SHS were not uniquely disadvantaged.

CONCLUSIONS: Exposure to SHS and low SES were independently associated with deficient knowledge and scores indicating more dismissive attitudes. Regarding knowledge/attitudes, the negative effect of exposure to SHS extended across all socioeconomic backgrounds and was not limited to women in either the low or the high SES group.

INTRODUCTION

Health promotion programs worldwide have long been premised on the idea that providing knowledge about the causes of ill health and the choices available will result in changes to attitudes and practices, to minimize the disease burden.[1] Several studies around the world have documented that exposure to daily passive smoking at home (usually from a partner) is an important risk factor for adverse health outcomes among mothers and their children.[2-5] Therefore, to prevent the burden of diseases relating to secondhand smoking (SHS) and to reduce tobacco consumption, it is important to improve women's knowledge and awareness regarding the risks of SHS.

A number of studies have assessed knowledge/attitudes regarding the risks of SHS in different population subgroups such as college and university students,[6,7] healthcare professionals[7,8] and ethnic minorities.[9] However, only very few studies have targeted women,[10,12] the group that bears the maximum brunt of SHS at home.

Previous studies that focused on women were conducted on restricted subgroups such as pregnant or working women with a higher educational profile. Since these studies ignored non-pregnant and uneducated or lower-educated women, they may have overestimated the magnitude of knowledge of the risks of SHS and attitudes towards these risks and may not reflect the real general situation among women. In addition, no studies have been conducted in Bangladesh to investigate knowledge and attitudes regarding the risks of SHS among women at home, despite the fact that nearly 40% of children[13] and 53.5% of women[14] are exposed to SHS at home in this country.

Up to now, women's knowledge and attitudes regarding the risks of SHS and their relationship to exposure to SHS at home have not been thoroughly investigated. There are several possible ways in which women's knowledge and attitudes regarding the dangers of SHS can influence exposure to SHS at home. It is believed that if women have relevant knowledge regarding the risks of SHS, they will be able to defend themselves against smoking perpetrated by men in these women's homes by imposing various degrees of restrictions on home smoking such as insisting that these men should do this privately or when out of the house. If women have proper knowledge and non-dismissive attitudes about the adverse health effects of exposure to SHS, they can also combat smoking perpetrated by men such as their husbands in their homes by convincing them that as good fathers, they have the responsibility to protect the family from the hazardous effects on health caused by exposure to SHS and therefore should not smoke at home.

Furthermore, knowledge and attitudes regarding the risks of SHS need to be examined in relation to different socioeconomic strata in low-resource settings like Bangladesh, where rapid industrialization and urbanization over recent decades have increased socioeconomic inequality.[15] In Bangladesh, it has been shown that there is a significant gradient in smoking prevalence across different socioeconomic groups,[14] such that the lowest socioeconomic group has the highest prevalence rates of smoking.[14]

Although epidemiological studies have found significant relationships between socioeconomic status (SES) and smoking behavior, studies on differences in knowledge/attitudes regarding the risks of SHS according to SES are scarce. Moreover, the relationship between SES and knowledge and attitudes regarding the risks of SHS remains unknown among Bangladeshi women in general. Women of low SES may be at a distinct disadvantage because of higher levels of smoking among their partners.[15] These women's lack of resources can restrict their development, educational opportunities, access to healthcare and decision-making autonomy,[16] thus creating a favorable setting for lack of knowledge and dismissive attitudes regarding this subject.

OBJECTIVE

We aimed to go further into this important field of inquiry by addressing (1) whether SES and exposure to SHS were independently associated with knowledge and attitudes regarding the risks of SHS; and (2) whether women in the group with low SES and exposure to SHS were uniquely disadvantaged in terms of deficient knowledge and more dismissive attitudes towards the risks of SHS.

METHODS

Design and population

This study had a cross-sectional design and was conducted in the Rajshahi district of Bangladesh, covering both rural and urban areas. Households were surveyed and female parents with one child younger than five years were selected in each of the households thus identified. We picked out the households that had at least one adult smoker and a non-smoking mother. Administratively, the urban area in the Rajshahi district is split into wards and the rural region is split into union parishads (UPs). In Bangladesh, wards are elective units of cities or towns and UPs are the smallest rural administrative and local government units.

The sample size was calculated using the following formula: $n = z^2xpxq/m^2$; where "n" is the number of subjects required; z is the 95% confidence level (standard value of 1.96); P = 53.5% (assuming exposure to SHS among women at home in Bangladesh);[14] q = 1 – P = 46.5%; and m = precision rate (value of 0.06). Thus, $n = (1.96^2 \times 0.535 \times 0.465) / 0.06^2 = 265$. Considering a design effect of 2, the minimum sample size became 530. We further increased our sample size to 541 to increase the power of the study. The sample was then further allocated to equal ratios in the rural area (n = 272) and urban area (n = 269)

A two-stage sampling approach was taken for selecting the households in the urban and rural areas of the Rajshahi district. In the first stage, out of 30 wards in the urban area of the Rajshahi district, two wards were randomly selected; and out of 70 UPs in the rural area, two were randomly selected. Since our target populations were not well identified or accessible, we therefore used the snowball sampling technique in the second phase. In this, we focused on one or two key individuals, who, we believed, knew about the field of study that we were investigating.

Questionnaire

The survey questionnaire was developed from the World Health Organization's Global Youth Tobacco Survey (GYTS),[17] in combination with questions retrieved from a demographic and health survey (DHS) that was conducted in Bangladesh.[18] Additional questions on knowledge and attitudes regarding SHS were developed by the project staff through reviewing relevant measures and related papers,[11-12,16,19] and these were tested extensively in the field. The questionnaires were outlined in English and then translated into Bangla, the national language of Bangladesh. The translation was judged by experts and volunteers. The content validity of the initial questionnaire was evaluated via a pilot test. The questionnaire was firstly pre-tested on 10% of the entire sample (n = 54) that were not selected for the survey. After correction of ambiguities that were identified in the questionnaires, the survey was administered in May and July 2017 (data not shown).

We also examined the reliability, internal consistency and reproducibility of the questionnaire. With regard to internal consistency, the homogeneity of the questions on knowledge and attitudes was evaluated using Cronbach's α coefficient. The Cronbach's α results were 0.77 and 0.72 for the knowledge and attitude instruments.

Regarding reproducibility, the two sets of answers from the patients in the test-retest group were examined using the intraclass correlation coefficient. A coefficient of 0.70 or higher was considered to be evidence of satisfactory test-retest reliability.[20]

Interviews and sources of potential bias

Trained and experienced field researchers conducted all household visits. There were seven interviewer teams, and each team comprised two interviewers. All of them received three days of training and two days of virtual sessions on the substance of the questionnaire, techniques to elicit more information and strategies for obtaining complete and dependable information. For clarification of the purpose of the research, an operational manual for interviewers and supervisors was provided two days before the training started, to ensure that they understood their duties and responsibilities.

Data quality standards were maintained through various actions. Since the sample only comprised women, we therefore only enrolled female interviewers. There were two quality control teams, and each team comprised one male and one female staff person. They were sent into the field to visit the interviewing teams throughout the data collection period. They observed one household and one individual interview conducted by each interviewer team and spot-checked the completed questionnaires. The teams also revisited half of the households seen by each study team and checked whether the households selected had been visited, and whether the eligible respondents had been properly named and questioned. Debriefing sessions were held between the fieldworkers' tours of duty to discuss any problems encountered in the field, provide clarifications and deal with administrative matters.

Measurements

First, we registered several sociodemographic and health-related variables: respondent's age, woman's education, husband's education, number of people in household, place of residence, woman's decision-making autonomy, religion, marital status and respondent's occupation.

The degree of knowledge and dismissiveness of attitudes towards the risks of SHS were the outcomes of interest in this study. The questionnaire on knowledge that was used in this study, which was modified from the GYTS mentioned above, consisted of five questions regarding: (1) awareness of the adverse effects on the health of children and adults caused by SHS; (2) awareness that children are more vulnerable to SHS than are adults; (3) awareness that SHS causes reproductive health problems among women; (4) awareness that smoking is prohibited in public places in Bangladesh; and (5) awareness that no legislation making homes smoke-free zones exists in Bangladesh. The questions on the women's knowledge were chosen based on inspection of relevant standards and related papers.[11-12,16,19] If the respondents gave positive responses to questions 1 to 4, scores of 1 point were given; otherwise, the score was "0". For question number 5, if the respondents gave a negative response, a score of 1 point was given. This yielded a total possible score of 5 points.

We used six statements to determine whether the women had dismissive attitudes towards the risks of SHS: (1) smoking should be totally banned in all public places; (2) smoking should not be allowed at home; (3) I have the right to require other people not to smoke in my presence; (4) presence of SHS encourages young people to begin to smoke; (5) I believe that allowing SHS at home discourages smokers from quitting; and (6) It is difficult to adopt a no-smoking policy at home. If the respondents agreed with statements 1 to 5, they scored 1 point for each of these. If the respondents disagreed with statement 6, they scored 1 point. Otherwise, the score was "0".

To obtain information for measuring the women's decision-making autonomy, the following questions were asked: 1) who decides how the household's income will be used? 2) who has the final say in making large household purchases? 3) who has the final say about making household purchases for daily needs? 4) who has the final say regarding the woman's own healthcare? 5) who has the final say regarding child healthcare? And 6) who has the final say on visits to family or relatives? For each of these questions, the responses were coded as: 1) respondent; 2) respondent and husband/partner jointly; 3) respondent and someone else; 4) husband/partner; or 5) someone else in the house. To assess the respondent's autonomy from these responses, binary variables were created for each of the questions. Responses 1, 2, and 3 were merged into a single category of having decision-making power; and responses 4 and 5 were merged into a single category indicating no decision-making power. From this, the decision-making power was ranked in terciles as low, medium or high.

Outcomes and statistical analysis

Exposure to SHS and socioeconomic status were the exposures of interest in this study. The women's self-reports were used to assess their exposure to SHS. They were asked, "Is smoking prohibited at home?" Those who responded "no" were considered to be exposed to SHS at home. We focused on standard of living (hereinafter referred to as wealth) as a measurement of SES. A wealth index was constructed from data on household assets, including ownership of durable goods (such as radio, television, mobile phone, landline phone, freezer, almirah/wardrobe, table, chair, watch, electric fan and DVD/VCR player), ownership of means of transportation (such as bicycle, motorcycle/scooter/tempo, car/truck, rickshaw/van or cart), ownership of agricultural land (such as homestead or other agricultural land) and access to electricity.

As a rule of thumb in constructing this wealth index, variables with prevalences below 3-5% (such as sources of drinking water, sources of toilet facilities, access to electricity, car/truck, landline phone and cart)[21] were excluded from the analysis. Each asset was assigned a weight (factor score) that was generated through principle component analysis, and the resulting asset scores were standardized in relation to a standard normal distribution with a mean of zero and a standard deviation of one. Each household was then assigned a score for each asset, and the scores were summed per household. The sample was then divided into terciles; each tercile was designated a rank, from one (poor) to three (rich), and individuals were ranked according to the total score of the household in which they lived.

We provided descriptive statistics for sociodemographic data, exposure to SHS and knowledge and attitude-related characteristics in our sample. Differences in knowledge and attitude between the exposed and non-exposed groups were assessed by means of cross-tabulation. Because the outcomes measured were ordinal, adjusted ordered logistic regressions were used. Parallel line tests confirmed that the proportional odds assumption was not violated. We included the following independent variables as potential confounders for the events in the logistic model: covariates of respondent's age, woman's education, husband's education, number of people in household, place of residence, woman's decision-making autonomy, religious belief and marital status.

All the covariates were entered simultaneously into the multiple regression models. The significance level for all analyses was set at $P < 0.05$. To ascertain whether the women who were in the group with low SES and exposure to SHS uniquely presented lower levels of knowledge about exposure to SHS and more dismissive attitudes towards the risks of SHS, we conducted ordinal logistic regression analyses to examine the adjusted association between SHS and knowledge and attitudes regarding exposure to SHS after stratification according to wealth level. We estimated odds ratios (ORs) to assess the strength of the associations and used 95% confidence intervals (CIs) for significance testing.

Indices of knowledge and attitudes were constructed using the sum of weighted binary input variables, and maximum and minimum values were chosen for each underlying indicator. The performance of each indicator was expressed through a unit-free index with values between 0 and 1 (which allows different indices to be added together), in accordance with the construction method of the Human Development Index,[22] as follows:

Dimension index = (actual value-minimum value)/(maximum value-minimum value)

The scores obtained for each of the indices were then recoded as terciles, with categories labeled low, middle and high knowledge and attitudes. The Statistical Package for the Social Sciences software (Version 22.0, Chicago, IL, USA) was used for performing all statistical analyses.

Ethical considerations

This study protocol was reviewed and approved by the ethics committee of the Institute of Biological Sciences, University of Rajshahi, Bangladesh (approval number 74/320/IAMEBBC/BSc, dated February 22, 2017). Prior to the survey, potential participants were informed about the study, invited to participate and informed of their right to decline to take part. All medical waste materials used for this study were disposed of safely.

RESULTS

Descriptive statistics

Table 1 shows self-reported exposure to SHS among the women according to their sociodemographic characteristics. A total of 541 women were included in the study. The prevalence of self-reported exposure to SHS was found to be 49.0%.

Table 2 shows the differences in knowledge regarding SHS between the exposed and non- exposed groups. The non-exposed group was significantly more knowledgeable in relation to all the indicators of knowledge, in comparison with the exposed group. Regarding knowledge grading scores, the women in the non-exposed group had significantly higher scores for levels of knowledge ($P < 0.001$) than those of their counterparts (32.2% versus 7.5%). However, out of the total sample, only one fifth of the respondents (20.1%) had higher levels of knowledge regarding SHS.

Table 2 also shows that there were differences in attitudes towards the risks of SHS between the exposed and non-exposed groups. The non-exposed group had significantly more non-dismissive attitudes towards the risks of SHS, in comparison with the exposed group, except in relation to the attitude of finding it difficult to prohibit smoking at home. Regarding attitude grading scores, the women in the non-exposed group had significantly higher scores for dismissive attitudes ($P < 0.001$), compared with their counterparts (55.1% versus 18.9%). Out of the total sample, 37.3% of the respondents had higher levels of dismissive attitudes towards the risks of SHS.

The poor women (8.3%) had the lowest scores for levels of knowledge, in comparison with the medium-wealth (17.2%) and rich women (34.8%), while the non-exposed group in all the three socioeconomic classes had higher scores for levels of knowledge than those of the exposed group. The poor women (18.9%) also had the lowest scores for dismissive attitudes, in comparison with the middle-wealth (33.9%) and rich women (59.1%), while the non-exposed group in all the three socioeconomic class had higher scores for dismissive attitudes than those of the exposed group. **Supplementary Figures 1** and **2** show the distribution of knowledge and attitude grading according to the exposed and non-exposed groups after stratification in terms of SES.

Table 1. Self-reported exposure to secondhand smoking among married women, according to sociodemographic characteristics (n = 541)

Characteristics	n (%)	Self-reported exposure to secondhand smoking
Age, years		
15-22	208 (38.4)	110 (41.5)
23-26	155 (28.7)	75 (28.3)
27-45	178 (32.9)	80 (30.2)
P-value		0.294
Education		
No education	37 (6.8)	24 (9.1)
Primary	108 (20.0)	52 (19.6)
Secondary	324 (59.9)	166 (62.6)
Higher secondary and above	72 (13.3	23 (8.7)
P-value		0.005
Husband's education		
No education	98 (18.1)	59 (22.3)
Primary	167 (30.9)	87 (32.8)
Secondary	199 (36.8)	88 (33.2)
Higher secondary and above	77 (14.2)	31 (11.7)
P-value		0.021
Marital status		
Divorce/separated/widowed	12 (2.2)	5 (1.9)
Currently married	529 (97.8)	260 (98.1)
P-value		0.608
Parity		
1	242 (44.7)	120 (45.3)
2	207 (38.3)	102 (38.5)
3+	92 (17.0)	43 (16.2)
P-value		0.892
Decision-making autonomy*		
Low	186 (34.4)	124 (46.8)
Medium	89 (16.5)	57 (21.5)
High	266 (49.2)	84 (31.7)
P-value		< 0.001
Religion		
Non-Muslim	14 (2.6)	9 (3.4)
Muslim	527 (97.4)	256 (96.6)
P-value		0.246
Occupation		
Employed	489 (90.4)	12 (4.5)
Household work	37 (6.8)	247 (93.2)
Unemployed/student	15 (2.8)	6 (2.3)
P-value		0.082
Place of residence		
Rural	272 (50.3)	183 (69.1)
Urban	269 (49.7	82 (30.9)
P-value		< 0.001
Number of people in household		
3-4	181 (33.5)	80 (30.2)
5-6	205 (37.9)	94 (35.5)
7+	155 (28.7)	91 (34.3)
P-value		0.016
Socioeconomic status		
Poor	180 (33.3)	112 (42.3)
Middle	180 (33.3)	92 (34.7)
Rich	181 (33.5)	61 (23.0)
P-value		< 0.001
Prevalence		265 (49.0)

*Aspects of family decision-making that the woman participated in, alone or jointly.

BMI = body mass index (defined as weight in kilograms divided by the square of height in meters); BMI categories were underweight (< 18.5), normal (18.5-24.9), or overweight/obese (≥ 25).

Table 3 shows the adjusted ordinal logistic regression model for the association between knowledge grading and self-reported exposure to SHS, SES and other sociodemographic factors. In the adjusted model, the respondents who reached the secondary level of education (adjusted odd ratio, AOR = 6.06; 95% confidence interval, CI = 2.56-14.38) or who reached the higher secondary level or

Table 2. Knowledge of and attitudes towards the risks of secondhand smoking (SHS) among the women according to whether they were in the exposed or non-exposed group (n = 541)

Variables	n (%)			P-value
	Exposed	Non-exposed	Total	
Knowledge regarding risks of SHS				
SHS has adverse health effects on children and adult	129 (48.7)	210 (76.1)	339 (62.7)	< 0.001
Children are more vulnerable to SHS than are adults	109 (41.1)	202 (73.2)	311 (57.5)	< 0.001
SHS causes reproductive health problems among women	125 (47.2)	161 (58.3)	286 (52.9)	0.009
Smoking is prohibited in public places in Bangladesh	128 (48.3)	175 (63.4)	303 (56.0)	< 0.001
There are no laws making homes smoke-free in Bangladesh	81 (30.6)	183 (66.3)	264 (48.8)	< 0.001
Knowledge grading				
Low	115 (43.4)	55 (19.9)	170 (31.4)	
Medium	130 (49.1)	132 (47.8)	262 (48.4)	< 0.001
High	20 (7.5)	89 (32.2)	109 (20.2)	
Attitudes towards the risks of SHS				
Smoking should be completely banned in all public places	165 (62.3)	164 (59.4)	329 (60.8)	0.498
Smoking should be prohibited at home	95 (35.8)	263 (95.3)	358 (66.2)	< 0.001
I have the right to ask other people not to smoke in my presence	145 (54.7)	183 (66.3)	328 (60.6)	0.006
It is difficult to adopt a no-smoking policy at home	152 (57.4)	89 (32.2)	241 (44.5)	< 0.001
Presence of SHS encourages young people to begin to smoke	183 (69.1)	237 (85.9)	420 (77.6)	< 0.001
I believe that allowing SHS at home discourages smokers from quitting	92 (34.7)	263 (95.3)	355 (65.6)	< 0.001
Attitude grading				
Low	142 (53.6)	72 (26.1)	214 (39.6)	
Medium	73 (27.5)	52 (18.8)	125 (23.1)	< 0.001
High	50 (18.9)	152 (55.1)	202 (37.3)	

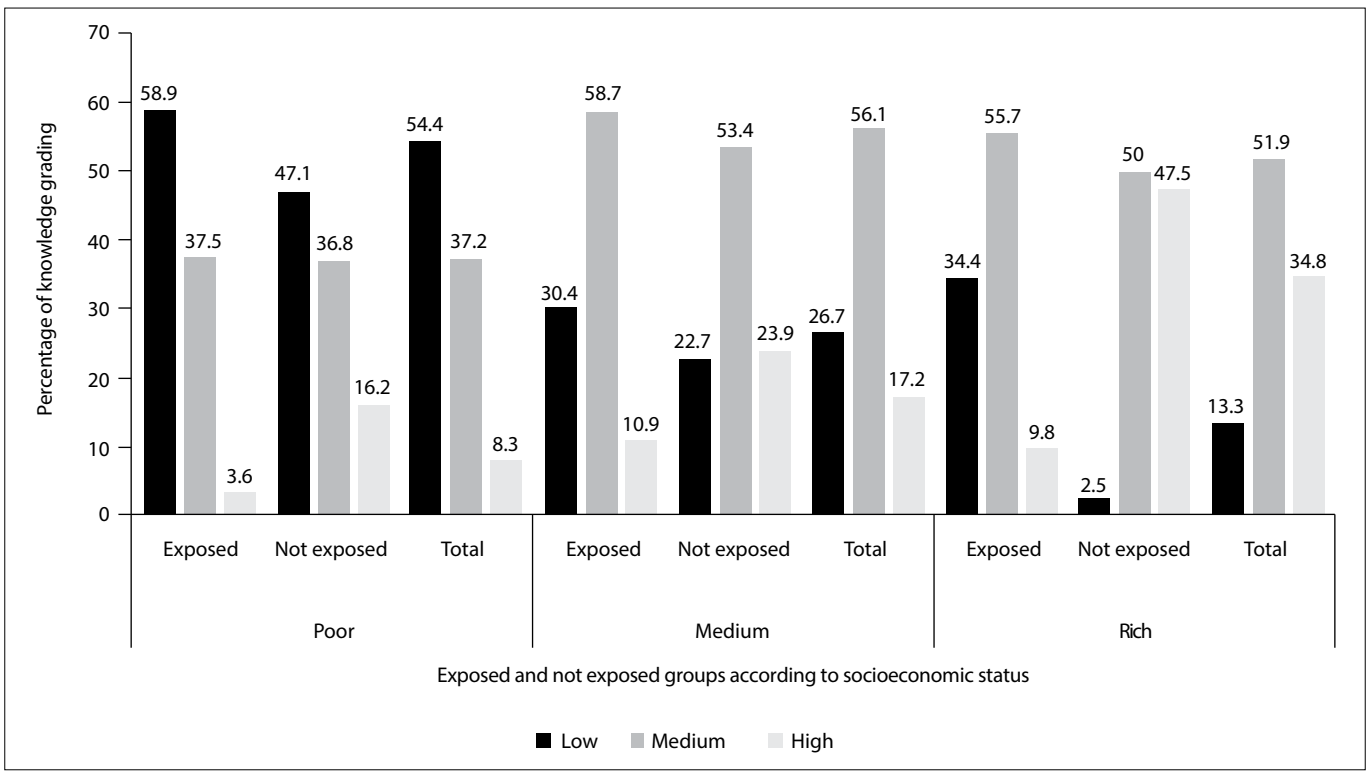

Figure 1. Distribution of knowledge grading according to exposure or non-exposure to secondhand smoking, after stratification according to socioeconomic status.

above (AOR = 8.46; 95% CI = 2.96-24.13) were more likely to have high knowledge scores than to have knowledge in the combined medium and low categories, in comparison with respondents who had not had any education.

Women with medium-level decision-making autonomy (AOR = 2.18; 95% CI = 1.26-3.78) or high-level decision-making autonomy (AOR = 6.33; 95% CI = 3.98-10.08), in comparison with low decision-making autonomy, were more likely to be associated with high knowledge scores than with the combined medium and low categories. Women belonging to the medium SES group (AOR = 2.82; 95% CI = 1.78-4.47) or rich SES group (AOR = 4.55; 95% CI = 2.73-7.60), in comparison with the poor SES group, were more likely to have high knowledge scores than to be in the combined medium and low categories. Likewise, the odds of being in the combined middle and high-knowledge categories rather than in the low-knowledge category were 6.06, 8.46, 2.18, 6.33, 2.82 and 4.55 times greater for respondents who reached secondary-level education or higher secondary and above, those with medium or high autonomy and those belonging to the middle or rich SES groups. In addition, respondents in the exposed group had 0.65 times lower odds of having higher knowledge scores.

Table 3 also shows the adjusted ordinal logistic regression model for the association between attitude grading and self-reported exposure to SHS, SES and other sociodemographic factors. In the adjusted model, respondents aged 23-26 years (AOR = 1.79; 95% CI = 1.08-2.95), versus 15-22 years, were more likely to be associated with high scores for dismissive attitudes than with the combined medium and low categories. Respondents who reached secondary-level education (AOR = 3.05; 95% CI = 1.17-7.91) or higher secondary and above (AOR = 8.03; 95% CI = 2.54-25.35), rather than having no education, were more likely to be associated with high scores for non-dismissive attitudes than with the combined medium and low categories.

Women with high decision-making autonomy (AOR = 2.63; 95% CI = 1.60-4.32), rather than low decision-making autonomy, were more likely to be associated with high scores for non-dismissive attitudes than with the combined medium and low categories. Likewise, the odds of being in the combined middle and high-score categories for dismissive attitudes, rather than the low-score category were 1.79, 3.05, 8.03 and 2.63 times greater for respondents aged 23-26 years, women with secondary-level education or higher secondary and above and women with high autonomy. Women living in rural areas, belonging to the rich wealth bands and having medium or high levels of knowledge grading scores presented higher odds of having higher scores for dismissive attitudes. In addition, women with parity of two and women belonging to the exposed group had 0.56 and 0.57 times lower odds of having higher scores for dismissive attitudes.

Table 4 shows the adjusted ordinal logistic regression model for the association between knowledge grading and the exposure or non-exposure group after stratification according to SES. Women belonging to the low SES group who were exposed to

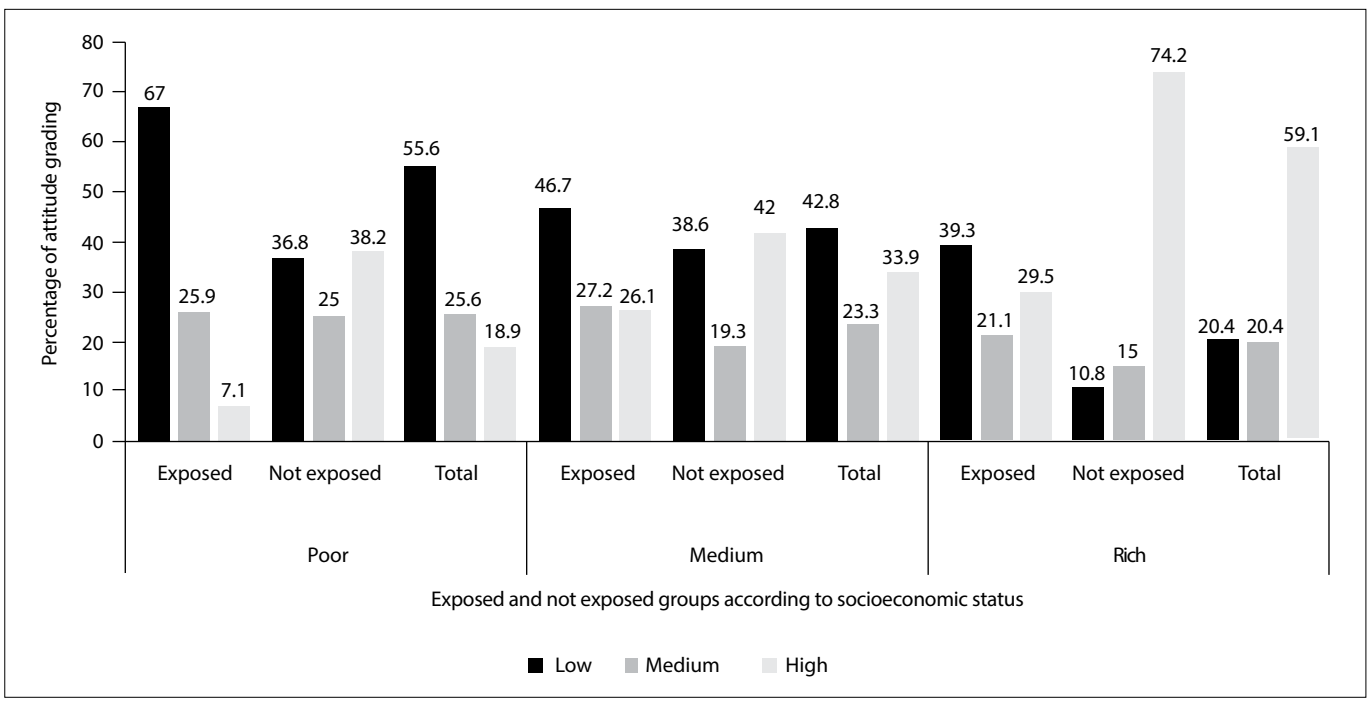

Figure 2. Distribution of attitude grading according to exposure or non-exposure to secondhand smoking, after stratification according to socioeconomic status.

Table 3. Odds ratios for the associations between knowledge/attitude grading and low socioeconomic status (SES), secondhand smoking (SHS) and other sociodemographic factors (n = 541)

Variables	Adjusted odds ratio (95% CI)	
	Knowledge of the risks of SHS	Non-dismissive attitudes towards the risks of SHS
Age, years		
15-22	1.00	1.00
23-26	0.99 (0.62-1.58)	1.79 (1.08-2.95)[c]
27-45	0.69 (0.41-1.17)	0.92 (0.52-1.62)
Education		
No education	1.00	1.00
Primary	2.40 (0.99-5.78)	1.68 (0.63-4.48)
Secondary	6.06 (2.56-14.38)[a]	3.05 (1.17-7.91)[c]
Higher secondary and above	8.46 (2.96-24.13)[a]	8.03 (2.54-25.35)[a]
Husband's education		
No education	1.00	1.00
Primary	0.92 (0.53-1.59)	0.86 (0.48-1.54)
Secondary	0.87 (0.50-1.53)	0.65 (0.36-1.18)
Higher secondary and above	0.70 (0.33-1.48)	0.61 (0.27-1.36)
Marital status		
Divorce/separated/widowed	1.00	1.00
Currently married	0.88 (0.26-3.00)	0.87 (0.22-3.37)
Parity		
1	1.00	1.00
2	1.35 (0.86-2.11)	0.56 (0.35-0.91)[c]
3+	1.46 (0.75-2.85)	0.57 (0.27-1.16)
Decision-making autonomy		
Low	1.00	1.00
Medium	2.18 (1.26-3.78)[b]	1.70 (0.94-3.07)
High	6.33 (3.98-10.08)[a]	2.63 (1.60-4.32)[a]
Religion		
Non-Muslim	1.00	1.00
Muslim	1.15 (0.35-3.80)	0.99 (0.31-3.19)
Occupation		
Employed	1.00	1.00
Household work	1.59 (0.77-3.30)	0.55 (0.25-1.23)
Unemployed/student	1.69 (0.46-6.19)	0.43 (0.10-1.77)
Place of residence		
Rural	1.00	1.00
Urban	2.45 (1.61-3.87)[a]	1.62 (1.03-2.55)[c]
No. of people in household		
3-4	1.00	1.00
5-6	0.96 (0.60-1.52)	1.38 (0.83-2.29)
7+	0.88 (0.54-1.41)	1.59 (0.96-2.64)
Knowledge of the risks of SHS		
Low		1.00
Medium	---	5.99 (3.63-9.90)[a]
High		26.09 (12.68-53.68)[a]
SHS		
Not exposed	1.00	1.00
Exposed	0.65 (0.44-0.98)[c]	0.57 (0.38-0.87)[b]
Socioeconomic status		
Poor	1.00	1.00
Middle	2.82 (1.78-4.47)[a]	0.93 (0.57-1.51)
Rich	4.55 (2.73-7.60)[a]	1.88 (1.08-3.28)[c]

CI = confidence interval. a, b and c indicate $P < 0.05$, $P < 0.01$ and $P < 0.001$.

SHS were less likely to have high knowledge scores (AOR = 0.48; 95% CI = 0.25-0.90) than were the women belonging to the low SES group who were not exposed to SHS. Rich women who were exposed to SHS were less likely to have high knowledge scores (AOR = 0.20; 95% CI = 0.07-0.52) than were the women belonging to the rich wealth bands who were not exposed to SHS.

Table 4 also shows adjusted ordinal logistic regression model for the association between attitude grading and the exposed and non-exposed groups after stratification according to SES. Women belonging to the low SES group who were exposed to SHS were less likely to have high scores for dismissive attitudes (AOR = 0.26; 95% CI = 0.12-0.58) than were the women belonging to the low SES group who were not exposed to SHS. Rich women who were exposed to SHS were less likely to have high scores for dismissive attitudes (AOR = 0.36; 95% CI = 0.15-0.87) than were the women belonging to the rich wealth bands who were not exposed to SHS.

DISCUSSION

To the best of our knowledge, this is the first study to assess the relationships between exposure to SHS, SES and knowledge of and attitudes towards the risks of SHS among married Bangladeshi women of reproductive age. We found that the prevalence of exposure to SHS at home among our sample was 49.0%. In comparison, a study conducted in Bangladesh among the adult population found a prevalence of 43.0%.[14]

The current levels of exposure to SHS at home among these married women are worrisome and constitute a matter for concern for public health researchers and practitioners. The findings likewise indicate that although the bulk of these women had knowledge regarding various indicators for exposure of SHS, their overall knowledge scores are lower (20.2%). Regarding attitude grading scores, only 37.3% of the respondents had more non-dismissive attitudes towards the risks of SHS.

This survey showed that there was a statistically significant correlation between higher knowledge and high scores for non-dismissive attitudes, in relation to exposure to SHS. This result was expected, since the respondents in the exposed group had low knowledge and low levels of non-dismissive attitudes and were therefore more likely to be exposed to SHS. Recently, several studies showed that poor awareness and knowledge regarding the risks of SHS were barriers hindering progress.[23-25] Conversely, good awareness and knowledge of the risks acted as a motivator.[26] When women were aware that exposure "presented a risk," this motivated them to make behavioral changes regarding smoking at home.[23] These findings therefore indicate that urgent effective interventions are needed in order to raise the level of knowledge and establish a good non-dismissive attitude towards avoidance of exposure to SHS among women.

Socioeconomic status is an important determinant of health and wellbeing because it influences people's attitudes, experiences and exposure to several health risk factors.[27] Indeed, several studies have shown that low SES is related to presence of a variety of chronic diseases and to all-cause mortality because of these individuals' lack of knowledge.[28,29] In line with these findings, our study also showed that participants in the low SES group were less likely to have high levels of knowledge of and more likely to have dismissive attitudes towards the risks of SHS, compared with individuals in the high SES group.

Consistent with the findings from previous studies in Bangladesh,[14,30] we also found high levels of knowledge of and non-dismissive attitudes towards the risks of SHS among the respondents who had reached at least the primary level of education. To maintain this high level of knowledge among the women, as well as among the rest of the adult population, the existing promotional campaigns towards tobacco control need to be continued on a regular basis. Graphic warning labels could be successful in reaching illiterate populations. Because there are differences in knowledge according to educational level, targeted campaigns with customized messages should be designed to reach illiterate populations.

Table 4. Odds ratios for associations between knowledge/attitude grading and belonging to the exposed or non-exposed group to secondhand smoking (SHS), stratified according to socioeconomic status (n = 541)

Variable	Poor	Middle	Rich
	Adjusted odds ratio (95% confidence interval)		
Knowledge			
SHS			
Not exposed	1.00	1.00	1.00
Exposed	0.48 (0.25-0.90)[c]	0.80 (0.40-1.57)	0.20 (0.07-0.52)[b]
Attitude			
SHS			
Not exposed	1.00	1.00	1.00
Exposed	0.26 (0.12-0.58)[b]	0.99 (0.51-1.92)	0.36 (0.15-0.87)[c]

[1,2,3]Models were adjusted according to age, education, husband's education, marital status, parity, decision-making autonomy, religion, occupation, place of residence, number of people in household and exposure to SHS. a, b and c indicate $P < 0.001$, $P < 0.01$ and $P < 0.05$.

Our findings also showed that rural respondents were less likely to have higher levels of knowledge and higher grading scores for non-dismissive attitudes. One possible explanation for this result is that in rural areas, the population may lack information and knowledge about passive smoking and may have a lower educational level than that of urban women. Another possible explanation is that, compared with rural areas, urban areas often participate in anti-smoking campaigns and receive tobacco control education,[31] thereby leading to greater knowledge and more non-dismissive attitudes towards the risks of SHS.

We also found that middle-aged mothers (23-26 years) and mothers with high decision-making power were more likely to have higher knowledge and more non-dismissive attitudes than were their counterparts. The possible explanation for this is that middle-aged women and women with higher autonomy have usually reached higher education levels.[32] Additional analyses were run to support this hypothesis, and we found that that the middle-aged women and women with higher autonomy did indeed have higher levels of education. There was also a significant positive correlation between knowledge of and non-dismissive attitudes towards the risks of SHS. Hence, it seems that high levels of knowledge could lead to good levels of non-dismissive attitudes towards the risks of SHS. This result was similar to the findings from a previous study, in which it was found that knowledge pertaining to smoking was predictive of having non-dismissive attitudes towards the risks of smoking, and that this contributed towards effective tobacco control.[33]

Our findings also demonstrated that in relation to higher levels of knowledge and higher scores for non-dismissive attitudes, women who were exposed to SHS and belonged to the poor SES group were not uniquely disadvantaged. Therefore, it is the exposure to SHS per se that disadvantages women, whereas belonging to the low SES group does not uniquely disadvantage women who are exposed to SHS. The importance of this finding needs to be underscored. When exposure to SHS adversely impacts women's knowledge and attitudes, it does so whether the woman has low SES or not. Because of the lack of high levels of knowledge and non-dismissive attitudes, the negative effect of exposure to SHS extends across all socioeconomic backgrounds and is not limited to women who belong either to the low or to the high SES group.

Some limitations need to be considered in explaining our findings. Foremost, the cross-sectional design of the study limits its causal inferences about determinations. Secondly, the current paper focused on household exposure to SHS and did not identify other sources of vulnerability such as in workplaces or outdoors. Therefore, our findings cannot be generalized to exposure to SHS outside of the home.

Thirdly, there may have been the possibility of underreporting of self-reported exposure to SHS. To decrease this underreporting, the following strategies were used: in-person interviews were used rather than a self-administered questionnaire; the questions were behaviorally specific; the women were given several opportunities to reveal their level of knowledge and their attitudes towards the risks of SHS at home within the same interview; and efforts were made to create an atmosphere of trust.

Fourthly, there may have been the possibility of confounding bias. Nevertheless, the confounders that were adjusted for in the present investigation were the factors that are most usually found to be interrelated with exposure to SHS, and to knowledge and attitudes relating to this within the contexts studied. Moreover, the socioeconomic index that was used in the present investigation reflected all the relevant factors associated with the situation of poverty.

Lastly, since the sampling frame was not known, and the sample was not chosen randomly, it is unlikely to have been representative of the population that was studied. However, the findings from this study might be relevant to other areas in Bangladesh and to neighboring low-income countries. The study areas manifested the typical features of rural and urban Bangladesh. The findings were generally consistent with those from other culturally and ethnically different study populations in Bangladesh.

CONCLUSIONS

Exposure to SHS and low SES were independently associated with deficient levels of knowledge and higher scores for dismissive attitudes regarding the risks of SHS. The findings also revealed that because of the lack of high levels of knowledge and because of the high scores for dismissive attitudes regarding the risks of SHS, the negative effects of exposure to SHS extended across all socioeconomic backgrounds and were not limited to women who belonged either in the low or in the high SES group. Future research is needed to understand the causal structures between the exposures and desired outcomes.

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Quality of life among patients with age-related severe macular degeneration assessed using the NEI-VFQ, HADS-A, HADS-D and SF-36 tests. A cross-sectional study

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ABSTRACT

BACKGROUND: Exudative age-related macular degeneration (e-AMD) may cause severe central vision loss. Patients with e-AMD can experience difficulties in daily basic activities and suffer from psychological problems. Our aim was to assess quality of life (QoL) and anxiety and depression status among patients with e-AMD.

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

METHODS: We included 200 e-AMD patients and 120 age and gender-matched controls. We assessed QoL using the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) and the Short Form (SF)-36 test; and anxiety and depression status using the Hospital Anxiety Depression Scales A and D (HADS-A and HADS-D).

RESULTS: The mean ages in the e-AMD and control groups were 68.40 ± 9.8 and 66.31 ± 8.98, respectively. Visual acuity among e-AMD patients was 0.37 ± 0.31 and 0.39 ± 0.32 in the right and left eyes, respectively. The e-AMD patients performed significantly worse than the controls in NEI-VFQ-25 ($P < 0.05$ for all items). The proportions of e-AMD patients scoring higher than the cutoffs in HADS-A and HADS-D were significantly higher than among the controls (41.5% versus 12.5% and 63.5% versus 27.5%; $P < 0.001$). The e-AMD patients had significantly lower mean scores than the controls for each of the SF-36 QoL items ($P < 0.001$). The NEI-VFQ-25 scores were significantly lower among patients with bilateral e-AMD than among those with unilateral disease ($P < 0.05$ for all). The HADS scores were positively correlated with duration of e-AMD and patient age, but negatively with vision levels ($P < 0.05$ for all items).

CONCLUSION: The e-AMD patients had higher depression and anxiety scores and lower QoL scores.

INTRODUCTION

Age-related macular degeneration (AMD) is a neurodegenerative disease of the retina characterized by loss of central vision in old age. In particular, wet-type or exudative AMD, which is characterized by choroidal neovascularization, may cause severe loss of vision in these patients. AMD is the leading cause of central blindness among patients aged over 65 years in developed countries. The prevalence of AMD among individuals aged between 65 and 75 years is 10% and it is 25% among those aged 75 years and over. Patients with AMD may face difficulties in relation to many of the basic activities of daily living, such as writing, housework, self-care, driving and shopping. They may also suffer emotional distress and depression, and have a reduced quality of life (QoL).[1] Furthermore, loss of vision increases the risk of falling and fall-related injuries.[2] In all of its aspects, AMD is recognized as an important public health problem.

Although the effects of exudative AMD (e-AMD) on quality of life, depression and physical and mental health have been studied more extensively in well-developed countries, data is relatively lacking from developing or underdeveloped countries. Moreover, differences in its effects may be seen between communities. Different social traits, belief sets and cultural characteristics in different communities may lead patients to be influenced psychologically in different manners from the same disease.

The hospital anxiety and depression scale (HADS) was designed to measure the risks of anxiety and depression and their levels. The test includes two subscales: HADS-A, which assesses anxiety, and HADS-D, which assesses depression, both including seven items. The cutoff points for HADS-A and HADS-D are ten and seven, respectively. Higher scores indicate a greater likelihood

of anxiety and depression. The validity and reliability of HADS in the Turkish population were assessed by Aydemir et al.[3]

The National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) scale was developed to determine QoL among patients with chronic blindness. The scale provides an evaluation of the impact of visual impairment on the emotional wellbeing, social relationships and daily activities of patients with chronic blindness. Its validity and reliability in the Turkish population were assessed by Toprak et al.[4]

Several other scales have been developed to assess physical and mental health.[5] The Short Form 36 (SF-36) test is a general QoL scale assessing the physical and emotional health of patients. It consists of a total of 36 questions, classified in eight domains: physical functioning, role-physical, bodily pain, general health, social functioning, role-emotional, mental health and vitality. The SF-36 scale is not specific to any disease, age or treatment group and represents measurements of general health. Because of its ease of use, the SF-36 test is particularly ideal for older patients. Its validity and reliability in the Turkish population were assessed by Kocyigit et al.[6]

OBJECTIVE

In the current study, we aimed to evaluate the impact of e-AMD on the QoL of patients, using the HADS-A, HADS-D, NEI-VFQ-25 and SF-36 questionnaires.

METHODS

This study was undertaken between February 2015 and May 2015. A cohort of consecutive patients with e-AMD was recruited from the medical retina department. Age and gender-matched controls with simple refractive errors were recruited from the eye polyclinic. We followed the principles of the Declaration of Helsinki; we obtained ethical approval from the Afyonkarahisar Clinical Research Ethics Board (approval number: 61; date of approval: January 29, 2015); and we obtained written informed consent from all of the patients and controls.

The patients with severe AMD were aged over 50 years, had exudative-type AMD and were already receiving anti-vascular endothelial growth factor (anti-VEGF) treatment on an as-needed basis to treat e-AMD. All of the patients in the study group had e-AMD in at least one eye, with Snellen visual acuity of 0.5 or less. Exudative AMD was defined and diagnosed as occurrences of intra-retinal and subretinal fluid caused by choroidal neovascularization. It was accompanied by drusen and retinal pigment epithelial detachments, which were demonstrated by means of fundus fluorescein angiography and spectral domain optical coherence tomography (Heidelberg Spectralis OCT and HRA, Heidelberg, Germany).

Patients with comorbid disorders were excluded from the study. In addition, patients with glaucoma, optic neuropathy, diabetic retinopathy, uveitis, amblyopia, degenerative myopia or cataracts were also excluded.

We recorded the age, education, gender, marital status, income levels and duration of the disease of all of the patients. We performed three tests on both the patients and the controls: the NEI-VFQ-25 test, the HADS test and the SF-36 questionnaire. Sociodemographic factors were also compared between the two groups.

The NEI-VFQ-25 test was developed to determine QoL among patients with chronic blindness. This test includes a total of 25 questions that assess general health, general vision, vision-specific mental health, vision-specific social functioning, vision-specific dependency, ocular pain, near and distant activities, role limitations, color vision and peripheral vision.

The HADS test consists of a fourteen-item scale that was developed to detect states of anxiety and depression in a hospital setting.[7] It has two subscales: HADS-A for assessing anxiety and HADS-D for assessing depression. Both scales include seven items that are scored from 0 to 3. Questions 1, 3, 5, 6, 8, 10, 11 and 13 are scored as 3, 2, 1 or 0; and questions 2, 4, 7, 9, 12 and 14 are scored as 0, 1, 2 or 3. While questions 1, 3, 5, 7, 9, 11 and 13 relate to anxiety, questions 2, 4, 6, 8, 10, 12 and 14 relate to depression. The total score ranges from 0 to 21 for both of the scales. The cutoff points for HADS-A and HADS-D are ten and seven, respectively. Total scores greater than these cutoffs indicate the existence of a risk of depression or anxiety.

The SF-36 QoL test includes a total of 36 self-assessment questions that are classified into eight domains: physical functioning with ten questions, role-physical with four, bodily pain with two, general health with five, social functioning with two, role-emotional with three, mental health with five and vitality with four. The reference period for all of the questions was the last four weeks prior to the interview.

The NEI-VFQ-25 test, the HADS test and the SF-36 questionnaire were applied to all the patients by one of the authors (SI).

We used the Statistical Package for the Social Sciences (SPSS) software, version 15.0, to perform the statistical analyses. We used the Kolmogorov-Smirnov test to assess the normality of distribution. We used the Pearson chi-square test to analyze any relationship between two categories of data. We used the Analysis of Variance test to analyze data with normal distribution and homogeneous variance. For continuous variables, we used the Student t test, Mann-Whitney U test and the Tukey HDS test. Existence of statistical significance was established at a p-value of < 0.05, and the confidence interval was taken to be 95%.

RESULTS

A total of 200 patients and 120 controls were enrolled in the study. The mean ages in the e-AMD and control groups were 68.40 $\pm$ 9.8 and 66.31 $\pm$ 8.98 years, respectively ($P = 0.06$). The mean binocular visual acuity (according to a Snellen chart line) was 0.52 $\pm$ 0.31 in the e-AMD group and 0.96 $\pm$ 0.04 in the control

group (P = 0.00). The visual acuity among patients in the e-AMD group was 0.37 ± 0.31 in the right eye and 0.39 ± 0.32 in the left eye (P = 0.80). There was no significant difference regarding smoking, education, sex or income levels between the control and patient groups (**Table 1**).

The patients in the e-AMD group performed significantly worse than the controls in all of the items of the NEI-VFQ-25 test (general health, general vision, vision-specific mental health, vision-specific social functioning, vision-specific dependency, ocular pain, near and distant activities, driving, color vision and peripheral vision) (P < 0.05 for all items). We were unable to compare driving performance. The driving test was not applicable to the patients with e-AMD, because many of them were not drivers even before the onset of the disease. The NEI-VFQ-25 scores for general vision, near vision, peripheral vision, color vision, dependency and ocular pain were significantly lower among the patients with bilateral e-AMD than among those who had unilateral disease (**Table 2**).

Based on binocular vision levels, the level of vision showed a positive correlation with the test scores in both groups. Similarly, as the level of vision decreased, so did the test scores. The scores were inversely and significantly correlated with the age and duration of the illness. The scores for emotional role difficulty, mental health, social functioning and pain on the SF-36 scale were negatively correlated with the duration of e-AMD and patient age, but were positively correlated with vision levels. The scores for HADS were positively correlated with the duration of e-AMD and patient age, but were negatively correlated with vision levels. The correlations of scores for the subscales of NEI-VFQ-25, SF-36, HADS-A and HADS-D with the duration of e-AMD, the best corrected visual acuity (BCVA) in the better-seeing eye and the patients' age are given in **Table 3**.

HADS-A and HADS-D scores were compared with visual acuity, laterality of disease and demographic characteristics among the patients with exudative AMD. This is shown in **Table 4**.

The patients with e-AMD had significantly lower mean scores than those of the controls for each of the items of the SF-36 QoL scale (P < 0.001). The test scores showed decreases with increasing age in both of the groups. The test scores declined with reduced vision, particularly in the domains of physical functioning and vitality, among the patients with e-AMD. The test scores also declined with extended disease duration (P < 0.001). The physical functioning and vitality scores were significantly higher among females than among males (P < 0.001) in the e-AMD group, but not in the control group. The data from the SF-36 scale in bilateral and unilateral e-AMD cases and in the control group are shown in **Table 5**.

DISCUSSION

The results from our study showed that patients with e-AMD were more likely to experience depression and anxiety symptoms and had lower QoL than did age-matched people with normal vision. These results have important personal and social implications. Older patients with impaired vision experience difficulties and anxiety in maintaining an independent lifestyle, since greater effort is required for participation in everyday activities, which leads to fatigue and limited mobility.

Table 1. Demographic characteristics of the patient and control groups

	e-AMD patients (n = 200)	Controls (n = 120)	P
Age			
Mean in years	68.40 ± 9.80	66.31 ± 8.98	0.06
Under 60 years	37	31	0.12
60 years and over	163	89	
Gender			
Female	111	61	0.24
Male	89	59	
BCVA (mean, Snellen chart line)			
Binocular	0.50 ± 0.30	0.98 ± 0.04	< 0.001
Right eyes with e-AMD	0.36 ± 0.30	0.97 ± 0.05	< 0.001
Left eyes with e-AMD	0.37 ± 0.30	0.95 ± 0.03	< 0.001
Duration of e-AMD (months)			
Right eyes	18.17 ± 20.02	-	-
Left eyes	18.74 ± 19.91	-	-
Laterality of e-AMD (n)			
Unilateral eyes	38 RE/24 LE	-	-
Bilateral eyes	138	-	-
Education			
Illiterate	22	17	0.930[a]
Literate	25	15	
Elementary	127	72	
High school	19	11	
University	7	5	
Income status			
Revenue smaller than expenditure	66	38	0.429[a]
Revenue equal to expenditure	108	60	
Revenue greater than expenditure	26	22	
Job			
Housewife	91	52	0.044[a]
Retired	72	31	
Farmer	20	12	
Public sector	7	12	
Private sector	6	8	
Not working	4	5	
Smoking			
Smoker*	39	26	0.641[a]
Non-smoker	161	94	

e-AMD = exudative age-related macular degeneration; BCVA = best corrected visual acuity; [a]chi-square test.

*Participants were considered to be smokers if they had smoked at least 100 cigarettes during their lifetimes and if they reported, at the time of the interview, that they smoked every day or on some days.

Table 2. Differences in subscale scores in the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25), between the exudative age-related macular degeneration (e-AMD) group and control group and between the unilateral and bilateral exudative AMD subgroups

Subscales	NEI-VFQ-25 scores					
	All e-AMD patients (n = 200)	e-AMD patients		P^a	Controls (n = 120)	P^b
		Unilateral e-AMD (n = 62)	Bilateral e-AMD (n = 138)			
General health	35.8 ± 23.8	38.7 ± 22.9	34.4 ± 24.2	0.28	65.5 ± 14.1	< 0.001
General vision	42.5 ± 17.9	45.6 ± 16.0	41.0 ± 18.6	0.04	81.6 ± 9.7	< 0.001
Mental health	43.6 ± 23.2	47.2 ± 21.5	41.9 ± 23.8	0.12	95.3 ± 4.4	< 0.001
Ocular pain	49.8 ± 26.4	54.8 ± 23.8	47.5 ± 27.3	0.05	88.5 ± 11.3	< 0.001
Near vision	48.0 ± 26.4	54.1 ± 24.4	45.4 ± 26.9	0.03	92.9 ± 7.7	< 0.001
Distance vision	50.1 ± 24.4	56.9 ± 22.2	50.5 ± 25.2	0.17	92.3 ± 6.5	< 0.001
Social functioning	62.6 ± 29.4	68.9 ± 26.9	61.2 ± 30.3	0.13	98.3 ± 5.0	< 0.001
Role difficulties	61.0 ± 23.9	44.3 ± 22.9	40.2 ± 24.2	0.24	97.1 ± 7.7	< 0.001
Dependency	48.8 ± 25.1	54.7 ± 23.2	46.1 ± 25.5	0.02	98.0 ± 4.5	< 0.001
Color vision	68.4 ± 30.5	75.0 ± 28.0	65.4 ± 31.2	0.04	97.5 ± 7.5	< 0.001
Peripheral vision	53.9 ± 27.9	60.8 ± 23.3	50.7 ± 29.3	0.02	93.2 ± 11.1	< 0.001

P^a = comparison of unilateral and bilateral cases; P^b = comparison of e-AMD and control groups.

Table 3. Correlation of subscale scores in the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25), Short Form-36 (SF-36) and Hospital Anxiety Depression Scales A and B (HADS-A and HADS-D) tests with the duration of exudative age-related macular degeneration (e-AMD), best corrected visual acuity (BCVA) in the better-seeing eye and age

Scores	Significantly correlated parameters		
	Duration of e-AMD (n = 200)	BCVA in better-seeing eye (n = 200)	Age (n = 200)
Subscales of NEI-VFQ-25			
General health	P = 0.031; r = -0.16	P < 0.001; r = 0.46	P < 0.001; r = -0.30
General vision	P < 0.001; r = -0.25	P < 0.001; r = 0.58	P < 0.001; r = -0.27
Mental health	P < 0.001; r = -0.32	P < 0.001; r = 0.61	P < 0.001; r = -0.29
Ocular pain	P < 0.001; r = -0.32	P < 0.001; r = 0.52	P = 0.001; r = -0.19
Near vision	P = 0.001; r = -0.24	P < 0.001; r = 0.52	P < 0.001; r = -0.31
Distance vision	P = 0.068; r = -0.14	P < 0.001; r = 0.45	P < 0.001; r = -0.33
Social functioning	P = 0.002; r = -0.23	P < 0.001; r = 0.48	P < 0.001; r = -0.25
Role difficulties	P < 0.001; r = -0.25	P < 0.001; r = 0.61	P < 0.001; r = -0.23
Dependency	P < 0.001; r = -0.28	P < 0.001; r = 0.59	P < 0.001; r = -0.27
Color vision	P < 0.001; r = -0.30	P < 0.001; r = 0.42	P < 0.001; r = -0.20
Peripheral vision	P = 0.002; r = -0.21	P < 0.001; r = 0.51	P < 0.001; r = -0.22
Subscales of SF-36			
Physical functioning	P = 0.061; r = -0.13	P < 0.001; r = 0.25	P < 0.001; r = -0.36
Role limitation due to physical health	P = 0.067; r = -0.13	P < 0.001; r = 0.29	P < 0.001; r = -0.24
Role limitation due to emotional problems	P = 0.005; r = -0.20	P < 0.001; r = 0.27	P < 0.001; r = -0.22
Energy/fatigue	P = 0.231; r = -0.08	P < 0.001; r = 0.26	P = 0.001; r = -0.18
Emotional wellbeing	P = 0.033; r = -0.15	P < 0.001; r = 0.21	P = 0.002; r = -0.18
Social functioning	P = 0.002; r = -0.22	P < 0.001; r = 0.24	P < 0.001; r = -0.24
Pain	P < 0.001; r = -0.31	P < 0.001; r = 0.29	P < 0.001; r = -0.24
General health	P = 0.051; r = -0.14	P < 0.001; r = 0.29	P < 0.001; r = -0.28
HADS scores			
HADS-A score	P = 0.131; r = 0.17	P < 0.001; r = -0.38	P = 0.001; r = 0.18
HADS-D score	P = 0.005; r = 0.19	P < 0.001; r = -0.32	P = 0.002; r = 0.17

Previous studies have shown that there is a significant association between chronic eye diseases and depression. Depression may develop either as a result of a chronic physical disorder or due to a limitation on daily activities following vision impairment.[8] Watson et al. reported that anxiety often accompanies depression,[9] and Mathew et al. found that 44% of the patients with AMD and 18% of the controls had depressive symptoms.[10] Although reduced visual acuity is used as the primary outcome measurement in the majority of trials, loss of contrast sensitivity and color vision and increased susceptibility to glare from light are also associated with decreased vision-specific QoL among patients with AMD.[11]

A series of cohort studies conducted by Casten et al. showed that the prevalence of depression among patients with AMD was between 20% and 43%.[12,13] Several researchers have assessed the relationship between severity of AMD and depressive symptoms.[14,15] One of these studies suggested that there was no relationship between AMD and anxiety.[15] A cross-sectional study found that the rate of depressive symptoms was not significantly different between patients with early AMD and those with late AMD (15.7%

Table 4. HADS-A and HADS-D scores in comparison with demographic characteristics among patients with exudative age-related macular degeneration (e-AMD)

Groups		Anxiety and depression scores					
		HADS-A			HADS-D		
		Above cutoff n (%)	Below cutoff n (%)	p*	Above cutoff n (%)	Below cutoff n (%)	p*
e-AMD (n = 200)		83 (41.5)	117 (58.5)	< 0.001	127 (63.5)	73 (36.5)	< 0.001
Control (n = 120)		15 (12.5)	105 (87.5)		33 (27.5)	87 (72.5)	
Demographic characteristics (e-AMD)							
Income status	High-income group	5 (19.2)	21 (80.8)	0.004[a]	11 (42.3)	15 (57.7)	0.007[a]
	Middle-income group	55 (50.9)	53 (49.1)	0.047[b]	76 (70.4)	32 (29.6)	< 0.01[b]
	Low-income group	23 (35.4)	42 (64.6)	0.13[c]	26 (40.0)	39 (60.0)	0.84[c]
Gender	Female	48 (43.2)	63 (56.8)	0.57	76 (68.5)	35 (31.5)	0.10
	Male	35 (39.3)	54 (60.7)		51 (57.3)	38 (42.7)	
Smoking	Smoker	13 (33.3)	26 (66.7)	0.25	20 (51.0)	19 (49.0)	0.08
	Non-smoker	70 (43.5)	91 (56.5)		107 (66.5)	54 (33.5)	
Laterality	Unilateral	20 (32.3)	42 (67.7)	0.07	35 (56.5)	27 (43.5)	0.16
	Bilateral	63 (45.7)	75 (54.3)		92 (66.7)	46 (33.3)	
BCVA	< 20/40	45 (51.7)	42 (48.3)	0.01	58 (66.7)	29 (33.3)	0.41
	≥ 20/40	38 (33.6)	75 (66.4)		69 (61.1)	44 (38.9)	

*Chi-square test; n = sample size; [a]comparison between high and middle-income groups; [b]comparison between middle and low-income groups; [c]comparison between high and low-income groups; HADS-A = anxiety scale; HADS-D = depression scale; BCVA = best corrected visual acuity in the better-seeing eye.

Table 5. Comparisons of SF-36 quality-of-life scale between exudative age-related macular degeneration group and control group, and between unilateral and bilateral cases

SF-36 subscales	Exudative age-related macular degeneration				Control (n = 120)	P[b]
	All cases (n = 200)	Unilateral cases (n = 62)	Bilateral cases (n = 138)	P[a]		
Physical functioning	50.91 ± 25.9	56.2 ± 23.2	48.6 ± 26.9	0.05	64.9 ± 26.5	< 0.001
Role limitation due to physical health	13.12 ± 18.4	16.7 ± 19.9	11.5 ± 17.5	0.04	24.9 ± 22.2	< 0.001
Role limitation due to emotional problems	15.66 ± 20.0	18.8 ± 21.2	14.3 ± 19.3	0.13	29.7 ± 23.0	< 0.001
Energy/fatigue	47.10 ± 20.6	49.5 ± 19.6	46.0 ± 20.9	0.19	57.5 ± 15.7	< 0.001
Emotional wellbeing	51.66 ± 18.8	52.8 ± 18.1	51.1 ± 19.1	0.42	61.6 ± 14.2	< 0.001
Social functioning	53.68 ± 24.0	57.6 ± 22.7	51.9 ± 24.4	0.12	68.8 ± 20.6	< 0.001
Pain	54.18 ± 23.9	60.4 ± 22.3	51.3 ± 24.2	0.00	67.8 ± 21.7	< 0.001
General health	40.66 ± 19.7	44.8 ± 17.4	38.7 ± 20.4	0.01	53.5 ± 16.7	< 0.001

P[a] = comparison of unilateral and bilateral cases; P[b] = comparison of exudative age-related macular degeneration group and control group.

versus 17.2%).[16] However, some other studies reported that the rate of depressive symptoms increased with the severity of e-AMD.[17]

In a cross-sectional study, the proportion of patients with e-AMD who presented depression was 17.9%.[27] In case-control studies, the percentage of depression is usually found to be significantly higher among patients with e-AMD.[17,18] Popescu et al. examined whether the percentage of depression among patients with AMD, glaucoma and Fuchs corneal dystrophy was higher than among controls and found that while it was 8% among the controls, it was 29% among patients with glaucoma and 39% among patients with AMD.[19] In a controlled study conducted on patients with glaucoma and AMD, Kocak et al. showed that the percentage of depression was significantly higher among the patients with glaucoma or AMD than among the controls.[20] However, the difference between the patients with glaucoma and those with AMD was not significant.

With regard to the relationship between AMD and anxiety, while several case-control studies failed to show any significant relationship,[18] several others showed higher rates of anxiety among patients with AMD.[17] Some studies did not find any relationship between the severity of AMD and anxiety symptoms.[17,18] In the current study, we found significant differences in both the HADS-A and the HADS-D score between the patients with e-AMD and the controls.

The NEI-VFQ-25 test is among the most commonly used vision-specific QoL scales. Orr et al. found that NEI-VFQ-25 scores were positively correlated with good vision.[21] In the Age-Related Eye Disease Study, the researchers assessed NEI-VFQ-25 scores twice, with a four-year interval between assessments, and demonstrated that there was a significant association between NEI-VFQ-25 scores and the progression of AMD and vision loss.[22]

A clinical study conducted on patients with e-AMD who received pegaptanib, ranibizumab or aflibercept showed that these treatments improved their QoL and reduced their dependence in relation to daily activities. In addition, it showed that these treatments decreased the incidences of depression and fall-related injuries.[23] In the EQUADE study, using the NEI-VFQ-25 test, the researchers demonstrated that poor QoL was associated with impaired visual functions, prolonged duration of illness and poor social support (paid caregivers and home healthcare services).[24] In a study conducted on patients with e-AMD who received photodynamic treatment, their QoL was assessed using pre and post-treatment NEI-VFQ-25 test scores. Although visual acuity was maintained in 71% of the patients, photodynamic treatment failed to improve their QoL. In the current study, we found a significant correlation between improved visual acuity and increased NEI-VFQ-25 test scores. Poor visual acuity and prolonged treatment duration were associated with lower test scores and poorer QoL.

The SF-36 test is a practical instrument for assessing QoL among older adults. This test has, particularly, been used among patients with glaucoma. In a study performed in Turkey, using the SF-36 scale, it was shown that QoL was lower among patients with glaucoma.[25] In another study, physical functioning, role-physical, bodily pain, social functioning and mental health scores were found to be significantly lower among the patients with glaucoma than among the controls.[26] In a study in which the participants were divided into three groups, comprising patients with glaucoma, patients with a suspicion of glaucoma and controls, the patients with glaucoma had the lowest SF-36 scores and those with a suspicion of glaucoma had the second lowest scores.[27] In the current study, the patients with e-AMD tended to score lower than the controls across all of the QoL domains. The test scores particularly showed that there were declines in the domains of physical functioning and vitality with increasing disease duration and reduced visual acuity.

Exudative AMD is a chronic disease that gradually causes significant central visual loss. Geographical, population and sociodemographic differences may lead to variable results regarding the scores on depression, anxiety and quality-of-life scales. These results can also be influenced by factors relating to patients' expectations. Patients' beliefs and fears relating to the disease and the ways in which they react to the disease need to be assessed. Compliance with treatment, in relation to chronic diseases, affects the course of the disease and the success of the treatment.

It should be borne in mind that psychiatric support may be needed in order to provide optimal compliance with treatment, in relation to mental health status and quality of life among e-AMD patients. The HADS-A, HADS-D, SF-36 and NEI-VFQ-25 scales can be used to fully ascertain the physical and mental health status of patients with e-AMD. Our study showed how our patient population with e-AMD was affected overall through undergoing treatment for chronic anti-VEGF treatment.

Compared with previous studies, the differences in the geographical, educational and sociodemographic characteristics of the participants in this study may, in part, account for the differences in the anxiety and depression rates and in the vision-specific QoL scores. Overall, we found that patients with e-AMD were especially at risk of impaired QoL. Therefore, these patients require close follow-up.

The limitations of this study include the small size of the sample that was used to investigate the outcome variables. The small population size may have limited the power of the study for making statistical differentiation to ascertain any slight significances in the subgroup analyses. In addition, the possible influence of the number of intravitreal anti-VEGF treatments for e-AMD on the quality-of-life scales was not evaluated. It would be valuable to study the different stages of the course of anti-VEGF treatment for e-AMD, such as the initial, midterm or long-term stage.

On the other hand, the use of three different scales to assess possible impairment of quality of life and emotional mood in the same population suffering from e-AMD was the strength of our study. Moreover, all the scales had also been validated in our country.

CONCLUSION

Our results showed that patients with e-AMD had higher levels of symptoms of depression and anxiety and lower QoL, in comparison with the controls. The quality of life of these patients with e-AMD decreased as the disease duration increased and their visual acuity decreased. Our study indicated that treatments for patients with e-AMD should be managed in terms of dealing with their overall health. Further multicenter studies with large sample sizes are required to provide better validated data.

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Immunoexpression of TS, p53, COX2, EGFR, MSH6 and MLH1 biomarkers and its correlation with degree of differentiation, tumor staging and prognostic factors in colorectal adenocarcinoma: a retrospective longitudinal study

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ABSTRACT

BACKGROUND: There are cases of colorectal tumors that, although small, show more aggressive evolution than large tumors. This motivated us to study whether there are any proteins capable of alerting about these changes. The aim here was to correlate the immunoexpression of the TS, p53, COX2, EGFR, MSH6 and MLH1 biomarkers in tumors in patients with colorectal adenocarcinoma, with the degree of cell differentiation, tumor staging and clinical-pathological prognostic factors.

DESIGN AND SETTING: Retrospective observational study at a public tertiary-level hospital.

METHODS: We analyzed tissue-microarray paraffin blocks of tumor tissues that had been resected from 107 patients. We used Fisher's exact test to study associations between tumor differentiation/staging and the immunoexpression of biomarkers. We also used Kaplan-Meier estimation, the log-rank test and the adjusted Cox regression model to investigate the patients' overall survival (in months) according to biomarkers and disease-free interval.

RESULTS: The degree of tumor differentiation and tumor staging were not associated with the biomarkers, except in cases of patients in stages III or IV, in which there was a correlation with MLH1 expression ($P = 0.021$). Patient survival and disease-free interval were not associated with the biomarkers.

CONCLUSION: There were no associations between the degree of tumor differentiation, staging, length of survival or disease-free interval and the immunoexpression of the TS, *p53*, COX2, EGFR or *MSH6* tumor markers. In advanced cases of colorectal adenocarcinoma (stages III and IV), there was a higher percentage of *MLH1*-negative results.

INTRODUCTION

Colorectal cancer (CRC) is considered to be the third most commonly diagnosed and the second greatest cause of mortality due to cancer in North America.[1] In Brazil, similar data have been reported from research carried out by the National Cancer Institute (Instituto Nacional do Câncer, INCA). In 2018, the estimate incidence of CRC was 36,360 new cases (17,380 men and 18,980 women), with the highest incidence in the age group between 50 and 70 years.[2] Approximately one in three people who develop the disease die of it.[3]

The most significant independent prognostic factor for CRC is the tumor-node-metastasis (TNM) stage and the "potential" residual disease after surgery.[4] Neoplastic recurrence is a frequent cause of death among patients undergoing primary disease resection with curative intent,[5,6] and this is one of the reasons for conducting further studies on CRC prognosis.

The *p53* tumor suppressor gene acts as a damage sensor in relation to deoxyribonucleic acid (DNA) and assists in the repair system using checkpoints to halt the cell cycle or induce apoptosis, thus preventing cell proliferation.[7] In *p53*-mutation cells there is no DNA repair in the cell cycle.[8] These genetically unstable cells tend to accumulate mutations, thereby leading to rapid proliferation of cell clones with mutated DNA, and thus to neoplastic transformation.[9]

Some authors agree that overexpression of epidermal growth factor receptors (EGFRs) is associated with lower survival rates and worse prognosis.[10] EGFRs are tyrosine kinase receptors that are involved in cascade-like activation, which leads to cell differentiation and multiplication.[11]

The cyclo-oxygenase-2 (COX-2) enzyme plays a key role in conversion of arachidonic acid (AA) into prostaglandins, which have been associated with colorectal carcinogenesis.[12] No conclusions have yet been reached regarding the relationship between COX-2 expression and patient survival.[13]

The major repair genes, i.e. MutS-homolog1 *(MLH1)*, MutS-homolog6 *(MSH6),* MutS-homolog2 *(MSH2),* postmeiotic segregation increased 1 *(PMS1)* and postmeiotic segregation increased 2 (*PMS2*), play important roles in correcting mutations associated with oxidative stress. It is important to correct for addition of CH_3 radicals to DNA bases.[14-16] It has been shown that oxidative stress caused by oxygen free radicals breaks single and double DNA strands, thus inducing errors in the nitrogenous base pairs, which may lead to genetic mutations.[17,18] Cells have defense mechanisms against these errors, consisting of DNA repair systems (i.e. mismatch repair, MMR).[16] Deficiencies in this DNA repair mechanism constitute an important molecular pathway for CRC development, which occurs in the cases of approximately 15% of colorectal neoplasms.[19]

OBJECTIVE

To study the immunoexpression of the TS, *p53*, COX2, EGFR, *MSH6* and *MLH1* biomarkers in patients with colorectal carcinoma; and to make correlations with the degree of cell differentiation, tumor staging and clinical-pathological prognostic factors.

METHODS

Study design, setting and ethics

We used tissues from patients who were operated at the Muriaé Cancer Hospital (Hospital do Câncer de Muriaé, HCM), in Muriaé, Minas Gerais, Brazil. We submitted the study protocol to the Ethics Committee of HCM and to the "Platform Brazil" Research Ethics Council (approval protocol number 347.449).

Samples, participants and surgical procedures

We analyzed the tissue samples of a convenience sample of all consecutive patients with colonic or rectal cancer who underwent operations between January 2003 and November 2008 and whose paraffin blocks were stored at the archives of the HCM Department of Pathology.

The inclusion criteria for these patients were that they underwent surgical resection of the colon or rectum due to adenocarcinoma, without presence of any other severe chronic degenerative diseases that would impair survival assessment, and with subsequent follow-up at the outpatient clinic. The following patients were excluded: those with past neoplasms, those who underwent palliative surgery and those who died in the immediate postoperative period. Our final sample comprised 107 specimens. We obtained data from the patients' medical records and we tried to reach patients through phone calls, calling them for follow-up visits, so that there would not be any lack of information in the records.

Patients who underwent elective surgery had been staged preoperatively, and all of these patients were operated by a single team, with postoperative follow-up performed in the outpatient ward. Colorectal carcinoma was diagnosed by means of anorectal examination and tests such as flexible sigmoidoscopy, colonoscopy and abdominal computed tomography (CT) scan.

Among cases of emergency surgery performed because of acute intestinal obstruction, the diagnosis was made by means of clinical examination, abdominal x-ray and CT scan, and laparotomy. Among the elective patients, the diagnosis and preoperative staging were done using the following: a) clinical examination; b) ancillary tests, i.e. measurement of carcinoembryonic antigen (CEA), colonoscopy, chest radiography, abdominal and pelvic CT scans and abdominal ultrasonography; c) colorectal tumor biopsy; d) biopsy of the metastatic lesion, when suspected; and e) pathology examination on the surgical specimen.

Colonic or colorectal resection surgery was performed after checking for neoplastic spread into other organs and for any structures affected by the tumor. The surgery potentially included regional lymphadenectomy, respecting the tumor resection criteria. The patients were postoperatively followed up early on, with periodic clinical evaluations and with laboratory (CEA), radiological and endoscopic procedures, to check for any early disease recurrence.

Tissue microarray analysis

We used tissue microarrays (TMAs) to study the immunoexpression of TS protein, *p53*, COX2, EGFR, *MSH6* and *MLH1*. The colorectal cancer tissues obtained from biopsies or surgical specimens were fixed in 10% formalin and were processed using the paraffin embedding method for histological analysis. Histological sections of thickness 3 mm were obtained from each block. The sections were stained with hematoxylin-eosin and were reviewed by two pathologists to confirm the diagnosis and reassess the histopathological findings. These evaluations helped select the parts of the specimens from which the cylinders of tissue used in the TMAs were taken. The TMA slides were subjected to five immunohistochemical reactions, following the specifications of the primary antibodies used for each biomarker.

The TMA methodology was as follows:

1. The area selected was marked out in the respective paraffin block;
2. A drained space ("*casela*") was created in the recipient block;
3. A tissue cylinder of 1 mm in diameter was extracted from the donor block of the respective area of interest that had previously been selected;

4. The tissue cylinder thus obtained was transferred from the donor block to the "*casela*" that had previously been created in the recipient block;
5. New positions within the recipient block were progressively reached (through movement measured in fractions of millimeters), in order to create a collection of tissue samples, following a matrix arrangement;
6. Final block quality was assessed for storage purposes.

Variables studied

We investigated the immunoexpression of the following variables, and described patients according to them: TS protein, *p53*, COX2, EGFR, *MSH6* and *MLH1*; along with the degree of tumor differentiation, tumor staging, overall survival and disease-free interval.

Surgery was registered as curative (radical) or palliative, according to whether residual macroscopic neoplastic lesions were found to exist postoperatively in staging tests and according to the results from histopathological examination of the surgical specimen. Curative procedures require radical excision of the tumor with adequate surgical margins, considering its vascular pedicle and the largest number of adjacent lymph nodes, with no positive margins seen in pathological evaluation. Palliative surgery involves incomplete tumor resection, tumor bypass or just making a stoma without resecting the tumor.

Recurrence was defined as tumor recurrence in local structures or in remote organs as metastases that originated from the colorectal tumor. Recurrence was confirmed based on clinical examination, laboratory tests, radiological imaging and/or endoscopic views.

The disease-free interval was considered to be the period of postoperative time within which there was no detection of cancer recurrence in patients who underwent a supposedly curative procedure. Survival was defined as the time interval between surgery and death for certain patients, or between surgery and the last visit to the clinic or telephone contact. The staging of lesions was carried out in accordance with the tumor, node and metastasis (TNM) classification system.

Statistical analysis

The statistical analysis was performed by an independent researcher. The data of interest were collected from the patients' records. The statistical analysis on all the data collected in this study was done descriptively.

For the quantitative variables (numerical variables), we calculated some summary measurements, such as average, minimum, maximum and standard deviation values. The qualitative variables (categorized variables) were analyzed by calculating the absolute and relative frequencies (percentages).[20] We performed inferential analyses to confirm or refute evidence that was found in the descriptive analysis, consisting of an extension of the Fisher exact test[21] to study associations between the degree of tumor differentiation and the immunoexpression of TS, COX2, EGFR, *MLH1*, *MSH6* and *p53*; and between tumor staging and the immunoexpression of TS, COX2, EGFR, *MLH1*, *MSH6* and *p53*.

Kaplan-Meier estimates,[22] the log-rank test[23] and the adjusted Cox regression model were used to investigate the individuals' overall survival (in months) according to their immunoexpression of TS, COX2, EGFR, MSH6, MLH1 and p53; and the disease-free interval of six subjects (in months) according to their immunoexpression of TS, COX2, EGFR, *MSH6*, *MLH1* and *p53*.

For inferential analysis purposes, we used the significance level $\alpha = 5\%$. We stored the data in Excel for Windows 2007 spreadsheets. For statistical analyses, we use the R statistical software, version 2.10.1.

RESULTS

Our sample involved 107 individuals, comprising 50 females (46.7%) and 57 males (53.3%). The women's average age was 64.3 years, ranging from 43 to 90 years, with a standard deviation of 11.7 years. The male group had a mean age of 57.2 years, ranging from 24 to 86 years, with a standard deviation of 16.8 years.

The inferential results regarding the association between the degree of tumor differentiation and the immunoexpression of TS, COX2, EGFR, MLH1, MSH6 and p53 showed that the degree of tumor differentiation was not associated with the immunoexpression of TS (P = 0.138), COX2 (P = 0.428), EGFR (P = 0.103), *MSH6* (P = 0.876), *MLH1* (P = 0.792) or *p53* (P = 0.884).

Subject clinical stage (CS) distribution according to TS expression

There was no statistically significant difference in the clinical staging of individuals, in relation to TS expression (P = 0.817). Similarly, there was no statistically significant difference in staging, in relation to the immunoexpression of COX2 (P = 0.842), EGFR (P = 0.344), MSH6 (P = 0.923), MLH1 (P = 0.021) or p53 (P = 0.666) (**Table 1**).

Clinical stage distribution of the subjects according to MLH1 expression

We found an association between stage and MLH1, such that the group of individuals in stages III or IV had a higher percentage of MLH1-negative results (28.3%) than did the subjects in stages 0, I or II (3.7%) (P = 0.021) (**Table 1**).

The inferential results from univariate analysis (log-rank test) revealed that overall survival was not associated with the immunoexpression of TS (P = 0.480), COX2 (P = 0.998), EGFR (P = 0.600), MSH6 (P = 0.318), MLH1 (P = 0.798) or p53 (P = 0.695) (**Table 2**). Even after disregarding the subjects with results that were classified as inconclusive, we were able to confirm that survival was

Table 1. Clinical stage distribution among the individuals with colorectal cancer according to immunoexpression of TS, COX2, EGFR, MLH1, MSH6 and p53

	Clinical stage						P
	0 (n = 2)	I (n = 16)	II (n = 27)	III (n = 46)	IV (n = 16)	Total (n = 107)	
TS							
Focal	2 (100.0%)	5 (31.3%)	5 (18.5%)	11 (23.9%)	7 (43.8%)	30 (28.0%)	
Inconclusive	-	-	1 (3.7%)	3 (6.5%)	-	4 (3.7%)	
Intense	-	2 (12.5%)	2 (7.4%)	3 (6.5%)	1 (6.3%)	8 (7.5%)	0.817[a]
Moderate	-	2 (12.5%)	4 (14.8%)	7 (15.2%)	3 (18.8%)	16 (15.0%)	
Negative	-	7 (43.8%)	15 (55.6%)	22 (47.8%)	5 (31.3%)	49 (45.8%)	
COX2							
Focal	1 (50.0%)	6 (37.5%)	13 (48.1%)	16 (34.8%)	5 (31.3%)	41 (38.3%)	
Inconclusive	-	1 (6.3%)	1 (3.7%)	2 (4.3%)	-	4 (3.7%)	
Intense	-	2 (12.5%)	6 (22.2%)	6 (13.0%)	2 (12.5%)	16 (15.0%)	0.842a
Moderate	-	5 (31.3%)	6 (22.2%)	17 (37.0%)	7 (43.8%)	35 (32.7%)	
Negative	1 (50.0%)	2 (12.5%)	1 (3.7%)	5 (10.9%)	2 (12.5%)	11 (10.3%)	
EGFR							
0	1 (50.0%)	-	-	3 (6.5%)	1 (6.3%)	5 (4.7%)	
1	-	2 (12.5%)	1 (3.7%)	1 (2.2%)	-	4 (3.7%)	
2	-	4 (25.0%)	4 (14.8%)	9 (19.6%)	6 (37.5%)	23 (21.5%)	0.344[a]
3	1 (50.0%)	9 (56.3%)	21 (77.8%)	31 (67.4%)	9 (56.3%)	71 (66.4%)	
Inconclusive	-	1 (6.3%)	1 (3.7%)	2 (4.3%)	-	4 (3.7%)	
MSH6							
Inconclusive	-	1 (6.3%)	1 (3.7%)	2 (4.3%)	-	4 (3.7%)	
Negative	2 (100.0%)	12 (75.0%)	19 (70.4%)	37 (80.4%)	12 (75.0%)	82 (76.6%)	0.923[a]
Positive	-	3 (18.8%)	7 (25.9%)	7 (15.2%)	4 (25.0%)	21 (19.6%)	
MLH1							
Inconclusive	-	1 (6.3%)	-	2 (4.3%)	-	3 (2.8%)	
Negative	-	-	1 (3.7%)	13 (28.3%)	4 (25.0%)	18 (16.8%)	0.021[a]
Positive	2 (100.0%)	15 (93.8%)	26 (96.3%)	31 (67.4)	12 (75.0%)	86 (80.4%)	
p53							
Inconclusive	-	-	1 (3.7%)	1 (2.2%)	-	2 (1.9%)	
Negative	2 (100.0%)	10 (62.5%)	14 (51.9%)	33 (71.7%)	10 (62.5%)	69 (64.5%)	0.666[a]
Positive		6 (37.5%)	12 (44.4%)	12 (26.1%)	6 (37.5%)	36 (33.6%)	

Table 2. Summary of the overall survival time (months) among the individuals with colorectal cancer, according to immunoexpression of MLH1

MLH1	Summary measurements				
	n	Average	Median	Minimum	Maximum
Inconclusive					
No death	3	30.8	20.3	16.5	55.7
Death	1	1.6	1.6	1.6	1.6
Total	4	23.5	18.4	1.6	55.7
Negative					
No death	12	26.1	21.6	4.3	59.5
Death	6	11.1	7.4	2.2	23.9
Total	18	21.1	15.4	2.2	59.5
Positive					
No death	61	29.0	23.6	2.6	66.6
Death	23	11.5	9.5	0.9	29.5
Total	84	24.2	20.0	0.9	66.6
Total					
No death	76	28.6	23.5	2.6	66.6
Death	30	11.1	7.4	0.9	29.5
Total	106	23.6	19.7	0.9	66.6

not associated with the immunoexpression of TS (P = 0.502), COX2 (P = 0.989), EGFR (P = 0.424), MSH6 (P = 0.129), MLH1 (P = 0.496) or p53 (P = 0.979).

The inferential results from univariate analysis (log-rank test) revealed that the subjects' disease-free interval did not correlate with their immunoexpression of TS (P = 0.356), COX2 (P = 0.885), EGFR (P = 0.786), MSH6 (P = 0.178), MLH1 (P = 0.691) or p53 (P = 0.441). Even after disregarding the individuals with inconclusive results, we were able to confirm that the disease-free interval was not associated with the immunoexpression of TS (P = 0.228), COX2 (P = 0.796), EGFR (P = 0.661), MSH6 (P = 0.071), MLH1 (P = 0.448) or p53 (P = 0.442).

It was noteworthy that there was a tendency for MSH6-positive individuals to have longer disease-free intervals than those of their MSH6-negative counterparts.

We used the statistical methodology of the multiple Cox regression model to confirm the findings obtained from univariate analysis (log-rank test). The multivariate analysis confirmed the evidence obtained in the univariate analyses, in which individuals'

length of survival was not associated with their immunoexpression of TS (P = 0.794), COX2 (P = 0.885), EGFR (P = 0.882), MSH6 (P = 0.142), MLH1 (P = 0.788) or p53 (P = 0.556). Moreover, the subjects' disease-free interval was not associated with their immunoexpression of TS (P = 0.481), COX2 (P = 0.756), EGFR (P = 0.843), MSH6 (P = 0.085), MLH1 (P = 0.464) or p53 (P = 0.164).

It is important to highlight that, to achieve Cox regression analysis of greater stability, we disregarded the individuals with results that were deemed inconclusive.

DISCUSSION

To explain our findings, one theory might be that the specimens contained in the paraffin blocks did not represent the invasive tumor. It is becoming increasingly common in the literature to see reports of different expressions of tumor markers in the same surgical specimen. It is important to remember that advanced tumors are almost always heterogeneous in nature (i.e. with randomly distributed tissues), and of variable sizes (such that large masses tend to more intensely express antigenic reactions). These properties can lead to cells of different degrees of differentiation within the same lesion, which can greatly influence immunoreactivity. Considering this theory, one solution might be to perform immunohistochemical examinations on tumor tissue by means of microarrays, as performed in this study.

Another possible way to explain our findings is to suggest that there might be an association with the type of antibody used. Monoclonal antibody sensitivities may differ, depending on the type used: some might react better with the basal membranes of epithelial tissues, and others with the cell cytoplasm.

A further way to explain our findings concerning the immunohistochemical tests relates to the issue of statistical power, i.e. whether the sample has the power to demonstrate a significant difference when this exists. It is possible that larger samples, with consequently higher statistical power, could overcome this potential shortcoming. This, however, is only a hypothesis.

Conflicting results regarding the TS, p53, COX2, EGFR, MSH6 and MLH1 immune markers in CRC have been reported, and these can be explained by the different numbers of samples, the techniques used and the wide variation in methodologies used in the various studies. Patient selection, tissue processing, immunohistochemical techniques, result interpretations and statistical analyses have been quite variable.[24] For these reasons, we were led to study the association between the immunoreactivity of the tumor markers TS, p53, COX2, EGFR, MSH6 and MLH1 in cases of colorectal cancer and the main clinical and pathological prognostic factors. These factors comprise recurrence, disease-free interval, survival, cell differentiation and staging. However, separate analysis on these markers showed that there were no associations with these prognostic factors, except in the group of patients at stages III or IV, in which there was a higher percentage of MLH1-negative individuals (28.3%) than in the group of individuals at stages 0, I or II (2.3%).

Recent studies have demonstrated that silencing of the MLH1 gene is related to development of errors associated with replication of CRC cells, as was depicted in a study on microsatellite instability.[25] It was also found that MLH1 repair gene expression is higher in normal tissue than in cancer tissue, which demonstrated the importance of this gene in maintaining DNA integrity.[24,26]

CONCLUSION

TS, COX2, EGFR, *MSH6*, *MLH1* and *p53* expression, as measured through immunohistochemical analysis, was not associated with the clinical-pathological factors of the patients with colorectal adenocarcinoma studied, except for *MLH1* in some cases. This marker showed a significant difference in expression between patients at stages III and IV and those at stages I to IV of colorectal adenocarcinoma.

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Anti-interleukin-1 treatment among patients with familial Mediterranean fever resistant to colchicine treatment. Retrospective analysis

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KEY WORDS:
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ABSTRACT

BACKGROUND: Up to 5% of familial Mediterranean fever (FMF) cases are unresponsive to colchicine, through resistance, side effects and toxicity. Anakinra is an alternative treatment for FMF patients whose disease remains uncontrolled with colchicine. We aimed to evaluate anti-interleukin-1 treatment regarding clinical findings, laboratory parameters and quality of life (QoL) among FMF patients presenting resistance and toxicity towards colchicine.

DESIGN AND SETTING: Descriptive observational study at the rheumatology clinic, Adnan Menderes University Medical School, Aydın, Turkey.

METHODS: Among the patients included, age, sex, *MEFV* genotypes, acute-phase reactants, hepatic/renal function tests, average colchicine dose, disease duration, attack frequency, attack duration, disease severity, proteinuria, amyloidosis and QoL were evaluated. Colchicine resistance was defined as > 6 typical episodes/year or > 3 per 4-6 months. Kolmogorov-Smirnov, Friedman and two-way analysis of variance tests were used for statistical analyses.

RESULTS: Between 2015 and 2017, 14 FMF patients receiving anakinra were enrolled. The mean colchicine dose was 1.7 ± 0.3 mg/day before use of anakinra. Ten patients were attack-free after treatment, while three showed reductions of at least 50% in attack frequency, attack duration and disease severity. Proteinuria levels in all patients with renal amyloidosis decreased after treatment. QoL among patients with renal amyloidosis differed significantly from QoL among non-amyloidosis patients. Mean visual analogue scale scores significantly improved in both groups after use of anakinra.

CONCLUSIONS: Use of anakinra reduced attack frequency and proteinuria and acute-phase reactant levels, and improved QoL, with only a few uncomplicated side effects among colchicine-resistant or intolerant FMF patients. Injection-site reactions of severity insufficient to require discontinuation of treatment were seen.

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common hereditary periodic fever syndrome and characterized by recurrent fever and serositis. This disease shows autosomal recessive inheritance and it is frequently observed in the Middle East and Mediterranean basin, especially among Arabs, Armenians, Jews and Turks.[1,2]

In 90% of FMF patients, clinical manifestations start to occur before they reach their second decade of life. Attacks usually last from 12 hours to 3-4 days and are characterized by fever, abdominal pain, chest pain, arthritis and erysipelas-like skin lesions. Amyloidosis is the most frightening complication because of its morbidity and mortality. The incidence of FMF-associated amyloidosis has been reduced through decreasing the delay in diagnosing this condition and through early treatment with colchicine.[1-3]

Colchicine is used both in preventing attacks and in treating amyloidosis. It is recommended that each FMF patient should receive continuous appropriate doses of colchicine.[4] However, up to 5% of these patients are unresponsive to colchicine because of side effects, tolerability problems and colchicine resistance.[5] Certain pyrin mutations and polymorphism of the drug transporter gene adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) may cause colchicine resistance. However, the exact mechanism remains unknown.[5,6]

The efficacy of serotonin reuptake inhibitors, interferon-alpha, thalidomide, azathioprine, anti-tumor necrosis factor agents and drugs that block interleukin-1, such as anakinra, canakinumab and rilonacept, has been investigated among colchicine-intolerant or resistant patients.[7-12] Anakinra is a recombinant non-glycosylated homologous human interleukin-1 receptor antagonist that competitively binds to interleukin-1α and interleukin-1β, which are interleukin-1 receptors. Studies on FMF patients taking anakinra have demonstrated that use of this drug leads to reduction in the frequency of attacks and in acute-phase reactant levels. Moreover, use of anakinra has been reported to reduce proteinuria levels.[13-17] Additionally, successful treatment of gout, chronic kidney disease and aplastic anemia through use of anakinra has been reported.[18]

OBJECTIVE

The aim of this study was to evaluate clinical parameters such as severity of illness, attack duration, attack frequency and presence of amyloidosis among FMF patients presenting resistance and toxicity towards colchicine. We also evaluated acute-phase reactants, proteinuria, side effects, genetic mutations and quality of life among patients with and without amyloidosis, in relation to treatment with anakinra.

METHODS

This was a single-center retrospective descriptive study, in which patients receiving anakinra between 2015 and 2017 were enrolled. These patients had been admitted to the rheumatology clinic of Adnan Menderes University Medical School, in Aydın, Turkey, with a diagnosis of FMF. They had been treated with anakinra (100 mg/day, subcutaneously) because they had presented side effects, intolerance or resistance to colchicine. Patients with histories of infection, malignancy or other autoinflammatory diseases were not included in the study.

A signed informed consent form was obtained from each patient for whom anakinra treatment was planned. Ethics committee approval was received for this study, from the ethics committee of our university (approval number: 2017/1258; approval date: November 9, 2017).

The Tel-Hashomer criteria were used to make the diagnosis of FMF.[19] The major criteria comprise presence of fever episodes accompanied by arthritis and/or serositis, AA-type amyloidosis without any predisposing disease and good response to colchicine. The minor criteria comprise presence of erysipelas-like erythema, occurrence of FMF in a first-degree relative and recurrence of fever attacks. A definitive diagnosis is made in the presence of two major or one major and two minor criteria. A probable diagnosis is made in the presence of one major criterion and one minor criterion.

Colchicine resistance was defined as more than six typical episodes per year or more than 3 episodes per 4-6 months.[3]

The relationship between quality of life and amyloidosis was evaluated, since amyloidosis is the most important complication that leads to morbidity and mortality among FMF patients. Quality of life was assessed using a visual analogue scale (VAS) from 0 to 10 cm that represented, respectively, from poor to good quality of life.

Clinical and laboratory data were obtained from the patients' records, retrospectively. Age, sex, *MEFV* genotypes, acute-phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], hepatic/renal function tests, average colchicine dose, disease duration, attack frequency, attack duration, disease severity, proteinuria and amyloidosis were evaluated. Also, side effects that limit colchicine use, such as hepatic, neuromuscular and hematological toxicities, including rhabdomyolysis, aplastic anemia leukopenia, neutropenia and thrombocytopenia, were evaluated.

The normal reference ranges for ESR, CRP and 24-hour urinary protein excretion are as follows: 0-20 mm/h, 0-5 mg/dl and < 150 mg. Renal biopsies were performed in cases of suspected renal amyloidosis. The results from 24-hour urinary protein excretion among the patients with renal amyloidosis, and their ESR and CRP levels, were evaluated and recorded at each visit.

The quantitative data were examined using the Kolmogorov-Smirnov test to ascertain whether they conformed to normal distribution. Descriptive statistics were presented as means ± standard deviations or medians and interquartile ranges for continuous variables and as frequencies and percentages for categorical variables. Wilcoxon's and Friedman's tests were used as non-parametric tests, while two-way analysis of variance (ANOVA) was used for repeated measurements. $P < 0.05$ was accepted as statistically significant. The Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA), was used to analyze the data.

RESULTS

Between 2015 and 2017, 14 patients (9 males and 5 females) receiving anakinra were enrolled. Most of the FMF patients included in this study were male and the mean age for all the FMF patients was 41.3 ± 10.7. The length of time for which they had had the diagnosis of FMF was 11.8 ± 8.8 years. The mean length of time that elapsed until the first follow-up visit was 11.4 ± 2.2 weeks, and it was 26.4 ± 4.7 weeks until the second visit and 47.5 ± 5.0 weeks until the third visit.

All of the patients were taking colchicine regularly. Among these patients with a diagnosis of FMF, 50% presented renal amyloidosis, 14.3% had ankylosing spondylitis and 7.1% had adult-onset Still's disease. The demographic and clinical features of the patients are summarized in **Table 1**.

Colchicine resistance was present in 13 of these patients. Use of anakinra was started among these patients because

of their intolerance of colchicine treatment and the toxic hepatitis that it led to. The mean colchicine dose was 1.7 ± 0.3 mg/day in the beginning and the mean duration of anakinra treatment was 16.2 ± 8.9 months. There were no attacks after treatment in 10 patients, while the remaining three patients had a reduction in attack frequency of at least 50%. Moreover, these same three patients presented decreases in the severity and duration of the disease of more than 50%. We were unable to evaluate the response in one patient who received anakinra because this patient died due to amyloidosis and renal failure that was unrelated to use of anakinra, on the 10th day of the therapy.

The mean age of the seven patients with renal amyloidosis (female-to-male ratio of 6:1) was 42 ± 10.9 years. The mean duration of their diagnosis of amyloidosis was 7.2 ± 5.5 years and their average colchicine dose was 1.8 ± 0.2 mg/day.

Genetic analysis results were available for 92.8% of all the FMF patients (13/14). The most frequently detected mutation was *M694V* (78.5%). The *MEFV* genotype of the patients with renal amyloidosis was *M694V* homozygote in three patients and there was one patient with each of the following: *E148Q* heterozygous/*M694V* heterozygous; *M694V* heterozygous/*R202Q* heterozygous; *M694V* homozygous/*R202Q* homozygous; and *R202Q* heterozygous mutation.

An injection-site reaction was observed in two patients. Neither of these was a serious reaction that would have required discontinuation of use of anakinra, and the reaction was controlled in both cases using topical corticosteroids and antihistaminic drugs. The treatment was halted in one of these two patients due to local injection-site infection and abscess development.

At the time of the first visit, a decrease in proteinuria levels was observed in four patients with amyloidosis, compared with the baseline. However, this did not reach statistical significance. A decrease in 24-hour urinary protein was observed in relation to all the patients with amyloidosis at the time of the third visit, compared with the pre-treatment values (**Table 2**).

The ESR and CRP levels of the FMF patients were higher before anakinra treatment. The median ESR was 65.5 mm/h (range: 24-93) at the first visit relating to the treatment with anakinra and 25 mm/h (range: 13.7-58) at the second visit. The levels of the acute-phase reactants diminished over the course of the patients' follow-up. There were significant differences in both ESR and CRP levels, compared with the pre-treatment situation. The ESR and CRP levels among the FMF patients at the baseline and at the first, second and third visits are shown in **Table 3**.

Furthermore, the quality of life score from the 10-cm VAS improved through use of anakinra, as observed at the first, second and third visits. The changes in VAS score among the FMF patients with and without amyloidosis are shown in **Table 4**.

Table 1. Demographic and clinical features of the patients with familial Mediterranean fever

	Total (n = 14)
Age (years), mean ± standard deviation	41.3 ± 10.7
Male, n	9
Female, n	5
Colchicine dose (mg/day), mean ± standard deviation	1.7 ± 0.3
Disease duration (years), mean ± standard deviation	11.8
Fever, n (%)	14 (100%)
Serositis, n (%)	10 (71.4%)
Arthritis, n (%)	8 (57.1%)
Febrile myalgia, n (%)	1 (7.1%)
Chronic renal disease, n (%)	3 (21.4%)
Amyloidosis, n (%)	7 (50%)
Sacroiliitis, n (%)	2 (14.3%)

Table 2. 24-hour urinary protein (mg) in familial Mediterranean fever patients with renal amyloidosis at baseline and at first, second and third visits

	24-hour urinary protein (mg)*
Baseline	13,995 (5,298.2-17,795)
First visit	5,875.1 (2,777.1-9,627)
Second visit	4,507 (2,596.8-10,197.3)
Third visit	2,508 (1,387.5-9,009.7)**

*Median (with interquartile range); **P = 0.02 (from analysis of variance, ANOVA), compared with before the treatment.

Table 3. Erythrocyte sedimentation rate and C-reactive protein (CRP) levels in familial Mediterranean fever patients at baseline and at first, second and third visits

Erythrocyte sedimentation rate (mm/h)	Median (with interquartile range)	P-value
Baseline	65.5 (24-93)	
First visit	28 (10.5-63.5)*	0.002
Second visit	25 (13.7-58)*	0.005
Third visit	15 (12-38)*	0.008
C-reactive protein (mg/dl)	**Median (with interquartile range)**	**P-value**
Baseline	41.9 (10.2-102.3)	
First visit	9.9 (3.1-24,1)*	0.002
Second visit	4.5 (1.4-10.8)*	0.005
Third visit	1.9 (0.8-17.3)*	0.02

*P < 0.05 (from analysis of variance, ANOVA) for the rates at the first, second and third visits, compared with baseline.

Table 4. Changes to visual analogue scale scores among familial Mediterranean fever patients with and without amyloidosis at baseline and at first, second and third visits

Visual analogue scale (mean ± SD)	With amyloidosis	Without amyloidosis	P-value
Baseline	2.1 ± 1.0	4.8 ± 0.7	0.001
First visit	5.8 ± 0.9*	6.8 ± 0.7**	0.03
Second visit	8.0 ± 1.2*	9.0 ± 0.7**	0.1
Third visit	8.5 ± 1.0*	9.0 ± 0.8	0.1

*P < 0.05 (from analysis of variance, ANOVA) for visual analogue scale scores at the first, second and third visits, compared with baseline (with amyloidosis); **P < 0.05 (from ANOVA) for visual analogue scale scores at the first and second visits compared with baseline (without amyloidosis).

DISCUSSION

In this study, we evaluated 14 patients with FMF who were treated with anakinra because of side effects, toxicity or resistance caused by colchicine. It was found at the third visit that the proteinuria levels in all the renal amyloidosis patients had decreased.

Azathioprine, anti-tumor necrosis factor agents, thalidomide, interferon-alpha, serotonin reuptake inhibitors, anakinra, rilonacept and canakinumab can be considered to be alternative treatment options for refractory FMF.[7-12] Because of FMF-associated mutations, inhibition of interleukin-1β and activation of nuclear factor kappa B are among the therapeutic aims of treatment targeted on interleukin-1.

Anakinra appears to be an alternative agent for treating colchicine-resistant or intolerant patients, with effects that have been reported in case reports, case series and some prospective studies.[12-17] In two recent cohorts, anakinra and canakinumab were shown to be effective for decreasing attack frequency, serum acute-phase reactants and proteinuria among refractory FMF patients.[17,20] Moreover, anakinra has been reported to be an effective and safe treatment among pregnant women with FMF.[21] In our study, there were no cases of use of anakinra during pregnancy among women with FMF.

Mutations such as *E148Q, M680I, M694V, M694I* and *V726A* have been shown to be responsible for the cases of more than 80% of FMF patients.[2] In our study, M694V was the most common mutation (78.5%).

AA-type secondary amyloidosis is typically seen in FMF cases. In a study conducted by the Turkish FMF study group, the frequency of amyloidosis among FMF patients was reported to be 12.9%.[22] In our clinic, this rate is 3.4%.

It has been reported that interleukin-1 inhibitors reduce proteinuria and stabilize or preserve renal functions over short-term follow-up.[23] In our study, decreased 24-hour urinary protein levels in all patients with amyloidosis were observed at the time of the third visit, compared with the pre-treatment situation (**Table 2**).

Colchicine is effective for preventing FMF attacks, and also for diminishing the development of amyloidosis.[24,25] It has been suggested that colchicine resistance is associated with mutation penetration in the *MEFV* gene, most frequently in individuals with the *M694V* homozygous mutation.[26,27] All of the patients included in the present study were using colchicine regularly. Colchicine resistance was present in 13 of these patients. In one patient, use of anakinra was started due to intolerance and toxic hepatitis. The mean colchicine dose was 1.7 ± 0.3 mg/day in the beginning. It was higher (1.8 ± 0.2 mg/day) among patients with amyloidosis than among those without amyloidosis. The median attack frequency was 8 (range: 6-8) among our patients, over the last six months before anakinra treatment.

In a randomized, double-blind, placebo-controlled study, a total of 25 patients were randomized such that 12 received anakinra and 13 received placebo.[28] It was found that the frequency of attacks was significantly lower in the anakinra group than in the placebo group, particularly regarding joint attacks.[28] We found that there was a complete response to anakinra in 10 patients, in terms of attack frequency, while the remaining three patients presented improvements of at least 50%. Moreover, these three patients presented decreases in the severity and duration of the disease of more than 50%.

FMF affects the quality of life adversely. It has been reported that the quality of life among FMF patients is lower than that of healthy controls.[29] Inverse correlations between the number of attacks, disease severity and quality of life have been found, without any difference between the sexes.[29] Depression and anxiety are also common among FMF patients, compared with healthy individuals.[30] Quality of life has been shown to be better among patients who received anakinra, compared with a placebo group, but without any significant difference in adverse events between the anakinra group (mean ± SD: 2.03 ± 1.75) and the placebo group (mean ± SD: 3.34 ± 2.5).[28]

The relationship between quality of life, as assessed using the Short Form-36 (SF-36) questionnaire, and disease parameters has also been investigated. It has been shown that FMF affected both mental and general health parameters, and also that it influenced the physical/physical role/emotional role functions.[31]

We used a VAS to assess quality of life. The mean VAS score of all the patients before use of anakinra was 3.5 ± 1.6 cm, and it became significantly higher among the FMF patients who were treated with anakinra. There was a significant difference in quality of life between the patients with renal amyloidosis (2.1 ± 1.0 cm) and those in the non-amyloidosis group (4.8 ± 0.7 cm) before the treatment (P = 0.001). At the time of the first visit, the mean VAS scores of both of these groups with use of anakinra were found to have increased significantly, compared with the pre-treatment situation.

The limitations of our study were that its nature was descriptive and observational, without any control group or randomization. Furthermore, we did not use SF-36 to evaluate the quality of life.

The highlight of our study was that it provided some evidence that use of anakinra reduced the attack frequency and proteinuria and acute-phase reactant levels, and that it improved quality of life. Consequently, although colchicine remains the first choice for treating FMF, it can be confirmed that anakinra is an effective and safe alternative treatment for colchicine-resistant patients. Use of anakinra decreased the frequency of attacks and led to decreased amounts of proteinuria in cases of renal amyloidosis. It was also found that use of anakinra led to improvement in quality of life.

CONCLUSIONS

Anakinra reduced attack frequency and proteinuria and acute-phase reactant levels and improved quality of life, with only a few uncomplicated side effects in most colchicine-resistant or intolerant FMF patients. Injection-site reactions were seen but were not severe enough to require discontinuation of treatment.

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Ultrasound-guided adductor canal block using levobupivacaine versus periarticular levobupivacaine infiltration after total knee arthroplasty: a randomized clinical trial

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KEY WORDS:
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Rehabilitation.
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ABSTRACT

BACKGROUND: Both postoperative pain control and range of motion are important in total knee arthroplasty (TKA). However, in the literature, there is little comparison of peripheral nerve blocks and periarticular infiltration techniques using levobupivacaine. The aim of our study was to measure pain with visual analogue scale (VAS) and knee range of motion (ROM) between in patients undergoing adductor canal block (ACB) for TKA using levobupivacaine compared to periarticular levobupivacaine infiltration (PAI-L).

DESIGN AND SETTING: Prospective randomized clinical trial in a university hospital.

METHODS: Patients aged 40-85 years who underwent unilateral TKA were included; 39 were treated with periarticular infiltration using 40 ml (0.125 mg) of levobupivacaine (PAI-L group); and 40 were treated with ACB using 20 ml of 0.25% levobupivacaine (ACB-L group). Postoperative pain scores at rest and during active physical therapy were assessed using a VAS, along with knee ROM in flexion and extension. In addition, 100-foot walking time results, total morphine consumption and time of first analgesia requirement were recorded postoperatively.

RESULTS: VAS scores at rest and during active physical therapy and the total amount of morphine consumed were lower in the ACB-L group than in the PAI-L group ($P < 0.05$). In contrast, knee ROM in flexion and extension and 100-foot walking times were greater in the PAI-L group than in the ACB-L group ($P < 0.05$).

CONCLUSION: ACB-L was superior to PAI-L regarding pain treatment after TKA; however, PAI-L was superior to ACB-L regarding postoperative ROM and walking ability.

CLINICAL TRIAL REGISTRY: ACTRN-12618000438257.

INTRODUCTION

Total knee arthroplasty (TKA) is a common surgical procedure that can cause severe postoperative pain.[1] Various methods for postoperative analgesia management are available, such as systemic opioids, epidural local anesthetic, peripheral nerve block and local anesthetic infiltration analgesia.[2] Use of systemic opioids can cause adverse effects that may affect functional rehabilitation, such as nausea, vomiting, pruritus, sedation and respiratory depression.[3,4] Hypotension, urinary retention, and pruritus are more common in patients with epidural analgesia.[5] In addition, use of long-acting intrathecal opioids causes adverse effects such as bilateral motor block, tremor and hypotension.[6] Systemic and intrathecal methods for postoperative analgesia are gradually being abandoned because of these negative effects.

Anesthesia management involving multimodal analgesic regimens, including regional anesthesia techniques such as femoral nerve block (FNB) and local infiltration analgesia (LIA), is commonly used for TKA.[3,6] Although FNB is widely used in TKA, it can cause weakness of the quadriceps muscle and require use of a knee immobilizer, which may prevent early ambulation and can delay discharge.[7,8]

The saphenous nerve is the largest contributor to sensory perception around the knee, while the adductor canal contains the nerve to the vastus medialis, the medial femoral cutaneous nerve, the medial retinacular nerve, articular branches from the posterior division of the obturator nerve and occasionally the anterior branch of the obturator nerve.[9,10] Although adductor canal block (ACB) can contribute towards motor blockade of the periarticular musculature, its effect on functional weakness of the quadriceps has been reported to be minimal, compared with FNB.[10,11]

One alternative analgesic technique for TKA is periarticular infiltration (PAI) using local anesthetic.[12,13] Periarticular infiltration is commonly used because of its simplicity, but its efficacy for diminishing postoperative pain after TKA is a matter of controversy.[14,15]

OBJECTIVE

The primary aim of this study was to compare postoperative pain scores from periarticular infiltration using levobupivacaine (PAI-L) and ultrasound-guided adductor canal block using levobupivacaine (ACB-L). Its secondary aims were to compare knee ROM, total morphine consumption and a 100-foot walking test data among patients undergoing elective unilateral TKA.

METHODS

This randomized clinical study was reviewed and approved by the Necmettin Erbakan University, Medical Faculty Ethics Committee (reference no. 27.09.2017/146) and was registered in the Australian New Zealand Clinical Trial Registry: ACTRN-12618000438257. After obtaining the participants' written informed consent, 94 patients aged 40-85 years whose American Society of Anesthesiologists (ASA) status was I-III and who had been scheduled to undergo unilateral TKA to treat degenerative joint disease were enrolled in the study.

The exclusion criteria were ASA status IV-V, age under 40 years or over 85 years, presentation of chronic pain syndrome or neuropathic pain, morbid obesity, presence of coagulation disorder, inability to walk without help due to known knee disease, and presence of allergic reactions to the medications used in the study. Another exclusion criterion was initially set as consumption of more than 5 mg/day of oral morphine or equivalent opioids. However, this was subsequently changed (after study registration) because patients did need larger amounts of morphine, so this ceased to be a reasonable exclusion criterion. Therefore, even patients consuming larger amounts of morphine were analyzed in this study.

Participants who were eligible for inclusion in the study were identified from the records before the date of the orthopedic surgery. During the preoperative anesthesia examination, these patients were interviewed. They were invited to participate in the study and they filled out an informed consent form.

A computer-generated randomization sequence was prepared by our statisticians. Each study patient was assigned a study number. To avoid loss of concealment, the group to which each patient was allocated could only be accessed by the researchers after each patient had been registered for surgery. However, since the study groups included analgesia applied in different manners (ACB and PAI), the data thus collected could not be blinded. Two anesthetists performed ACB and PAI, while two other anesthetists collected the data.

Anesthesia and surgical technique

The patients were admitted to the operating room without any premedication. Spinal anesthesia was administered by means of a 22-gauge spinal needle (Atraucan, Braun Germany), consisting of 15 mg (3 ml) of 0.5% spinal bupivacaine (Marcaine, Abbott Laboratories, Chicago, IL, USA) to each patient after both ACB and PAI. All operations were performed by the same surgical team using a similar technique.

Intervention in the ACB-L group

Ultrasound-guided ACB was performed using a linear probe (10-18 MHz) (Esaote MyLab 30 US, Florence, Italy). The probe was placed midway between the inguinal ligament and the medial condyle of the knee under aseptic conditions, with the patient in the supine position, the knee slightly externally rotated and the leg outstretched (frog-leg position). An ultrasonographic image of the saphenous nerve was captured in the adductor canal, laterally to the femoral artery under the sartorius muscle. After negative aspiration, 20 ml of 0.25% levobupivacaine (Chirocaine, Abbott, Elverum, Norway) was administered into the nerve sheath using a 20-gauge, 100-mm, sloped, Teflon-coated unipolar needle (Stimuplex Ultra 360, B. Braun, Melsungen, Germany). The spreading of the local anesthetic spread in the adductor canal was viewed using ultrasonography.

Intervention in the PAI-L group

A total of 40 ml (0.125 mg) of levobupivacaine was infiltrated into the posterior capsule, femur and tibia, medially and laterally to the joint capsule; and into the quadriceps tendon, vastus medialis obliquus, patellar tendon and dermal-epidermal junction.

Postoperative protocol

Each patient received 50 mg of IV dexketoprofen (Arveles, Ufsa, Istanbul, Turkey) in the recovery room. Use of a patient-controlled analgesia (PCA) device for morphine delivery was started, and morphine consumption was recorded at 24 and 48 hours. Antibiotic prophylaxis was continued, consisting of 3×1 g cefazolin (Cefozin, Bilim, Istanbul, Turkey) for 24 hours. The patients were given dexketoprofen every 12 hours and a 1 g paracetamol tablet (Paranox, Sanofi, Istanbul, Turkey) every 8 hours until discharge. Twenty milligrams of IV metoclopramide (Metpamid, Recordati, Istanbul, Turkey) was given only to patients with nausea and vomiting. All patients were fitted with a knee immobilizer between 12 and 24 hours after the operation, until quadriceps muscle function was restored. Physical therapy was started 24 hours after surgery. Use of a continuous passive motion machine (CPM) (Kinetec, Smith & Nephew, Memphis, TN, USA) in a room in the orthopedic department was started with an initial setting of 45 degrees. CPM was used to the patients on

the second postoperative day, for two-hour periods. The patients were also encouraged to starting on active motion of the knee.

Clinical evaluation

Sociodemographic and clinical data such as age, sex, weight, height, body mass index (BMI), ASA status, side operated, length of operation and duration of tourniquet use were recorded. Pain levels at rest and during active physical therapy were recorded during the preoperative period, 30 minutes after the operation and 2, 6, 12, 24, 36 and 48 hours after the operation, according to scores on a visual analogue scale (VAS). Postoperative maximal ranges of flexion and extension on the 1st, 2nd and 7th days, and in the 2nd and 6th weeks, were also recorded. In addition, total morphine consumption and a 100-foot walking test data during the preoperative period, at 24 and 48 hours after the operation and at the time of the first requirement for analgesic were recorded.

The sample size calculation was based on a pilot study that we conducted on sixteen patients (whose data were not included in the present study). In this prior study, the mean difference and standard deviation (SD) of the VAS scores 24 hours after the operation between the ACB and PAI groups were 0.40 and 0.19, respectively. From this, it was determined that 39 subjects would be required to reach an α value of 0.05 and a power of 85%. Moreover, based on data from a retrospective study by Perlas et al.,[16] the primary outcome SD was assumed to be approximately 3.0. It was estimated that the attrition rate due to canceled surgery or reasons of late patient ineligibility could be up to 20% and, therefore, to account for this, the final sample size selected was n = 94 (47 per group).

The statistical analyses in this study were performed using the Statistical Package for the Social Sciences (SPSS) 20.0 software. Continuous variables were presented in the form of mean ± standard deviation or error. The Kolmogorov-Smirnov normality test was used to assess continuous variables. Group comparisons on the variables that showed normal distribution were performed using one-way analysis of variance. Mann-Whitney U variance analysis was used for discrete numerical variables that did not show normal distribution. Relationships between the categorical variables were determined by preparing crosstabs and using the chi-square (χ^2) test. $P < 0.05$ was accepted as statistically significant.

RESULTS

A total of 94 patients underwent elective unilateral TKA procedures between March 2017 and September 2017. A total of 14 patients were excluded for the following reasons: age over 85 years (n = 3); delay in admission to subacute rehabilitation (n = 3); admission to the intensive care unit because of respiratory failure (n = 1); bilateral TKA was performed (4); and not wishing to participate (n = 3). Thus 80 patients were enrolled. One patient in the PAI group was further lost to follow-up because of non-attendance at follow-ups, and was therefore not included in the study analysis. Detailed information on enrollment of patients into the study is depicted in the CONSORT flow diagram in **Figure 1.** The patients' demographic profiles and clinical characteristics were similar ($P > 0.05$) (**Table 1**).

Over the first 48 postoperative hours, the VAS data at rest (mean ± standard error) for the ACB-L and PAI-L groups respectively were as follows: at 30 min, VAS 0.30 ± 0.08 and 1.38 ± 0.10 ($P < 0.001$); at 2nd hour, VAS 0.58 ± 0.11 and 1.35 ± 0.10 ($P < 0.001$); at 6th hour, VAS 1.08 ± 0.11 and 1.92 ± 0.09 ($P < 0.001$); at 12th hour, VAS 1.80 ± 0.14 and 2.38 ± 0.15 ($P = 0.012$); at 24th hour, VAS 2.30 ± 0.16 and 2.80 ± 0.12 ($P = 0.028$); at 36th hour, VAS 1.80 ± 0.10 and 2.35 ± 0.12 ($P = 0.002$); and at 48th hour, VAS 2.00 ± 0.17 and 2.55 ± 0.12 ($P = 0.016$) (**Figure 2**).

Over the first 48 postoperative hours, the VAS data with activity (mean ± standard error) for the ACB-L and PAI-L groups respectively were as follows: at 30 min, VAS 0.98 ± 0.09 and 2.40 ± 0.13 ($P < 0.001$); at 2nd hour, VAS 0.95 ± 0.11 and 2.25 ± 0.13 ($P < 0.001$); at 6th hour, VAS 1.85 ± 0.13 and 2.52 ± 0.17 ($P = 0.008$); at 12th hour, VAS 2.25 ± 0.15 and 2.80 ± 0.15 ($P = 0.022$); at 24th hour, VAS 2.70 ± 0.15 and 3.20 ± 0.14 ($P = 0.027$); at 36th hour, VAS 1.93 ± 0.19 and 2.43 ± 0.12 ($P = 0.039$); and at 48th hour, VAS 1.83 ± 0.17 and 2.43 ± 0.12 ($P = 0.025$) (**Figure 3**).

With the exceptions of the preoperative scores and the postoperative 2nd and 6th week scores, the ACB-L group had less range of flexion and extension than the PAI-L group on the 1st, 2nd and 7th days after surgery. There were significant differences in range of flexion and extension between the groups ($P < 0.05$) (**Table 2**).

Differently to the preoperative measurements, the time taken to perform the 100-foot walking test was significantly longer in the ACB-L group than in the PAI-L group at 24 and 48 hours postoperatively (218.9 ± 33.9 versus 192.2 ± 24.6 sec and 139.8 ± 19.5 versus 112.0 ± 16.4 seconds, respectively; $P < 0.001$) (**Table 2**).

The total morphine consumption was significantly lower in the ACB-L group than in the PAI-L group at 48 hours postoperatively (21.9 ± 8.9 versus 33.0 ± 9.5 mg; $P < 0.001$) (**Table 3**). The times of first requirement for analgesia in the ACB-L and PAI-L groups were 405.3 ± 41.0 and 316.7 ± 36.3 minutes, respectively. The difference between the groups was significant ($P < 0.001$) (**Table 3**).

DISCUSSION

In the present study, the ACB-L group had better postoperative analgesia both at rest and during active mobilization, compared with the PAI-L group over the first 48 hours after elective unilateral TKA. In addition, less morphine consumption was seen in the ACB-L group. However, during the first week, we found that the PAI-L group presented better flexion and extension knee movements. Moreover, the PAI-L group achieved better results in the walking test than did the ACB-L group. A number of studies

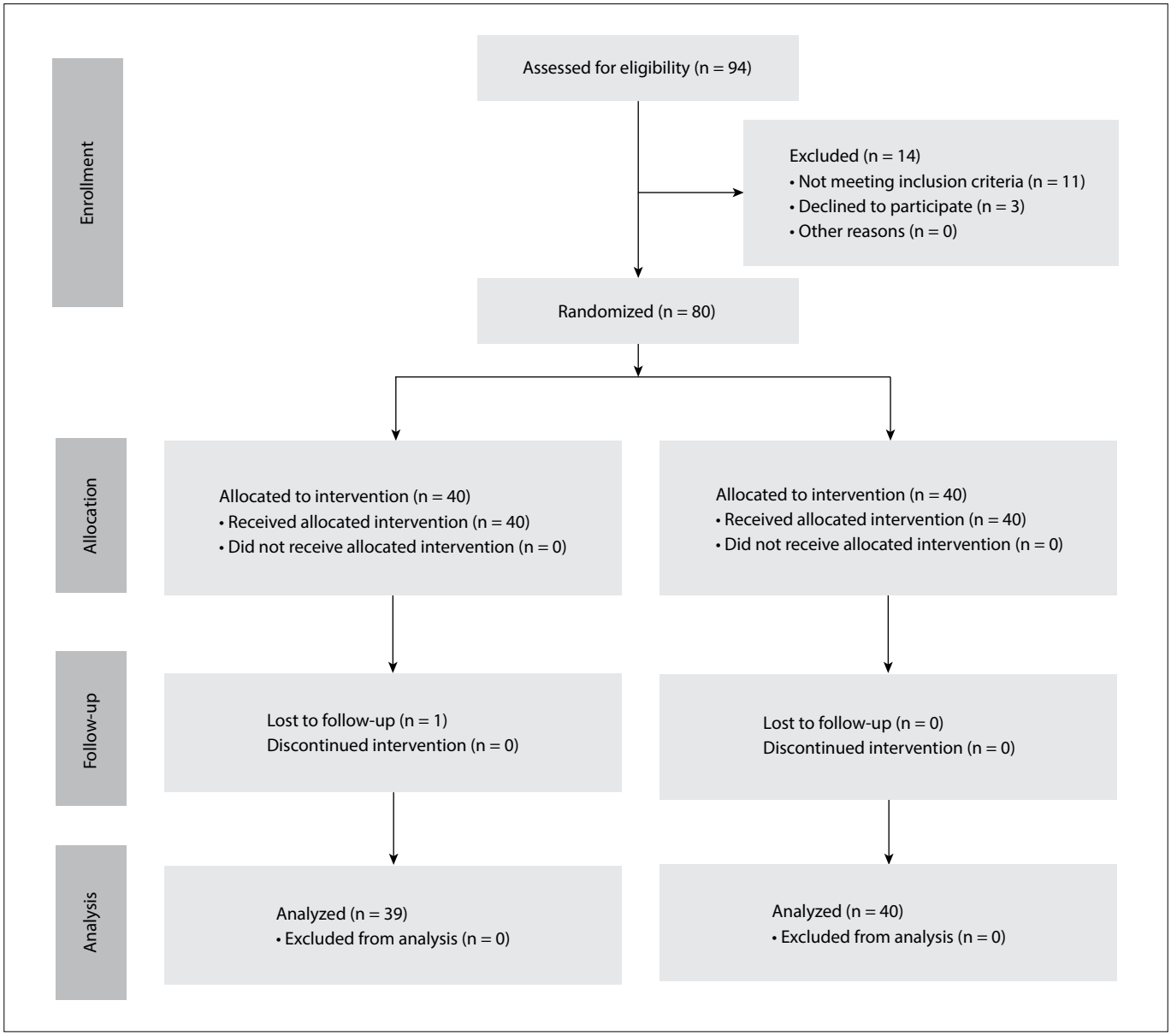

Figure 1. CONSORT flowchart diagram. ACB-L, adductor canal block using levobupivacaine; PAI-L, periarticular infiltration using levobupivacaine.

Table 1. Patients' characteristics

	ACB-L group n = 39	PAI-L group n = 40	P
Age (years)	69.1 ± 7.3	68.5 ± 7.5	0.697
Gender (F/M)	28/12	30/10	0.710
Weight (kg)	90.5 ± 10.5	88.4 ± 12.4	0.418
Height (cm)	165.9 ± 6.5	165.7 ± 6.4	0.904
BMI (kg/m^2)	32.5 ± 1.2	32.0 ± 0.4	0.917
ASA (I/II/III)	3/31/6	2/29/9	0.586
Side of surgery (R/L)	22/18	23/17	0.823
Duration of surgery (minutes)	82.3 ± 16.9	84.9 ± 14.8	0.489
Duration of tourniquet use (minutes)	89.0 ± 16.6	90.8 ± 19.6	0.532

Values are presented as mean ± standard deviation or number of patients. ACB-L = adductor canal block using levobupivacaine; PAI-L = periarticular infiltration using levobupivacaine; F/M = female/male; BMI = body mass index; ASA (I/II/III) = American Society of Anesthesiologists status grade I/II/III; R/L = right/left.

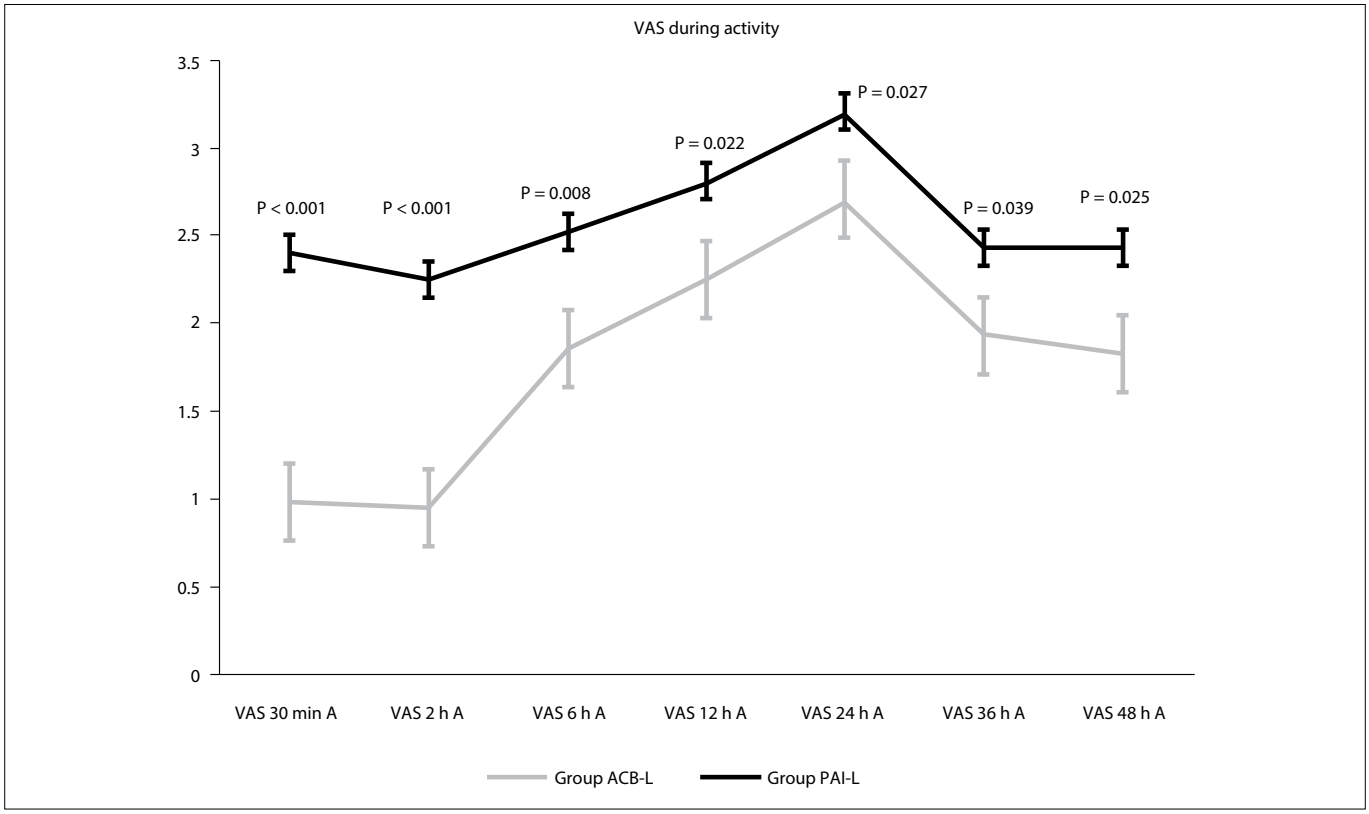

Figure 2. Comparison of postoperative visual analogue scale (VAS) scores during activity (A) between the two groups. There were statistical differences in VAS scores at all time points.

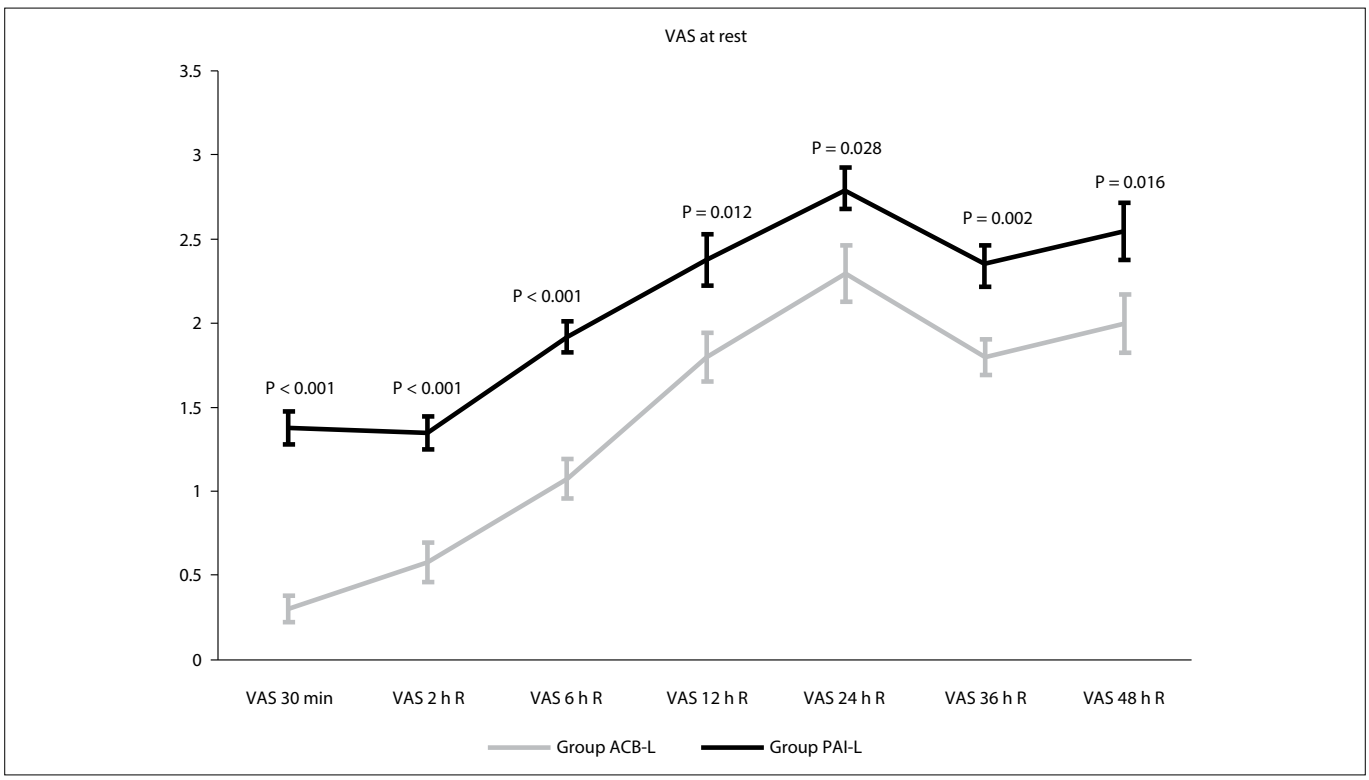

Figure 3. Comparison of postoperative visual analogue scale (VAS) scores at rest (R) between the two groups. There were statistical differences in VAS scores at all time points.

have compared use of PAI and nerve block by means of local anesthetic agents for pain control in TKA,[2,6,17] but our study was the first to use levobupivacaine in comparing ACB and PAI.

The adductor canal contains several nerve branches that supply sensory innervations to the knee. These nerve branches consistently include the saphenous nerve (which innervates the infrapatellar skin and the anterior knee capsule) and a distal branch of the motor nerve to the vastus medialis (which provides sensory innervation to the superomedial aspect of the knee and the knee capsule).[16] Ultrasound-guided ACB is used as a theoretical alternative to FNB because the latter has adverse effects such as quadriceps weakness, lack of early ambulation and limitation of physical therapy. With ACB, a rather pure sensory block is obtained instead of the motor block on the knee, while equivalent pain control is achieved.[9,18]

Periarticular local infiltration of anesthetic is one of the most important procedures in multimodal pain control protocols.[19] This analgesic technique has been specially developed to provide early mobilization and discharge, to avoid sedation and to facilitate rapid physiological recovery after lower-limb arthroplasty. Contrary to femoral nerve block, periarticular infiltration does not inhibit quadriceps function and, at the same time, it reaches the posterior capsule of the knee joint.

Chaumeran et al. conducted a study on FNB and PAI using bupivacaine. They found that the VAS scores and ROM values at rest and in movement were similar, but that PAI gave better results than FNB over the walking distance.[20]

In recent studies on liposomal bupivacaine, the VAS scores, total morphine consumption and ROM values were found to be similar in the PAI and FNB groups until the 48th postoperative hour.[17,21,22] Yu et al. showed that FNB using liposomal bupivacaine provided better analgesia but less walking distance than did PAI.[23]

In a variety of studies that compared use of ropivacaine for ACB and PAI, the VAS scores at rest and during activity, the

Table 2. Range of motion (ROM) in flexion and extension and time taken to perform 100-foot walking test before the operation and at different times after the operation, compared between the two groups

	ACB-L group n = 39	PAI-L group n = 40	P
Range of motion in flexion (degrees)			
Preoperative	109.2 ± 6.9	108.5 ± 6.7	0.625
Postoperative 1st day	51.1 ± 6.4	69.3 ± 6.7	< 0.001
2nd day	64.3 ± 6.2	86.3 ± 10.9	< 0.001
1st week	96.2 ± 7.7	104.7 ± 11.9	< 0.001
2nd week	121.7 ± 6.4	124.2 ± 5.7	0.071
6th week	125.6 ± 6.8	125.6 ± 4.2	0.908
Range of motion in extension (degrees)			
Preoperative	4.3 ± 3.2	4.5 ± 3.3	0.866
Postoperative 1st day	11.0 ± 3.6	8.3 ± 3.0	0.001
2nd day	9.2 ± 2.6	4.8 ± 2.1	< 0.001
1st week	4.2 ± 2.4	1.2 ± 2.1	< 0.001
2nd week	0.3 ± 1.3	0.2 ± 1.1	0.649
6th week	0.2 ± 1.1	0.2 ± 1.1	1.000
Time taken to perform 100-foot walking test (seconds)			
Preoperative	82.2 ± 12.3	79.1 ± 13.3	0.392
Postoperative 24th hour	218.9 ± 33.9	192.2 ± 24.6	< 0.001
Postoperative 48th hour	139.8 ± 19.5	112.0 ± 16.4	< 0.001

Values are presented as mean ± standard error.
ACB-L = adductor canal block using levobupivacaine; PAI-L = periarticular infiltration using levobupivacaine.

Table 3. Time that elapsed until first requirement for analgesia and the total amount of morphine consumed over the first 48 hours after surgery

	ACB-L group n = 39	PAI-L group n = 40	P
Time that elapsed until first requirement for analgesia (minutes)	405.3 ± 4.1	316.7 ± 36.3	< 0.001
Total amount of morphine consumed via PCA (mg)	21.9 ± 8.9	33.0 ± 9.5	< 0.001

Values are presented as means ± standard deviation.
ACB-L = adductor canal block using levobupivacaine; PAI-L = periarticular infiltration using levobupivacaine; PCA = patient-controlled analgesia.

morphine consumption and the walking distance results were similar in the two groups until 48 hours postoperatively.[16,24] In contrast to the studies of Perlas et al.[16] and Sawhney et al.[24], our study found that the total morphine consumption was significantly lower than the ACB-L group at 48 hours postoperatively. In a study by Li et al. that compared three groups (ACB, FBN and PAI), these authors reported that the VAS values were the same at rest and during movement between the three groups, and that ACB and PAI were also the same in terms of muscle strength.[25]

Levobupivacaine is the S (-) enantiomer of bupivacaine, with less cardiac toxicity and motor block than bupivacaine, but longer duration of action.[26] Kovalak et al. reported that use of continuous femoral nerve block (CFNB) gave rise to superior VAS scores at rest and during activity, better passive and active ROM, lower total opioid consumption and better two-minute walking test results than did use of PAI.[27] However, in their study, levobupivacaine infiltration was administered to the knee joint capsule of all patients in both groups. In a study by Wall et al.,[28] it was reported that the effects of levobupivacaine for FNB and PAI on postoperative VAS values were similar. The authors[28] showed that ACB gave rise to better VAS scores at rest and during activity than did FNB, over the first 48 postoperative hours.

Preoperative range of motion is the biggest indicator of postoperative range of motion. Many factors determine the range of motion after surgery. Rehabilitation programs after total knee arthroplasty should not be halted until at least 90° of knee flexion has been achieved, so that patients can resume normal social life.[29] Ritter et al. found that age, preoperative range of motion, intraoperative range of motion and posterior capsule relaxation during surgery were important. They explained that after the first year, there was no further effect on the degree of flexion from the passage of time, and that the range of motion acquired in the first six months was important.[30] Consequently, after knee prosthetic surgery, the preoperative range of motion, the degree of relaxation of the posterior capsule during surgery, the patient's age and the etiology of osteoarthritis take on importance.

The ability of a patient to perform functional activities, such as walking, rising from a chair and climbing stairs, depends on sufficient postoperative knee ROM. Isometric quadriceps exercises are started on the first postoperative day in our service. Knee ROM exercises for the first 3 days 0-30° flexion, at least 90° knee flexion between days.[31] A meta-analysis on the range of knee flexion that compared use of periarticular local infiltration with FNB did not find any significant difference between these two groups.[32] However, another meta-analysis suggested that post-TKA patients who underwent ACB showed better outcomes regarding ROM than did those who underwent FNB, throughout the first 72 h (i.e. post-anesthesia and after 24, 48 and 72 hours).[33] This latter meta-analysis showed that PAI provided better flexion and extension ROM values postoperatively on the 1st and 2nd days and after the 1st week than did ACB[34].

According to the common milestones used in relation to TKA treatments, patients who can walk 100 feet (= 30.48 meters) with an assistive device, go to the toilet, make transfers, perform basic daily activities and do home exercise programs independently are in a condition in which they can be discharged home. In the present study, the results from 100-feet walking tests over the first 48 postoperative hours were better with use of PAI than with use of ACB. A placebo-controlled randomized trial on ACB suggested that administration of ropivacaine into the adductor canal provided effective analgesia, such that it significantly reduced pain and improved postoperative mobility, compared with placebo.[24]

In our study, we found that the VAS scores were better and the total amount of morphine consumed was lower in the ACB-L group than in the PAI group. However, the ROM data and walking results were shown to be superior in the PAI-L group. These results can be explained by the blocking of the saphenous nerve in the adductor canal through use of levobupivacaine over the first 48 hours after the operation. However, a possible attenuating effect on quadriceps muscle strength from ACB also accounts for the knee ROM results and the walking results in the PAI-L group.[34,35]

The main limitation of the current study was the inability to blind both the participants and the physicians to comparisons between peripheral nerve blockade and periarticular injection. This lack of blindness may have introduced some risk of bias from both the patients and the physicians. The outcome assessments from the adjudicators and all the statistical analyses were conducted in a blinded manner. In addition, the impossibility of measuring quadriceps muscle power before and after the operation using special instruments was another limitation. If this had been possible, the evaluation between the ACB-L and the PAI-L groups could have been more objective.

CONCLUSION

This randomized clinical trial found that after total knee arthroplasty, ultrasound-guided adductor canal block with levobupivacaine was associated with shorter time taken to perform 100-foot walking test (24 hours post-operatively) and lower post-operative consumption of morphine when compared to periarticular infiltration with levobupivacaine. However, no difference between these interventions was found for range of knee motion after six weeks, pain at rest after 48 hours and pain during activities after 48 hours.

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Chest pain score: a novel and practical approach to angina pectoris. A diagnostic accuracy study

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ABSTRACT

BACKGROUND: The chest pain classifications that are currently in use are based on studies that are several decades old. Various studies have indicated that these classifications are not sufficient for determining the origin of chest pain without additional diagnostic tests or tools. We describe a new chest pain scoring system that examines the relationship between chest pain and ischemic heart disease (IHD).

DESIGN AND SETTING: Cross-sectional study conducted in a tertiary-level university hospital and two public hospitals.

METHODS: Chest pain scores were assigned to 484 patients. These patients then underwent a treadmill stress test, followed by myocardial perfusion scintigraphy if necessary. Coronary angiography was then carried out on the patients whose tests had been interpreted as positive for ischemia. Afterwards, the relationship between myocardial ischemia and the test score results was investigated.

RESULTS: The median chest pain score was 2 (range: 0-7) among the patients without IHD and 6 (1-8) among those with IHD. The median score of patients with IHD was significantly higher than that of patients without IHD (P = 0.001). Receiver operating characteristic analysis showed that the score had sensitivity of 97% and specificity of 87.5% for detecting IHD.

CONCLUSION: We developed a pre-test chest pain score that uses a digital scoring system to assess whether or not the pain was caused by IHD. This scoring system can be applied easily and swiftly by healthcare professionals and can prevent the confusion that is caused by other classification and scoring systems.

INTRODUCTION

Chest pain is the most common complaint leading to hospital admission[1,2] and is a common symptom of numerous diseases.[3] All physicians, and particularly cardiologists, want to rule out ischemic heart disease (IHD) as fast as possible when they are confronted with a patient complaining of chest pain. The patient's history is crucial for the diagnosis of IHD; therefore, history-taking needs to be done with the utmost care.[4]

Currently, the chest pain classification defined by Diamond in the 1980s is still used (with minor changes) to determine whether or not the cause of the chest pain is myocardial ischemia.[5] Three features of the pain are evaluated in this classification: (1) the duration of the chest pain (which can range from 2 to 15 minutes) and degree of discomfort, and whether it is located in the retrosternal region; (2) whether the discomfort was triggered by effort or emotional stress; and (3) whether the pain promptly disappeared after rest and/or nitrate administration. If the characteristics of the chest pain include all three features mentioned above, the pain is classified as "typical chest pain". If only two of these features are present, the pain is classified as "atypical chest pain". If only one or none of these features is present, the pain is classified as "non-cardiac chest pain".

However, this classification is not sufficient for making the diagnosis of ischemia in the absence of stress tests.[6,7] Furthermore, these statements may result in erroneous results among elderly patients and those with diabetes mellitus, because pain perception may be impaired in these groups.[8,9] Another problem is that this classification is largely subjective, which results in disagreements among physicians and even among cardiologists, as to what constitutes "typical/atypical" chest pain.

Symptoms that may be typical for IHD can be overlooked in cases with prolonged resting angina or angina that was triggered by an effort so minimal that the patients did not realize that the symptom was caused by this effort. Furthermore, lung diseases or peripheral arterial diseases may restrict exercise capacity and the complaints of these patients may very well subside with rest. These disorders may cause increases in symptoms of chest pain during exercise and

decreases in discomfort during resting period, thus causing high suspicion of angina pectoris, even though the origin of the symptoms was non-cardiac.

In addition to these problems, as mentioned in several studies and as seen in our own clinical experience, the nomenclature of "typical", "atypical" and "non-cardiac" is often insufficient and may lead to misunderstandings.[6] Therefore, it is apparent that a new evaluation method that can accurately identify cardiac chest pain without any such pitfalls is required.

OBJECTIVE

In this study, our aim was to create a chest pain score that was accurate, swift, more comprehensive and more objective in determining whether or not the chest pain in question was related to IHD.

METHODS

Study group

All patients who presented to the cardiology clinics or emergency departments (ER) of Eskisehir State Hospital (a secondary-level healthcare center) or Canakkale Onsekiz Mart University Hospital (a tertiary-level healthcare center) complaining of chest pain between June 2017 and February 2018 were included in this study. Patients with prior ST segment elevation myocardial infarction, pregnant patients and individuals under 18 years of age were excluded from the study.

After exclusion of any patients who refused to participate in the study and those presenting exclusion criteria, data were collected from the remaining subjects, as our sample of patients. A cardiology specialist applied the chest pain score to all subjects through face-to-face interviews.

Ethical approval

Implementation of this study was endorsed by our institution's Internal Review Board (date: September 27, 2017; number: 2017-15).

Risk score development

After the patients had been assessed for typical risk factors such as age, gender, diabetes mellitus, hypertension, coronary artery diseases (CAD) and smoking status, the chest pain score developed for this study was applied to them.

Data collection was planned before the index test was performed and before the reference standard was implemented. A group consisting of 10 experienced cardiology specialists was given the task of creating the scoring system. This group initially determined which cardiac complaints were typical, according to their own clinical experience, and this was followed by meticulous evaluation of the literature on this topic.

A total of 10 major questions regarding chest pain properties and the patients' characteristics were formulated and evaluated by this group of 10 cardiologists. Through this assessment, unnecessary questions were omitted, such that the number of questions was reduced to five. The test consisting of these five questions was then applied to a preliminary group of 20 patients and the questions were then weighted according to the results from this test.

The final chest pain scoring system that was proposed in the present study thus consisted of five questions that could only be answered as "yes" or "no". "No" answers were scored as zero points. For the first and fifth questions, a "yes" answer was scored as 2 points. For the second and fourth questions, a "yes" answer was scored as 1 point. The third question consisted of two sub-questions: for each sub-question, a "yes" answer was counted as 1 point, such that the maximum score was 2 points. After the total score from the questions had been obtained, 1 point was added to the score of patients with diabetes and/or those older than 75 years of age (**Table 1**).

After final scores for the patients evaluated in this study had been obtained, patients who had been found to present a high risk of ischemic heart disease underwent coronary angiography without a stress test. The remaining patients then underwent a treadmill stress test. The treadmill stress test was considered positive for patients who presented 1 mm of horizontal or downsloping ST segment depression in three consecutive leads, or ST segment elevation, or chest pain triggered by the stress test. Myocardial perfusion scintigraphy (MPS) was performed on the patients with suspicious treadmill stress test results. MPS imaging was performed using the imaging protocol developed by the American Society of Nuclear Cardiology.[10] Lastly, coronary angiography was performed on patients who had positive non-invasive ischemia test results.

The patients were divided into three groups depending on the results from coronary angiography. Patients with > 50% stenosis in the left main coronary artery (LMCA) or > 70% stenosis in any

Table 1. Chest pain score

Chest pain:	No	Yes
1. Is it in the form of pressure, fullness, burning, discomfort or tightness in your chest?	0	2
2. Is the duration of chest pain less than 10-15 minutes but longer than about a minute?	0	1
3. a) Is it behind the sternum? (spreading on the sternum, not localized) b) Is it in the left or right arm in the ulnar part, the lower cannula, the epigastric region, the scapula region, or does it radiate to these regions?	0 0	1 1
4. Is it accompanied by shortness of breath, sweating, nausea, fatigue or syncope?	0	1
5. Is it triggered by effort or emotional stress and eased by rest or nitrates?	0	2

One point is added to the sum if diabetes mellitus is present and/or the patient is > 75 years old.

vessel with a diameter > 2 mm were classified as the "critical coronary artery disease" group. Patients with any lesion not classified as critical or patients with slow coronary flow were classified as the "non-critical coronary artery disease" group. Patients with normal coronary arteries were classified as the "normal coronary arteries" group. The ischemia-positive group included the critical CAD patient group, the non-critical CAD patient group and the group of patients whose non-invasive stress tests were positive. Patients with a positive stress test and normal coronary arteries were included in the ischemia-negative group.

Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS) software for Windows, version 15.0 (IBM Corp. Armonk, NY, USA), was used for data analysis. The demographic characteristics of the study group were reported using descriptive statistics (frequencies, proportions, means and medians) and dispersion measurements (standard deviation and minimum-maximum). Initially, the normality of the total scores was tested using the Kolmogorov-Smirnov normality test and graphs. Frequency data were analyzed by using the chi-square test as univariate analysis. Receiver operating characteristic (ROC) analysis was used for calculating the sensitivity, specificity and positive and negative predictive values of cutoff scores from the scale. Median scores were compared using the Mann-Whitney U and Kruskal-Wallis tests. If any comparison yielded a P value less than 0.05, it was considered statistically significant.

RESULTS

A total of 484 patients were included in this study. The patients' mean age (± standard deviation, SD) was 52.0 ± 15.0 years (minimum-maximum: 18-84) for the entire study group, while the mean for males was 52.0 ± 14.0 years and the mean for females was 52.0 ± 15.0 years (P = 0.585). The study group consisted of 229 males (47.3%) and 255 females (52.7%).

The median chest pain score of those with positive treadmill stress test results was found to be 6, while the median score of the patients with negative results was 1. The scores of those who had positive exercise test results were significantly higher than the scores of those who had negative results (P < 0.001).

Regarding MPS results, those with positive results had a median score of 6, while those with negative results had a median score of 3. The chest pain scores of MPS-positive patients were significantly higher than the scores of MPS-negative patients (P < 0.001).

Comparison of the chest pain scores of patients with normal carotid arteries and those with critical and non-critical CAD showed that the median score of the critical and non-critical CAD group (median score: 6) was significantly higher than the score of those with normal carotid arteries (median score: 3) (P < 0.001).

The median chest pain scores for hypertensive and non-hypertensive patients were 3 and 2, respectively; while the scores for diabetic and non-diabetic patients were also found to be 3 and 2 respectively. Statistical analysis revealed that the scores for hypertensive and diabetic patients were significantly higher than the scores for those without the respective conditions (P < 0.001). Furthermore, it was observed that the chest pain score increased with age and that there was a significant relationship between age and chest pain score (P = 0.001). Regarding sex, the median chest pain scores were 3 and 2 for males and females, respectively. The chest pain scores of males were significantly higher than those of females. There was no significant relationship between chest pain score and the history of CAD, smoking status, peripheral artery disease or heart failure. The chest pain score was 6 for IHD patients and 2 for non-IHD patients. The chest pain score for IHD patients was significantly higher (P = 0.001). The relationships between ischemia and chest pain score are shown in **Table 2**.

The patients were divided into four groups according to chest pain score, presence of IHD and pre-test risk factors for IHD (**Table 3**). The first group was defined as "low IHD risk", consisting

Table 2. Relationship between ischemia and chest pain score

Questions	Ischemia-negative n (%)	Ischemia-positive n (%)	x^2; P
Question 1			
0 points	278 (57.4%)	10 (2.1%)	**128,186**
2 points	106 (21.9%)	90 (18.6%)	**< 0.001**
Question 2			
0 points	203 (41.9%)	29 (6.0%)	**18,105**
1 point	181 (37.4%)	71 (14.7%)	**< 0.001**
Question 3			
0 points	231 (47.7%)	9 (1.9%)	
1 point	132 (27.3%)	44 (9.1%)	**141,296**
2 points	21 (4.3%)	47 (9.7%)	**< 0.001**
Question 4			
0 points	322 (66.5%)	73 (15.1%)	**6,228**
1 point	62 (12.8%)	27 (5.6%)	**0.013**
Question 5			
0 points	360 (74.4%)	30 (6.2%)	**206,037**
1 point	24 (5.0%)	70 (14.5%)	**< 0.001**

Table 3. Risk groups and relationships with ischemia

Score points	Ischemia-negative n (%)	Ischemia-positive n (%)	x^2; P
0-2 points (Low risk)	255 (52.7%)	2 (0.4%)	**347,954 < 0.001**
3-4 points (Moderate risk)	113 (23.3%)	8 (1.7%)	
5-6 points (High risk)	15 (3.1%)	57 (11.8%)	
7-8 point (Very high risk)	1 (0.2%)	33 (6.8%)	

of patients with scores of 0-2. There were two IHD patients and 255 non-IHD patients in the first group (2:255). The second group consisted of patients with a score of 3-4 and was defined as the "moderate IHD risk" group. There were eight patients with IHD and 113 without IHD in this group (8:113). The third group included patients with a score of 5-6 and was defined as the "high IHD risk" group. The ratio of patients with IHD (n = 57) to those without IHD (n = 15) in this group was 57:15. The fourth group consisted of patients with a score of 7-8 and was defined as the "very high IHD risk" group. The ratio of patients with IHD (n = 33) to those without IHD (n = 1) in this group was 33:1. There were significant differences between the groups in terms of IHD (P < 0.001).

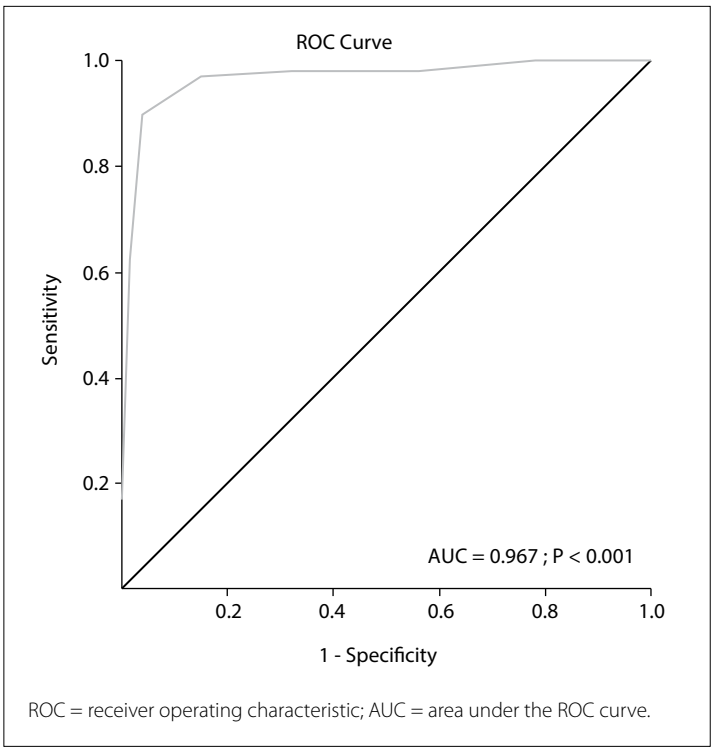
We also performed ROC curve analysis for each of the questions and for the total score. The results showed that a chest pain score threshold of 4.5 demonstrated sensitivity of 90% and specificity of 95.83% for detecting IHD, while the positive predictive value (PPV) and negative predictive value (NPV) were found to be 84.91% and 97.35%, respectively (**Figure 1**). The ROC analysis also revealed that question 4 could not differentiate between patients with and without IHD; however, when the analysis was repeated without question 4, significantly lower specificity and PPV were observed. Therefore, although the question itself could be considered unsuccessful, it was effective in the overall results and was not omitted (**Table 4**).

DISCUSSION

In this study, we applied a chest pain scoring system consisting of five questions, to patients who had complaints of chest pain, to determine whether or not the chest pain originated from IHD. The study was initially planned because we noticed that the classical classifications for chest pain (typical, atypical and non-cardiac) were insufficient without additional stress tests.[6,7] Furthermore, Luke et al. reported that typical angina patients may not have inducible myocardial ischemia, while myocardial ischemia may be induced in patients with atypical angina, which means that the current nomenclature can lead to serious errors.[6] Therefore, we aimed to create a better alternative to the current chest pain score system.

The classical chest pain classification created by Diamond suggests that two positive answers among the three questions that evaluate the association between exercise and pain (except the first question) are enough to determine that the source of pain is myocardial injury. However, in cases of acute coronary syndrome, pain may be triggered without stress or exertion.[11-13] A study of the literature concerning stable angina pectoris revealed that vasospastic angina (a type of resting angina) is considered to be stable angina.[14,15] However, this pain type is considered non-cardiac according to the aforementioned classical chest pain classification.

Another widely accepted chest pain classification score, the WHO-Rose angina questionnaire,[16] is similar to the Diamond classification in terms of pain evaluation. This questionnaire was



ROC = receiver operating characteristic; AUC = area under the ROC curve.

Figure 1. ROC curve of total score (cutoff: 4.5).

Table 4. ROC curve analysis results

	Sensitivity	Specificity	PPV	NPV	Area under the ROC curve				P	Cutoff
					Area	Standard error	Confidence interval			
Total score	90.00	95.83	84.91	97.35	0.967	0.011	0.946	0.988	< 0.001	4.5
Question 1	90.00	72.40	45.92	96.53	0.812	0.023	0.768	0.856	< 0.001	1.0
Question 2	71.00	52.86	28.17	87.50	0.619	0.031	0.559	0.679	< 0.001	0.5
Question 3	91.00	60.16	37.30	96.25	0.825	0.023	0.779	0.870	< 0.001	0.5
Question 4	27.00	83.85	30.34	81.52	0.554	0.033	0.489	0.620	0.094	0.5
Question 5	70.00	93.75	74.47	92.31	0.819	0.028	0.763	0.875	< 0.001	1.0
Total score (without Q4)	97.00	87.50	66.90	99.12	0.964	0.012	0.941	0.987	< 0.001	3.5

ROC = receiver operating characteristic; PPV = positive predictive value; NPV = negative predictive value.

first introduced by Rose et al. in the 1970s and was later adopted by the World Health Organization (WHO), hence the name. In the following years, the WHO-Rose angina questionnaire was shortened and the final form comprised three questions.[16] However, this questionnaire also overlooks cases in which patients may misinterpret their pain due to factors such as age and diabetes.

Given these facts, we aimed to develop a chest pain scoring system that would inherently solve this problem and could be implemented by all physicians regardless of specialty, and also by other medical staff. The proposed chest pain score is a swift and easy method for determining whether the chest pain in question is caused by myocardial injury, and it can be used in both the ER and the outpatient setting. The scoring system in this study can be used to assess patients' risk of ischemia and can group patients based on these scores.

In this scoring system, we tried to evaluate the association between patients' complaints and the presence of ischemia, without initially considering risk factors for cardiovascular diseases. In establishing this score, we took into account the four features of chest pain, as described in the European Cardiology Community guidelines: the characteristics of the pain, its location and extent, its duration and its relationship with exercise; while also evaluating other symptoms that accompany chest pain.[17]

In the past, various scoring systems for evaluating chest pain were proposed.[18] However, the majority of these scoring systems included risk factors, electrocardiography findings and laboratory results (such as troponin levels).

The present chest pain assessment score is the first, since publication of the chest pain classification of 1983,[5] to classify pain and examine its relationship with ischemia via questions that focus only on chest pain and its characteristics. We used this score to calculate the likelihood of pre-test ischemia from symptoms alone and to determine numerical values indicating the necessity for non-invasive tests. We also tried to define standard expressions that would be easier to understand in all healthcare environments, instead of the current "typical, atypical and non-cardiac" classifications, through examining the likelihood of ischemia using four separate risk groups categorized as low, medium, high and very high. The results from our analysis demonstrated that the proposed chest pain score increases with increasing likelihood of ischemic heart disease.

Old age and diabetes are risk factors for IHD but are also misleading factors for physicians because they can affect the anamnesis of patients. Since chest pain and insufficient capacity for exertion can be explained by diabetes and old age, their association with ischemia may be overlooked. Experiencing pain during exertion is a very specific finding in IHD, but this is difficult to detect in elderly patients because they are often not active enough to sense effort-related chest pain. It has been reported in many studies on diabetes and the elderly that pain can be expressed atypically even when it is associated with IHD.[8,9,19] However, the classical chest pain classification and the WHO-Rose questionnaire do not take these characteristics into account, and therefore may cause misdiagnosis. Through the chest pain score in this study, we believe that physicians' ability to identify ischemia in such patients is increased, even though we do not evaluate risk factors in the scoring system. This particular feature is achieved through accurate evaluation of atypical pain in patients whose cases could be overlooked if the classical chest pain questionnaires are used, because of differences in pain perception among patients.

The ROC analysis on the scoring system showed that this system has very high sensitivity and specificity for detecting IHD. Although question 4 was not successful on its own, for discriminating whether pain was associated with IHD, it was effective within the overall sensitivity and specificity of the scoring system. Therefore, the question was not omitted.

Although men were found to have significantly higher chest pain scores in the current study, we did not attempt to change our scoring system to evaluate differences between the sexes. This was because various studies have shown that there is no significant correlation between sex and the explanations for typical and atypical pain in patients with angina.[20]

This study was conducted with 484 patients in two separate centers. This may be considered to be a limitation of the study. Repeating this work with larger populations and different ethnic groups might yield different results. In this study, we used coronary angiography in an attempt to exclude false positive results from non-invasive tests, but the results may still have been impaired by false negative tests. However, we were unable to perform coronary angiography to exclude false negative results due to ethical concerns. There is a need to support this work through using larger populations and multinational studies in which patients are followed for longer periods.

CONCLUSION

We developed a chest pain score that can easily and rapidly be applied by all healthcare workers, and which focuses solely on patients' chest pain characteristics. The results from ROC analysis indicate that the proposed chest pain scoring system is very successful in identifying patients with pain due to cardiac injury. We believe that this scoring system can be used safely to accurately identify IHD in patients who present chest pain, without the use of non-invasive stress tests.

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Fine particulate matter and ischemic heart diseases in relation to sex. An ecological time series study

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ABSTRACT

BACKGROUND: Exposure to some air pollutants is associated with cardiovascular diseases. The objective of this study was to quantify the effect of exposure to fine particulate matter in hospitalizations due to ischemic heart disease and the costs to the healthcare system.

DESIGN AND SETTING: Time-series ecological study conducted in Taubaté, Brazil.

METHODS: Data on hospitalizations due to ischemic heart diseases (ICD I-20 to I-24) in the municipality of Taubaté (SP), Brazil, among adults of both sexes aged 40 years and over, from August 2011 to July 2012, were obtained from DATASUS. Fine particulate matter ($PM_{2.5}$) concentrations were estimated from a mathematical model. Poisson regression was used in statistical analyses to estimate the relative risks of exposure to $PM_{2.5}$ for both sexes and after stratification according to sex. The excess of hospitalizations and consequent excess expenditure for the healthcare system were calculated.

RESULTS: There were 1040 admissions, among which 382 had ischemic heart diseases (257 males). The mean $PM_{2.5}$ concentration was 13.2 μg/m³ (SD = 5.6). Significant effects from exposure were noted 4 and 5 days after exposure (lag 4 and lag 5) for both sexes and for male sex; for female sex, the effect was 2 days after exposure (lag 2). There were 59 excess hospitalizations for an increase in $PM_{2.5}$ concentration of 5 μg/m³ and excess expenditure of US$ 150,000 for the National Health System.

CONCLUSIONS: An excess of hospital admissions due to ischemic heart disease, with excess expenditure, was identified consequent to $PM_{2.5}$ exposure.

INTRODUCTION

Over the period from August 2011 to July 2012, cardiovascular diseases accounted for 1.1 million hospitalizations in Brazil, generating a cost of approximately US$ 1 billion. In the state of São Paulo, the most populous and developed state in Brazil, there were approximately 260,000 hospitalizations, costing approximately US$ 300 million. Specifically, the 65,000 hospitalizations due to ischemic heart diseases consumed resources of the order of US$ 130 million.[1]

Cardiovascular diseases are typically associated with factors such as smoking, hypercholesterolemia, systemic arterial hypertension, family history of ischemic diseases of the heart, smoking, obesity and sedentary lifestyle. Moreover, some studies have identified an association between exposure to air pollutants and these diseases. Several positive associations have been found in relation to exposure to fine particulate matter ($PM_{2.5}$), i.e. particles with an aerodynamic diameter of less than 2.5 μ. In urban areas, $PM_{2.5}$ constitutes about 50 to 60% of PM_{10} (particulate material with an aerodynamic diameter of less than 10 μ).[2] These particles result from burning fuels such as coal, gasoline, oil and biomass; from processes involving high temperatures such as smelting and steel production; and from soil dust. The particles can reach the terminal portions of the respiratory tree. The material adsorbed onto the particle's surface depends on the region of the city from which it originated.[3,4]

In the region of the Paraíba valley, in the state of São Paulo, these particles present high ion concentrations of SO_4^{2-}, NH_4^+ and K^+, with long half-lives of the order of days to weeks. The particles have the capacity for dispersal over long distances, of the order of 100 to 1000 km.[3,4]

Higher risk of death due to ischemic heart disease, arrhythmia, heart failure and cardiac arrest has also been correlated with long-term exposure to $PM_{2.5}$.[5,6] On the other hand, over the last decade, epidemiological studies have highlighted that the effects of pollution

and the risk of cardiovascular diseases are more evident among women than among men,[7-9] but without reaching any consensus in this regard.

The $PM_{2.5}$ concentration is usually quantified by state environmental agencies, but this monitoring does not exist in all municipalities or in all states in Brazil. One alternative for estimating these concentrations is to use modeling methods such as the Coupled Chemistry Aerosol and Tracer Transport model for the Brazilian Atmospheric Modeling System (CCATT-BRAMS). This considers the emission and transportation of various aerosol gases and forms of particulate matter, with daily estimates of various pollutants.[10] The Center for Weather Forecasting and Climate Studies of the Brazilian National Institute for Space Research (Centro de Previsão de Tempo e Estudos Climáticos, Instituto Nacional de Pesquisas Espaciais, CPTEC-INPE) runs this model in an operational manner, producing daily data every three hours, with a horizontal resolution of 25 km by 25 km, 40 meters above ground level, covering all of South America.[10] This model has been used in some Brazilian studies.[11,12]

OBJECTIVE

The objective of this study was to estimate the association between exposure to fine particulate matter ($PM_{2.5}$) and hospitalizations due to ischemic heart disease in the city of Taubaté, a medium-sized city in the state of São Paulo, according to the sex of the patients, using data estimated through mathematical modeling.

METHODS

A time-series ecological study was carried out in the city of Taubaté, based on estimates of $PM_{2.5}$ concentrations that were obtained from the CCATT-BRAMS daily monitoring system (http://meioambiente.cptec.inpe.br/).

Taubaté is located in the mesoregion of the Paraíba valley, in the state of São Paulo, between the two largest economic axes of Brazil: 130 km from São Paulo and 280 km from Rio de Janeiro. Its geographical coordinates are 23°01'S and 45°33'W, and it has an approximate population of 300,000 inhabitants in a territorial area of 625 km^2. It has a humid subtropical climate and lies alongside the Dutra Highway, which links São Paulo to Rio de Janeiro and is characterized by intense vehicular traffic. It has two hospitals that attend patients within the Brazilian National Health System (Sistema Único de Saúde, SUS).

The data from hospitalizations due to ischemic heart disease that were used in this study related to conditions classified under codes I-20 to I-24 of the International Classification of Diseases, 10th revision (ICD-10). These data covered the period from August 1, 2011, to July 31, 2012, and were collected from the SUS website (DATASUS) (http://www2.datasus.gov.br/DATASUS/index.php?area=0203&id=6926&VObj=http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/ni). The values were organized in columns, separated according to municipality code, date of hospitalization, diagnosis and age. Only adults aged 40 years and over were considered in this study, and these subjects were subsequently stratified as male and female.

The following variables were considered in analyzing the data. The dependent variable was the daily number of hospitalizations due to cardiovascular diseases, obtained from DATASUS. The independent variables were the concentration of the pollutant $PM_{2.5}$ ($\mu g/m^3$), temperature (°C) and relative humidity (%), which were obtained from CPTEC-INPE. Days of the week and long-term seasonality were the control variables.

In studies on the impact of air pollution on health, it is necessary to take into account the short-term trend represented by the days of the week because, at weekends, the number of hospital visits is lower than on weekdays. Long-term seasonality is another important time trend, since meteorological factors and pollutant concentrations vary during the year. Regarding air temperature and relative humidity, these climatic variables are correlated with hospital admission rates and their inclusion changes the coefficients and, consequently, the relative risks in an important way. It is also important to note that practically all studies on this topic have included these variables, which has made these studies comparable with each other.[5-9]

The frequency distributions of the different independent variables, i.e. $PM_{2.5}$ concentration, temperature and relative air humidity, and the daily numbers of cases of hospitalization were expressed as means, standard deviations and minimum and maximum values. This was done using the Statistica v.7 software.

The data were analyzed using the Poisson regression generalized additive model because the hospitalizations were numerical data that followed Poisson distribution. This regression is expressed by equation (1):

$$\text{Ln (HA)} = \beta_0 + \beta_1 \text{ (CONC)} + \beta 2 \text{ (RH)} + \beta 3 \text{ (T)} + \beta_4 \text{ (SEASON)} + \beta_5 \text{ (D)} \quad (1)$$

where:
β's are regression coefficients;
HA is daily hospital admission;
CONC is the air pollutant concentration;
RH is the relative humidity value;
T is the temperature value;
SEASON is the long-term trend (seasonality); and
D is the day of the week.

This model provided a coefficient (coeff) that could be transformed into the relative risk (RR) of occurrence of the outcome, according to the expression $RR = \exp^{(coeff)}$. These RRs were calculated

with their respective 95% confidence intervals for hospitalizations due to ischemic heart diseases for females, males and both sexes.

We also tested whether the effect estimates were statistically different between males and females by computing the 95% confidence interval using the following equation (2):

$$Q_1 - Q_2 \pm 1.96\sqrt{\left(SE_1^2\right)+\left(SE_2^2\right)} \quad (2)$$

where:
Q_1 and Q_2 are coefficients of these categories; and
SE_1 and SE_2 are the respective standard errors.[13]

Since the effects of exposure may occur either on the same day or on subsequent days, lags of 0 to 7 days after exposure were taken into consideration.

In these analyses, an increase in exposure to the $PM_{2.5}$ pollutant of 5 μg/m³ was calculated to determine the percentage increase (PI) in RR, and this was expressed through equation (3):

$$PI = [\exp(ß * \Delta C) - 1] * 100 \quad (3)$$

where:
ß is the value provided by the Poisson regression; and ΔC is the variation in the fine particulate concentration, which in this case was 5 μg/m³. Considering that $PM_{2.5}$ constitutes approximately 50% of PM_{10}, this value can even be used for comparison purposes with other studies.

From this increase in $PM_{2.5}$ concentration, for both sexes and separately for the male and female sexes, we estimated the proportional attributable risk (PAR), which was given by PAR = [1-1/RR]. The excess of hospitalizations was also estimated through the expression PAF = (PAR * N), where PAF is the population attributable fraction and N is the number of hospitalizations for both sexes and separately for the male and female sexes. From this excess number of hospitalizations, it was possible to estimate the excess expenditure in accordance with the number of hospitalizations due to ischemic heart diseases, which was obtained from the DATASUS website.

Ethical criteria

This study was not evaluated by an internal review board (ethics committee), because the records used are available from DATASUS, which is a public website.

RESULTS

During the study period, 1040 hospitalizations relating to diseases of the cardiovascular system (ICD-10 codes I-00 to I-99) occurred, among which 903 (87.0%) were cases of individuals aged 40 years and over. There were 382 hospitalizations due to ischemic heart disease among individuals aged 40 years and over in the city of Taubaté (SP) and 257 (67.3%) of these cases were among men.

The pollutant values observed over this period and the hospitalizations due to ischemic heart diseases were expressed as averages, as shown in **Table 1**. The $PM_{2.5}$ concentrations showed a significant increase from October to July. The safe limit established by the World Health Organization (25 ug/m³) was exceeded on eight days, reaching a maximum value of 41 μg/m³.

Table 2 shows the Pearson correlation matrix with the study variables. **Table 3** presents the values of the coefficients provided through Poisson regression with the respective standard deviations

Table 1. Daily mean, maximum (Max) and minimum (Min) values and the respective standard deviations (SD) for $PM_{2.5}$ concentrations (μg/m³), temperature (°C), relative humidity (%) and hospitalizations due to ischemic heart diseases. Taubaté, São Paulo, 2011-2012

Variables	Mean	SD	Min	Max
$PM_{2.5}$	13.2	5.6	0.4	41.2
Temperature	22.9	3.9	9.8	38.4
Relative humidity	95.3	8.7	45.0	100.0
Hospitalizations	0.9	0.9	0	4

$PM_{2.5}$ = fine particulate matter.

Table 2. Correlation matrix for the variables of fine particulate matter ($PM_{2.5}$), temperature (Temp), relative humidity (RH), hospitalizations (Hosp) and male and female sexes. Taubaté, São Paulo, 2011-2012

	$PM_{2.5}$	Temp	RH	Hosp	Male	Female
$PM_{2.5}$	1.00	0.52*	0.13*	0.04	0.04	0.02
Temp		1.00	-0.07	0.15*	0.10	0.13*
RH			1.00	0.02	0.08	-0.08
Hosp				1.00	0.86*	0.60*
Male					1.00	0.12*
Female						1.00

*P-value < 0.05.

Table 3. Coefficients provided by Poisson regression for hospital admissions in relation to fine particulate material concentrations, according to lags (0 to 7 days) and according to sex. Taubaté, São Paulo, 2011-2012

	Both sexes	Male	Female
Lag 0	0.01158 (0.01543)	0.01109 (0.01928)	0.01207 (0.02589)
Lag 1	0.01774 (0.01448)	0.01676 (0.01789)	0.01795 (0.02468)
Lag 2	0.02118 (0.01261)	0.01034 (0.01675)	0.04300 (0.01935)*
Lag 3	0.01927 (0.01443)	0.01383 (0.01776)	0.02587 (0.02487)
Lag 4	0.03552 (0.01266)*	0.03463 (0.01534)*	0.03634 (0.02247)
Lag 5	0.03520 (0.01274)*	0.04478 (0.01470)*	0.01560 (0.02559)
Lag 6	0.00669 (0.01440)	0.00619 (0.01670)	0.01217 (0.02823)
Lag 7	-0.01189 (0.01335)	-0.00848 (0.01566)	-0.01943 (0.02569)

*P-value < 0.05.

for hospitalizations due to ischemic heart diseases, with delays of 0 to 7 days after $PM_{2.5}$ exposure, among individuals of both sexes and stratified according to male and female sex. It was seen that admission was significantly associated with exposure to $PM_{2.5}$ in the following situations: unstratified analyses at lag 4 (RR = 1.04; 95% CI: 1.01–1.06) and at lag 5 (RR = 1.04; 95% CI: 1.01–1.06); among males at lag 4 (RR = 1.03; 95% CI: 1.00–1.07) and at lag 5 (RR = 1.05; 95% CI: 1.02–1.08); and among females at lag 2 (RR = 1.04; 95% CI: 1.00–1.08). Thus, it was observed that the response among females was different and earlier.

In comparing the significant exposures between males and females (at lags 2, 4 and 5) and using equation (1), it was not possible to find any significant differences in the risks shown by the respective coefficients and standard errors. No overdispersion was identified.

Figure 1 shows the relative risk values and respective 95% confidence intervals for both sexes and for the male and female sexes separately, according to an increase of 5 μg/m³ in $PM_{2.5}$ concentrations. It was evident that the relative risk occurred earlier among females, i.e. at lag 2, without any corresponding occurrence in the analysis on males, or in the analysis on both sexes.

An increase of 5 μg/m³ in $PM_{2.5}$ concentration increased the risk of hospitalization for both sexes by up to approximately 18%. The PAR was estimated at approximately 15% and the PAF resulted in an excess of 59 hospitalizations, with expenditure of approximately US$ 150,000.00, assuming an average cost of hospitalization of approximately US$ 2,600.00.

DISCUSSION

This, to the best of our knowledge, was the first study estimating the effects of exposure to fine particulate matter in a medium-sized city, in relation to the number of hospitalizations due to ischemic heart diseases. The data used were estimated through mathematical modeling and the possible responses to exposure were estimated separately for males and females. An earlier female response was found, occurring two days after exposure (lag 2), but there was no significant difference in relation to the corresponding relative risk among males.

Tuan et al.[14] examined pollutant concentration data that had been quantified by an environmental agency and found differences in the responses to these pollutants according to the subjects' sex, regarding the time of occurrence of the hospital admission. In the present study, the data used were estimated through mathematical modeling, whereas Tuan et al.[14] used data quantified by the environmental agency of the state of São Paulo (CETESB).

Regarding the differences between the sexes, a study on deaths due to ischemic heart diseases that was conducted in all states of the United States between 2004 and 2007 showed that the mortality rate was higher among women than among men, especially among women aged less than 50 years.[15,16] We found in our study that there were differences in lag, regarding exposure and hospitalization, and that the effect occurred earlier among females (lag 2) than among males (lags 4 and 5), i.e. four and five days after this exposure, in analyses on both sexes and on the male sex alone after stratification. Among females, this outcome occurred earlier in the study (only two days after exposure), and this result was concordant with the findings of Chen et al.,[17] who observed that the risk of dying from coronary disease was higher among women, especially among those in the postmenopausal period, than among men.[17] One possible explanation for the difference in the effects of exposure to PM_{10} and $PM_{2.5}$ between men and women may be that the deposition of these particles is more localized and more intense in females. The smaller number of red blood cells in women may make them more sensitive to the toxic effects of air pollutants.[21]

In studies conducted in Brazil, the effects of exposure to air pollutants have been shown to be associated with hospitalizations due to cardiovascular diseases such as hypertension, acute myocardial infarction and stroke.[6,18-20] Specifically in relation to the association between exposure to particulate matter and hospitalizations due to ischemic heart disease, a study carried out in São José dos Campos, a city near Taubaté, showed that an increase in PM_{10} concentration of 16 μg/m³ led to a 10% increase in the relative risk of hospitalization. However, in that study, the subjects were not stratified according to sex.[18]

In the case of cardiovascular diseases, the data estimated through this model in another study made it possible to identify an excess of hospitalizations, of the order of 650, in São José do Rio Preto, that occurred through an increase in $PM_{2.5}$ concentrations, with excess expenditure of US$ 1 million. That study was the only previous study carried out in the state of São Paulo, to the best of our knowledge.[20]

The direct effects of this exposure may occur through agents that cross the pulmonary epithelium in the circulation, such as gases and possibly ultrafine particles (< 0.1 μ), along with soluble constituents

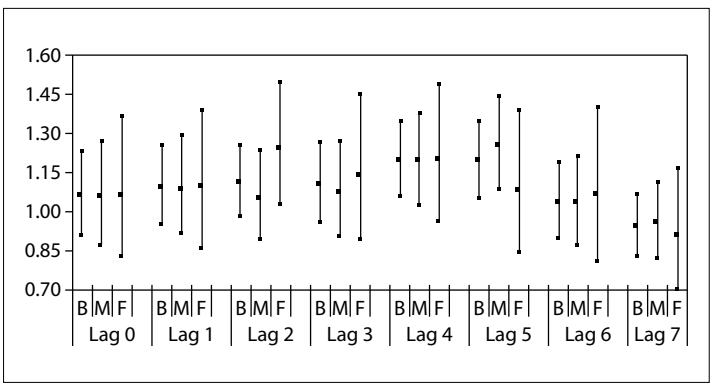

Figure 1. Relative risk with respective 95% confidence intervals, according to a 5 μg/m³ increase in fine particulate matter concentration, for both sexes (B) and for males (M) and females (F). Taubaté (SP), 2011-2012.

of $PM_{2.5}$ (e.g. transition metals). In addition, activation of pulmonary neural reflexes secondary to interactions between particulate matter and pulmonary receptors may play an important role. These direct effects of air pollution provide a plausible explanation for occurrences of rapid cardiovascular responses (within a few hours), such as myocardial infarction. The less acute (several hours to days) and chronic indirect effects of air pollution may occur through pulmonary oxidative stress/inflammation induced by inhaled pollutants. Subsequently, this may contribute towards a systemic inflammatory state, which may, in turn, be able to activate hemostatic pathways, impair vascular function and accelerate atherosclerosis.[25]

The present study had some limitations, and the way in which pollutant concentrations were estimated was one of them. This was done through mathematical modeling and may have provided incorrect data. Another limitation was that the hospitalization data were secondary, even though they came from an official source. These data had the potential to incorporate diagnostic errors or incorrect addresses for the subjects. Additionally, this data source does not contain information on habits such as smoking or sedentary lifestyle, or on comorbidities or family history. It is also important to note that the results presented here do not represent causality, but show an association between the exposure and the outcome. Nonetheless, use of data estimated through the CCATT-BRAMS model, which has already been implemented in other studies, may form an alternative for studies on the effects of exposure to fine particulate matter on human health, such as in relation to respiratory and cardiovascular diseases.[22-25]

CONCLUSIONS

Notwithstanding the possible limitations, the findings from this study, using data estimated through a mathematical model, suggest that an association exists between exposure to $PM_{2.5}$ and hospitalizations due to cardiovascular diseases and that this exposure may differ according to sex.

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Left lateral intercostal region versus subxiphoid position for pleural drain during elective coronary artery bypass graft surgery: randomized clinical trial

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ABSTRACT

BACKGROUND: The pleural drain insertion site after coronary artery bypass graft (CABG) surgery may alter lung function, especially respiratory muscle strength. The main objective of this study was to compare the effectiveness and safety of use of the left lateral intercostal region versus the subxiphoid position for pleural drainage during elective CABG surgery using extracorporeal circulation (ECC).

DESIGN AND SETTING: Randomized trial conducted in a tertiary-level hospital in Porto Alegre, Brazil.

METHODS: 48 patients were assigned to group 1 (pleural drain in the left lateral intercostal region) or group 2 (pleural drain in the subxiphoid position). Respiratory muscle strength was measured in terms of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), in cmH_2O, by means of manovacuometry preoperatively, 24 and 72 hours after drain removal and before discharge from hospital. Pain and dyspnea scales, presence of infections, pleural effusion and atelectasis, duration of drain use, drainage volumes and surgical reinterventions were also evaluated.

RESULTS: After adjustments, there were no significant differences between the groups at the end of the study (before discharge), in predicted percentages either for MIP (delta group 1: -17.21% versus delta group 2: -22.26%; P = 0.09) or for MEP (delta group 1: -9.38% versus delta group 2: -13.13%; P = 0.17). There were no differences between the groups in relation to other outcomes.

CONCLUSION: There was no difference in maximal respiratory pressures in relation to the pleural drain insertion site among patients who underwent CABG surgery using ECC.

TRIAL REGISTRATION: ReBEc V1111.1159.4447.

INTRODUCTION

Coronary artery bypass graft (CABG) surgery is associated with higher survival rates and better quality of life among patients with coronary artery disease.[1,2] Use of left internal thoracic artery (LITA) grafts has been correlated with long-term benefits,[3] but this often requires pleurotomy and insertion of tubes to drain the cavity.[4,5]

Pleural drains can be inserted into the subxiphoid region or the intercostal space with the main objective of maintaining or restoring the negative pressure of the pleural space.[6] However, they may impair the integrity of the ventilatory system, thereby compromising the respiratory mechanics and gas exchange after surgery.[7-9]

Respiratory muscle strength may be evaluated through maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), which indicate the strength of the inspiratory and expiratory muscle groups respectively.[10] Predictions for MIP and MEP according to age and sex should preferably be considered within their clinical setting, because they may lead to a prognosis of postoperative pulmonary complications like respiratory muscle fatigue or failure.[11-13] MIP and MEP can be measured with the aid of a manometer or manovacuometer. In addition to being practical and non-invasive, this equipment has low cost, is easy to apply at the bedside and only requires simple inspiration and expiration movements from the patient.

Studies on individuals undergoing CABG surgery have shown that insertion of the pleural drain in the subxiphoid position can minimize the chance of trauma to the thoracic wall, may preserve respiratory function in the immediate postoperative period and may lead to lower levels of subjective pain, compared with lateral intercostal insertion.[14-20] However, most of these studies

were conducted among patients undergoing CABG surgery without extracorporeal circulation (ECC),[15-17,20,21] without prior pulmonary disease,[14-16,18,19] and with use of spirometry rather than manovacuometry to evaluate respiratory muscle strength.[14,15,18-20]

OBJECTIVE

The main objective of this study was to compare the effects of pleural drain insertion in the subxiphoid region with insertion in the left lateral intercostal region, on MIP and MEP measured via manovacuometry, among patients undergoing elective CABG surgery with ECC and use of LITA grafts. The secondary aims were to compare pain, dyspnea, infections, pleural effusion, atelectasis, drainage volumes, surgical reintervention and number of hours with the drain between the groups.

METHODS

Study design and setting

This was a parallel randomized clinical trial conducted among candidates for CABG with ECC and use of LITA grafts who were admitted to the Cardiology and Cardiac Surgery Service of the Nossa Senhora da Conceição Hospital (HNSC, Porto Alegre, Brazil). The research project was approved by the Research Ethics Committee (REC) of the University Foundation of Cardiology (UP protocol 4904/13) in August 2013 and by the REC of the Conceição Hospital Group under number 14-226 in May 2014. The protocol was registered in the Brazilian Registry of Clinical Trials (ReBEc) under the number V1111.1159.4447. All participants signed an informed consent form. Data collection was carried out from July 2014 to August 2015. We used the CONSORT Statement for reporting this trial.

Study population

Patients aged between 40 and 80 years, with an indication for CABG surgery with LITA graft[2] and associated pleurotomy, were included in the study. Patients with severe neuropsychiatric deficits who required concomitant surgical interventions such as valve replacement or aortic surgery, or who presented symptomatic abdominal hernias, stroke prior to or during the study period or any other conditions that impeded use of a manovacuometer (strength deficit, sensory deficit, facial paralysis or pleurocutaneous or pulmonary fistulas), were excluded.

Randomization and allocation concealment

The block randomization sequence was generated with the aid of the website www.randomization.org and the numbers were allocated through using individual opaque sealed envelopes. After checking the eligibility criteria and after patients had signed the consent form, the participants were allocated to either of two groups (1:1 randomization): group 1: with use of a left lateral drain, inserted at the intersection of the 6th or 7th left intercostal space with the middle axillary line; or group 2: with use of a drain inserted in the subxiphoid region. Only one researcher had access to the randomization list and he did not participate in the enrollment. The patients, surgeons and researchers involved in both allocation and data collection (including the operators who performed the manovacuometry) were aware of the group to which the participants were randomized because these patients were identified by means of a green or orange patch on their hospital bracelet, to indicate to the surgeon which pleural drain insertion site should be used (green label: lateral insertion; orange label: subxiphoid insertion). The clinical cardiologists, radiologists and other professionals who evaluated the patients' examinations, along with the professionals involved in the statistical analysis, were blinded to the randomization groups.

Primary outcomes

The primary outcomes were MIP and MEP, in cmH_20, evaluated by means of manovacuometry. This was performed in accordance with standardized protocols, at the baseline and at another three times: 24 hours and 72 hours after drain removal and at hospital discharge.[21,22] We used an analogue manovacuometer (M120; Globalmed, Porto Alegre, RS, Brazil) that had been certified by the Brazilian standards agency Inmetro and which was capable of making measurements over the range from -150 to +150 cmH_20.

Predicted MIP and MEP values were calculated using the equations proposed by Neder et al.[23] for individuals aged 20 to 80 years, separately for males (MIP = 155.3 - 0.80*height; MEP = 165.4 - 0.81*height) and for females (MIP = 110.4 - 0.49*height; MEP = 115.6 - 0.61*height). The predicted percentages for maximal respiratory pressures were calculated individually based on the formula: (measured MIP or MEP/predicted MIP or MEP)*100.

Secondary outcomes

Subjective degree of pain

The subjective degree of pain at the site of drain insertion was ascertained at 24 hours and 72 hours in the postoperative period and before hospital discharge, with the aid of a visual analogue scale graded from zero to ten,[24] on which zero represented absence of pain and ten, the most intense pain.

Subjective degree of dyspnea

The subjective degree of dyspnea was assessed at 24 hours and 72 hours in the postoperative period and before hospital discharge using the modified Borg dyspnea scale,[25] graded from zero to ten, in which zero characterized absence of dyspnea and ten, the worst sensation of dyspnea.

Respiratory and surgical wound infection

Respiratory infection was defined, in accordance with clinical criteria,[26] as an association of hyperthermia, infectious leukogram and compatible radiological examination. Surgical wound infections were diagnosed from occurrences of local phlogistic signs such as heat, redness, pain, purulent secretion and edema, along with the presence of sternum instability, fever and an infectious leukogram.[26-29]

Pleural effusion and atelectasis

The presence of pleural effusion was evaluated through simple chest x-ray examinations in the posterior-anterior and lateral incidences, which were interpreted by two independent blinded physicians. The first x-ray was performed between 48 hours and 72 hours after drain removal; the second examination was performed between 73 hours and 120 hours after drain removal. Pleural effusion was categorized as absent, small or medium, and was assessed as present on the right or left side. Atelectasis was also evaluated based on radiological examinations and was registered in the medical records.

Duration of drain use and pleural drainage

The duration of pleural drain use was recorded as the number of hours. The volumes collected through mediastinal and pleural drainage (in milliliters) were ascertained from the hospital records. The need for medical reinterventions during the hospital stay was evaluated considering the need for pleural drainage after removal of the chest drain, through insertion of a tubular drain or thoracocentesis.

Other variables

At the first assessment (preoperative), sociodemographic data (sex and age) and clinical data regarding the patients' current and previous medical histories and use of medications were collected by means of interviews and from hospital records. Existence of a smoking habit was categorized as "current", "former" (if the individual had stopped smoking for more than a year) or "never". Alcohol consumption and/or alcohol abuse (consumption of ≥ 30 g/day for men and ≥ 15 g/day for women) was identified from the medical records and clinical history. Patients were deemed to be former alcoholics if they had ceased their abusive consumption of alcoholic beverages more than one year previously. Body mass index (BMI) was calculated as the ratio between body mass (in kilograms) and squared height (in meters) and was expressed as kg/m^2.

Clinical and cardiological history

Clinical and cardiological information were collected from the hospital medical records, including the current disease history (symptoms and their characteristics), previous disease history (hypertension, diabetes mellitus, dyslipidemias, previous myocardial infarction and angina) and previous examinations. Family histories of previous diseases and treatments, such as percutaneous myocardial revascularization or non-cardiological surgery were also taken into consideration.

All the patients underwent a baseline electrocardiogram, which was used for comparative evaluations between the pre and postoperative periods. The professionals involved were blinded to the study objectives. The anesthetic technique used was the same for both groups (balanced general anesthesia, with inhalants and venous agents). Epidural analgesia was not used in any case. The chest tube caliber was 38 French for both groups.

Intraoperative period variables

Intraoperative variables were obtained from the medical records in both the surgical and the intensive care unit, as follows:

- Total duration of ECC: length of time with extracorporeal circulation, in minutes;
- Duration of surgery: length of time, in hours, that elapsed from the arrival of the patient in the surgical room until entry to the intensive care unit (ICU);
- Duration of mechanical ventilation: length of time, in hours, that elapsed between orotracheal intubation of the patient in the surgical room and extubation in the ICU;
- Length of stay in the ICU: length of stay in the ICU, in hours, until referral to the inpatient unit;

Outcomes were collected from the medical records. Myocardial infarction and revascularization followed by death in the same hospital was adjudged to be cardiovascular death.

Sample calculation

The sample size calculation was performed using the WinPepi software for Windows. Based on data from a previous randomized trial that assessed maximal respiratory pressures among patients undergoing CABG surgery,[16] we found that we would need a sample size of 20 participants in each group to find a difference in predicted percentage for MIP of 14% between the groups, considering standard deviations of 15% both in group 1 and in group 2, a study power of 80%, and an alpha level of 0.05. After adding 20% to cover for losses, the final sample size would need to be 48 individuals.

Statistical analyses

The data were recorded in a database in the Excel software, version 2013. The analyses were carried out in the Statistical Package for the Social Sciences (SPSS), version 20 for Windows. All the analyses were performed using the intention-to-treat principle. Continuous variables were described as means and standard

deviations (for symmetrical variables) and/or medians and interquartile ranges (for asymmetrical variables). Categorical variables were described as absolute frequencies and numbers. Student's t test was used to compare means, and the Wilcoxon-Mann-Whitney test to compare medians. Comparisons between proportions were made using Pearson's chi-square test or Fisher's exact test. Generalized estimated equation (GEE) tests and Bonferroni post-hoc tests were used for intergroup and intragroup comparisons between different times. A significance level of 5% was used.

RESULTS

During the enrollment period, from July 2014 to August 2015, 85 patients were admitted electively or urgently to the Cardiology and Cardiac Surgery Service of the HNSC with a surgical indication and thus were eligible for inclusion in the study. Of these, five were discharged for an elective return and did not return to undergo the CABG procedure, and 32 individuals had indications for other surgeries. In the end, 48 patients underwent randomization (**Figure 1**). Among these, five patients who were allocated to group 1 did not complete the study: three because of death (two due to cardiovascular causes, i.e. cardiogenic shock on the first postoperative day, and one due to an infectious cause, consisting of pulmonary sepsis); and two because they suffered incapacitating strokes during the perioperative period. Thus, 19 patients randomized to the lateral drain group and 24 randomized to the subxiphoid drain group completed the study.

Table 1 presents the characteristics of the participants according to the randomized groups at the baseline. There were no significant differences between the groups. The previous surgeries that were identified were valve replacement, prostatectomy, cholecystectomy and mastectomy, with no difference in prevalence between the groups (P = 0.72). The individuals allocated to the lateral group presented higher prevalence of prior myocardial infarction associated with percutaneous revascularization, compared with the subxiphoid group (P = 0.038).

Table 2 shows the perioperative data on the patients according to the randomized groups. There were no significant differences in the variables at the preoperative assessment (heart rate, oxygen

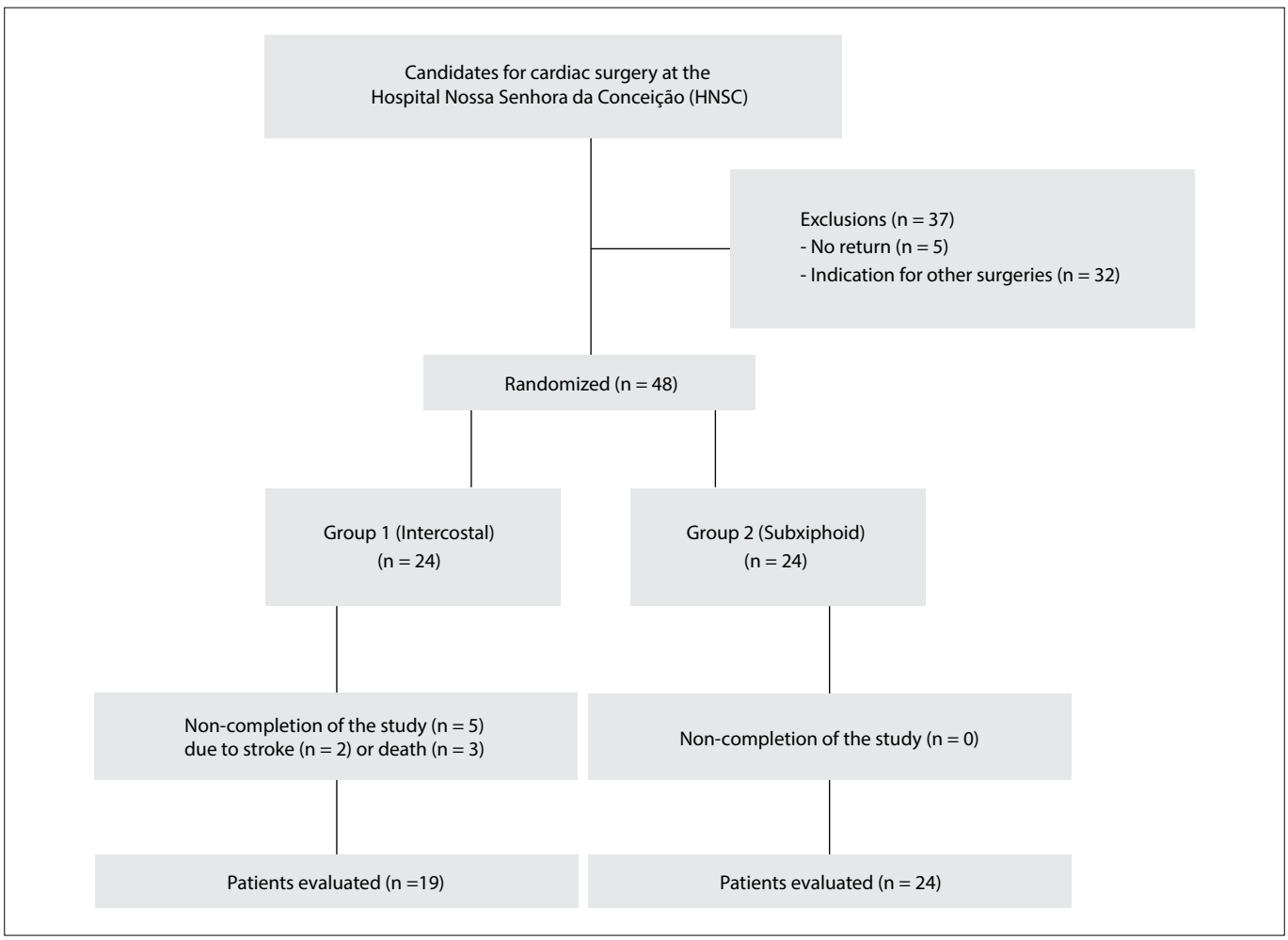

Figure 1. Flowchart of study participants.

saturation, maximal respiratory pressures and predicted percentages for pressures). In the subxiphoid group, longer duration of ECC (P = 0.028), higher pleural volume drained (P = 0.01) and higher frequency of atelectasis were observed, although these differences were not statistically significant (P = 0.10). With regard to pleural effusion (**Table 3**), there was a higher frequency on the left side in the subxiphoid group, both in the first (P = 0.17) and in the second (P = 0.18) radiographic examination, compared with the lateral group.

Table 4 shows the differences in the predicted percentages for maximal pressures (inspiratory and expiratory) according to the time of assessment and treatment group, after adjustment for smoking, diagnoses of asthma/chronic obstructive pulmonary disease and duration of mechanical ventilation. No significant difference was observed either in inspiratory pressure (P = 0.83) or in expiratory pressure (P = 0.76), in relation to the treatment (kind of drain) at the end of the study period. In both groups, a significant

Table 1. Baseline characteristics according to study groups [mean ± standard deviation; n (%)]

	Lateral drain N = 24	Subxiphoid drain N = 24	P-value
Male	15 (62.5)	16 (66.7)	0.76*
Age in years	65.58 ± 9.50	61.75 ± 9.58	0.17‡
Body mass index in kg/m²	27.45 ± 4.72	28.93 ± 3.49	0.22**
Diabetes mellitus	13 (54.2)	10 (41.7)	0.56*
Hypertension	20 (83.3)	23 (95.8)	0.35*
Dyslipidemia	17 (70.8)	21 (87.5)	0.29*
Asthma/chronic obstructive pulmonary disease	4 (16.7)	4 (16.7)	> 0.90*
Chronic kidney disease	2 (8.3)	3 (12.5)	> 0.90*
Peripheral obstructive disease/peripheral arterial obstructive disease	5 (20.5)	2 (8.3)	0.42*
Previous stroke	3 (12.5)	2 (8.3)	> 0.90*
Smoking			
Current smoker	2 (8.3)	2 (8.3)	0.32*
Former smoker	13 (54.2)	8 (33.3)	
Never smoked	9 (37.5)	14 (58.3)	
Alcohol consumption			
Former alcoholism	2 (8.3)	2 (8.3)	> 0.90*
No alcoholism	22 (91.7)	22 (91.7)	
Coronary artery disease			
Previous acute myocardial infarction	8 (33.3)	3 (12.5)	0.038*
Acute myocardial infarction with percutaneous revascularization	3 (12.5)	0	
Angina	9 (37.5)	10 (41.7)	
Angina with percutaneous revascularization	0	4 (16.7)	
No history of coronary artery disease	4 (16.7)	7 (29.2)	
Family history of CAD	3 (12.5)	3 (12.5)	> 0.90**
Reason for hospital admission			
Acute myocardial infarction	9 (37.5)	9 (37.5)	> 0.90*
Angina	15 (62.5)	15 (62.5)	
Lesions identified by means of coronary artery angiography			
Left coronary trunk	1 (4.2)	0	0.35*
Left coronary trunk + other coronary arteries	2 (8.3)	5 (20.8)	
Multiarterial	20 (83.3)	19 (79.1)	
Intra-stent restenosis (previous)	1 (4.2)	0	
Chronic-use medications			
Acetylsalicylic acid	22 (91.7)	19 (79.2)	0.42**
Clopidogrel	7 (29.2)	6 (25)	> 0.90**
Statins	20 (83.3)	17 (70.8)	0.49**
Beta-blockers	16 (66.7)	15 (62.5)	> 0.90**
Resting electrocardiogram			
Sinus rhythm	22 (91.7)	21 (87.5)	0.36*
Atrial fibrillation	1 (4.2)	3 (12.5)	
Others	1 (4.2)	0	

Statistical tests used: *Pearson's chi-square test; ‡ Student's t test; **Fisher's exact test.

Table 2. Perioperative data according to group [mean ± standard deviation; median (interquartile range; N [%])

	Lateral drain N = 24	Subxiphoid drain N = 24	P-value
Preoperative			
Heart rate in bpm	75 ± 10.5	72 ± 11.29	0.33‡
Saturation of oxygen in %	95.50 ± 1.56	96.25 ± 2.69	0.24‡
MIP in cmH_2O	53.83 ± 22.71	61.46 ± 24.58	0.27‡
MEP in cmH_2O	67.50 ± 25.02	73.75 ± 22.95	0.37‡
Percentage of predicted MIP, in %	58.93 ± 24.91	63.37 ± 20.96	0.51‡
Percentage of predicted MEP, in %	38.69 ± 14.13	40.86 ± 10.95	0.56‡
Intraoperative and IPO			
Duration of extracorporeal circulation, in minutes	113.96 ± 29.18	134.79 ± 34.32	0.028‡
Time in the operating room, in hours	7.06 ± 1.26	7.08 ± 1.22	0.94‡
Duration of mechanical ventilation, in hours	24 (20; 27)	24.5 (15; 44)	0.73*
Length of ICU stay, in hours	94.8 (71; 190)	119 (86; 181)	0.65*
Acute myocardial infarction	5 (20,8)	4 (16.7)	> 0.90**
Stroke	1 (4.2)	1 (4.2)	> 0.90**
Cardiorespiratory arrest	4 (16.6)	1 (4.2)	0.35**
Arrhythmia	12 (50)	8 (33.3)	0.38**
Postoperative			
Duration of drain use, in hours	47 (43; 55)	52.5 (45; 72)	0.11*
Drained pleural volume, in milliliters	133 (107; 171)	190 (140; 251)	0.01*
Atelectasis	1 (4.5)	6 (25)	0.10*
Respiratory infection	4 (18.2)	8 (33.3)	0.32**
Surgical wound infection	3 (13.6)	5 (20.8)	0.70**
Surgical reoperation	2 (8.3)	1 (4.2)	> 0.90**

Statistical tests used: ‡Student's t test; *Mann-Whitney test; **Fisher's exact test.
IPO = immediate postoperative; ICU = intensive care unit; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure.

Table 3. Characterization of pleural effusion according to group [n (%)]

Radiographic examination 1 (48 h to 72 h after drain removal)					Radiographic examination 2 (73 h to 120 h after drain removal)				
	Absent	Small	Medium	P-value*		Absent	Small	Medium	P-value*
Right				0.64	**Right**				0.21
Lateral	3 (15.8)	6 (31.6)	10 (52.6)		Lateral	13 (68.4)	4 (21.1)	2 (10.5)	
Subxiphoid	3 (12.5)	11 (45.8)	10 (41.7)		Subxiphoid	12 (50)	11 (45.8)	1 (4.2)	
Left				0.17	**Left**				0.18
Lateral	8 (42.1)	9 (47.4)	2 (10.5)		Lateral	9 (47.7)	10 (52.6)	0	
Subxiphoid	4 (16.7)	15 (62.5)	5 (20.5)		Subxiphoid	6 (25)	16 (66.7)	2 (8.3)	

Statistical tests used: *Pearson's chi-square test.
Number of patients with lateral intercostal drain insertion who completed the study = 19.
Number of patients with subxiphoid drain insertion who completed the study = 24.

Table 4. Predicted percentages for maximal inspiratory (%PMIP) and expiratory (%PMEP) pressures according to time assessed and randomized group (mean difference ± standard error)

	Lateral	Subxiphoid	P-value*	P-value**	P-value***
%PMIP			0.83	< 0.001	0.09
24 hours – Preoperative	-34.14 ± 4.32	-32.83 ± 3.41			
72-24 hours	7.83 ± 2.10	4.42 ± 1.20			
Discharge – 72 hours	9.10 ± 1.98	6.15 ± 1.57			
%PMEP			0.76	< 0.001	0.17
24 hours – Preoperative	-18.76 ± 2.76	-20.25 ± 200			
72-24 hours	3.32 ± 1.01	2.83 ± 0.93			
Discharge – 72 hours	6.06 ± 1.34	4.29 ± 0.73			

*Difference between groups (treatment); **Difference between times; ***Treatment x time interaction. Generalized estimation equations (GEE) adjusted for smoking, diagnosis of asthma/chronic obstructive pulmonary disease and mechanical ventilation.

reduction in the predicted percentage for inspiratory pressure was observed 24 hours after pleural drain removal ($P < 0.001$), and also in the predicted percentage for expiratory pressures ($P < 0.001$). No interaction between treatment and time was detected at the end of the study period regarding the predicted values for inspiratory pressure ($P = 0.09$) and expiratory pressure ($P = 0.17$).

Both groups showed significant reductions in Borg score (thus indicating improvement in dyspnea) at the 72-hour assessment, compared with the 24-hour assessment (after adjusting for smoking and diagnoses of asthma/chronic obstructive pulmonary disease; $P > 0.0001$). However, no differences between the groups were seen at the end of the study period ($P = 0.23$). A similar result was observed in relation to the subjective degree of pain (mean Borg score), which presented a decrease (thus suggesting an improvement) at 72 hours after drain removal (group 1: 1.39; group 2: 1.89), compared with the 24-hour assessment (group 1: 2.96; group 2: 3.54), in both groups ($P < 0.0001$). However, there were differences between the groups at the assessment at the time of discharge ($P = 0.17$).

DISCUSSION

This study evaluated the impact of insertion of pleural drains on the behavior of respiratory muscle strength, by means of a manovacuometer, in patients undergoing CABG surgery with ECC and LITA graft implantation. No significant differences in the predicted percentages for MIP and MEP at the end of the study period were observed in relation to the drain insertion site, i.e., in a lateral or subxiphoid position. On the other hand, the lateral group presented higher predicted MIP values before the time of discharge.

As expected, the patients included in this study had high prevalence of cardiovascular risk factors, along with a differentiated profile in relation to the severity of the cardiac lesions identified through coronary artery angiography. In the group of patients allocated to the lateral drain positioning, some characteristics associated with greater in-hospital cardiovascular morbidity and mortality were highlighted, and this group contained a greater proportion of individuals undergoing drug therapy. This suggests that these individuals have a profile of higher risk and vulnerability.[30] Thus, the likelihood of occurrence of outcomes such as death and stroke in this group could be higher than among patients allocated to the subxiphoid drain.

The low predicted percentages for MIP and MEP among the patients in both groups (38 to 63%) in the preoperative assessments indicated that features associated with decreased respiratory muscle strength were present: advanced age, lung diseases and smoking; along with the progression of the cardiovascular disease itself. It is known that increased or improved maximal respiratory pressure prior to surgery is associated with fewer postoperative complications such as atelectasis, respiratory infections, duration of mechanical ventilation and length of hospital stay.[31] On the other hand, lower maximal respiratory pressure is associated with increased incidence of cardiovascular events such as myocardial infarction, stroke and death among elderly patients.[32]

As expected and previously demonstrated,[33] the MIP and MEP decreased significantly over the first 24 hours after the CABG and, at discharge, they still had lower values than those observed in the preoperative assessment. In previous studies in which spirometers were used as the means of assessing respiratory pressures, it was concluded that insertion of the pleural drain in the subxiphoid position was associated with lower impairment of respiratory muscle strength.[8,15,20] However, in the present study, the pleural drain position was not found to have any significant influence on maximum respiratory pressures.

The patients allocated to group 2 had significantly longer ECC and drainage times than those in group 1. These factors are directly associated with reduced pulmonary compliance and with dysfunction,[15,34] and this may explain our results, which were different from those of previous studies. The tendency among the patients allocated to the lateral group to present higher inspiratory pressure values before hospital discharge than those of the patients in the subxiphoid group may be partially explained by their lower BMI[35] and by the presence of lower prevalence of atelectasis and respiratory infections and the shorter drainage time.

Unlike other studies that correlated drain insertion in the subxiphoid position with lower intensities of pain and dyspnea,[14-16,18] we did not observe any differences between the groups regarding the subjectively assessed degrees of dyspnea and pain. The shorter time for which the pleural drain was used in the lateral group may have influenced these results.

Among the limitations of our study, we can cite: the sample size, which may have been insufficient after the losses; the number of deaths that occurred in only one of the groups, which may have occurred at random, but also may have represented a selection bias; and the socioeconomic (low-income) and cultural (low-education) conditions of the participants, which may also have negatively influenced our results (participants with low income and low education may have worse understanding of and compliance with medical recommendations).

CONCLUSION

We did not observe any difference in the effect of pleural drain insertion site after CABG surgery on the respiratory pressures among patients who underwent this surgery with the use of ECC, LITA grafts and pleurotomy. A slight decline in maximal respiratory pressures in the patients with a lateral intercostal drain was identified, but with better recovery during hospitalization. In addition, higher prevalences of small and medium

pleural effusion, dyspnea, respiratory infection and atelectasis in the group with a drain inserted in the subxiphoid region were observed. Despite greater initial pain sensitivity among the patients with lateral drainage, no differences were observed in relation to subjective pain and dyspnea between the groups at the end of the study. A greater number of studies conducted among candidates for CABG surgery with use of ECC and LITA grafts are needed to broaden the validation of our results.

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Sports participation and muscle mass affect sex-related differences in bone mineral density between male and female adolescents: A longitudinal study

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ABSTRACT

BACKGROUND: Sports participation plays an important role in bone gain during childhood and adolescence. The aim here was to identify sex-related determinants of bone mineral density (BMD) differences between male and female adolescents, with emphasis on the role of sports participation.

DESIGN AND SETTING: Longitudinal study conducted in a public university in Presidente Prudente, Brazil.

METHODS: The sample comprised 48 adolescents aged 11-17 years, of both sexes, who were matched according to sex, age and sports participation. BMD was the main outcome, while muscle mass, sports participation, calendar age and biological maturation were treated as covariates. Participants were followed up after nine months.

RESULTS: At baseline, BMD values were similar between the sexes. However, adjustment for covariates showed that BMD was higher among girls at all sites, with a contribution from lean soft tissue (LST) in the model (partial eta-squared, ES-r = 0.619 in upper limbs; 0.643 in lower limbs; 0.699 in spine; and 0.599 in whole body). Sports participation only explained the upper-limb variance (ES-r = 0.99). At the follow-up, the results resembled the baseline except in the lower limbs (P = 0.109), in which BMD was similar between the groups. BMD gain over time was similar between girls and boys in all segments, and baseline LST affected upper-limb and whole-body BMD accrual (ES-r = 0.396 and 0.107, respectively).

CONCLUSION: Whole-body and specific-site BMD differed between baseline and follow-up. However, BMD accrual was similar between the sexes, given that muscle mass constituted the most relevant determinant of the difference between them.

INTRODUCTION

Bone health has become a concern in modern society due to the economic burden and impairment in quality of life caused by osteoporosis.[1] Osteoporotic fractures increase both healthcare costs and the risk of early mortality.[2-4] Taking into account the epidemiology of osteoporosis, women exhibit greater risk of developing osteoporosis than do men. This greater risk for the female sex is strongly determined by specific events that occur during adolescence.[5]

The current literature shows how childhood and adolescence are complex phases that are critical periods for the development of bone mineral density (BMD) accrual. There is increasing acceptance of the hypothesis that osteoporosis may be a pediatric metabolic disease, with manifestations during adulthood.[6] Therefore, the peak bone mass reached during this period is a determinant of BMD observed during adulthood, and this constitutes a relevant determinant of the risk of osteoporosis in adulthood.[7]

Among the variables capable of affecting bone health, sports participation plays an important role in the process of boosting bone gains during childhood and adolescence.[8] Thus, it is important to consider sports and resistance training as relevant tools for improving bone mineral density (BMD)[8-9] and joint stability, with consequently stronger bones.[11] Another relevant fact is that the rate of sports participation may differ between boys and girls, such that it is higher among males.[9,10-13] Moreover, during adolescence, there are several correlates affecting sex-related differences in gains of bone mineral content among athletes and non-athletes, such as maturation, muscle mass and dietary factors.[14,15]

The abovementioned background identifies a significant difference regarding bone density between boys and girls.[14,15] However, it does not quantify the burden of each covariate in this process.

Therefore, the purpose of this nine-month longitudinal study was to identify determinants of sex-related BMD differences between male and female adolescents, and to identify the role of sports participation in this phenomenon. We hypothesized that bone density differences between boys and girls would disappear after controlling for these variables, and that sports participation would maintain its impact on bone density even after controlling for these confounders.

METHODS

Ethical considerations

The Research Ethics Board of the School of Science and Technology of São Paulo State University (Universidade Estadual Paulista, UNESP), in Presidente Prudente, Brazil, approved this study (procedural number 02891112.6.0000.5402, May 7, 2012). All parents/guardians of potential participants signed a written consent form before their children participated in the study.

Design, setting and participants

This longitudinal study (ABCD-Growth Study) was conducted over a nine-month period with two evaluations: at the baseline and at a follow-up after nine months. This nine-month period was determined through examining previous studies reported in the literature and through work done by our research group, in which it was identified that nine months of exercise practice/sports participation was sufficient for this to promote positive effects on bone health among adolescents.[9,16-17]

The study was conducted in the metropolitan region of the city of Presidente Prudente, which is in the western part of the state of São Paulo, with a population of 200,000 inhabitants and a human development index of 0.806.

The sample consisted of 48 adolescents aged between 9 and 17 years, who were matched according to sex (1:1 boy/girl pairs), chronological age and sports participation: nine pairs in a control group (n = 18) and 15 pairs in an impact sports practice group (n = 30). The adolescents in the sports participation group were engaged in impact sports (soccer and combat sports, i.e. karate and judo) and the control group were not engaged in any sports. In relation to the three sports, the adolescents in the impact sports group were matched according to their sport. The adolescents engaged in sports participation were contacted at private and public sports clubs located in the metropolitan area of the city. The control group was contacted in public and private schools in the metropolitan area of the city.

In the sports participation group, the inclusion criteria adopted were as follows: (i) engagement in only one sport over the previous 12 months; and (ii) the participant's legal guardian had signed a written consent form. In the control group, the inclusion criteria adopted were: (i) six months without any engagement in organized sport outside school; (ii) participation in school physical education classes; (iii) no orthopedic disease that prevented the adolescent from practicing sports; (iv) not being pregnant; (v) the subject's legal guardian had signed a written consent form.

Dependent variable: bone mineral density

Whole body BMD (g/cm^2) was estimated by means of dual-energy X-ray absorptiometry (DEXA) (GE model, Lunar-DPX-NT, United Kingdom). BMD measurements were made at the baseline and after nine months of study, in different body segments: upper limbs, lower limbs and spine; these were performed by a technician with extensive experience in these measurements. All the examinations were carried out in the same place at the university (UNESP). During the DEXA scans, the participants wore light clothes, were barefoot (with no metal on the body) and remained immobile for approximately 15 minutes. The results were generated by means of specific software that was provided with the equipment. The DEXA measurements at the baseline were repeated after nine months of follow-up.

Covariates

Sex (male or female) and the quantity of lean soft tissue (LST) (measured using DEXA and expressed in kg) were treated as covariates. LST, composed of muscle mass and residuals, is a widely used surrogate measurement of muscle mass. Moreover, somatic maturation, through estimated peak height velocity (PHV) was used as an indicator of biological maturation. PHV was estimated at baseline using anthropometric measurements (height),[18] based on the mathematical models described by Moore et al.[19] PHV identifies the time (in years) until (negative scores) or after (positive scores) the moment of greatest height accrual during adolescence. Sports participation was also considered to be a covariate. In the statistical models, sports participation was treated as follows: 0 = control and 2 = soccer/combat (high impact) sports.

Statistical analysis

Mean and standard deviation (SD) values were used to describe the characteristics of the sample. Initially, crude comparisons between boys and girls were performed using Student's t test for independent samples (top of the tables). Secondly, the same sex comparisons were simultaneously adjusted for all covariates (PHV, LST, sports participation and vitamin D score) using analysis of covariance (ANCOVA) at the baseline and at the follow-up. The models at the follow-up are presented as comparisons

of BMD after nine months and comparisons of BMD percentage accruals after nine months. In the ANCOVA models, the descriptive statistics were composed of estimated marginal means and 95% confidence intervals (95% CI), and effect-size measurements were expressed as partial eta-squared measurements (ES-r). All statistical procedures were performed in the BioEstat software (version 5.0) and the significance level (P-value) was previously set at $P < 0.05$.

RESULTS

The descriptive statistics are presented in **Table 1**. The boys and girls presented similar body mass (P = 0.331) and height (P = 0.118). However, the boys presented higher LST at the baseline (P-value = 0.001) and gained more LST after nine months (boys, 3.9 kg, versus girls, 2.2 kg; P = 0.001). Somatic maturation (PHV) was different between the groups at the baseline (P = 0.007) and the age at PHV was 13.2 years for boys and 12.0 years for girls ($P \leq 0.001$). In addition, the adolescent sports participants presented greater quantities of LST than did the control group (adjusted for sex and somatic maturation).

Table 1. Summary of the characteristics of the boys and girls at the baseline (n = 48)

	Boys (n = 24)	Girls (n = 24)	P-value
	Mean (SD)	Mean (SD)	
Numerical data			
Age (years)	12.0 (1.6)	12.1 (1.6)	1.000
Body mass (kg)	45.7 (12.0)	44.6 (14.7)	0.331
Height (cm)	154.7 (12.1)	149.5 (10.2)	0.118
PHV (years)	-1.2 (1.3)	0.9 (1.4)	0.007
APHV (years)	13.2 (0.4)	12.0 (0.5)	< 0.001
LST (kg)	34.7 (8.3)	28.6 (5.9)	0.001
LST gains (kg)	3.9 (2.2)	2.2 (1.3)	0.001
Categorical data	**n (%)**	**n (%)**	
Sports participation, n*			
Control, n	9 (50)	9 (50)	
Impact sports, n	15 (50)	15 (50)	

*Sports participation values refer to sample size per group.
SD = standard deviation; PHV = peak height velocity; APHV = age peak height velocity; LST = lean soft tissue.

The comparisons of bone mineral density (BMD) at the baseline between the boys and girls are presented in **Table 2**. The crude analysis showed that the BMD values were similar between the boys and girls. In the multivariate models, after adjustment for covariates, the girls showed higher bone density in the upper limbs. This variance was explained in terms of sex (ES-r = 0.144, i.e. a high effect size), LST (ES-r = 0.619, i.e. a high effect size) and sports participation (ES-r = 0.099, i.e. a moderate effect size). The spinal variance was explained in terms of sex (ES-r = 0.198, i.e. a high effect size) and LST (ES-r = 0.643, i.e. a high effect size). For the lower limbs and whole body, the variance was explained in terms of sex (ES-r = 0.081, i.e. a moderate effect size for the lower limbs, and ES-r = 0.207, i.e. a high effect size for the whole body) and LST (ES-r = 0.699, i.e. a high effect size for the lower limbs, and ES-r = 0.599, i.e. a high effect size for the whole body).

At the nine-month follow-up, the boys did not present higher BMD values in the crude analysis (**Table 3**). In the multivariate equation, while sex better explained the model for the upper limbs (ES-r = 0.171, i.e. a high effect size), spine (ES-r = 0.275, i.e. a high effect size) and whole body (ES-r = 0.241, i.e. a high effect size), LST significantly explained the variance observed in the upper limbs (ES-r = 0.807, i.e. a high effect size), spine (ES-r = 0.681, i.e. a high effect size), lower limbs (ES-r = 0.616, i.e. a high effect size) and whole body (ES-r = 0.681, i.e. a high effect size), which were significantly higher among the girls.

Table 2. Comparisons of bone mineral density (BMD) at the baseline, between the boys and girls (n = 48)

BMD (g/cm²)	Boys (n = 24)	Girls (n = 24)	Sex	PHV	LST	Sport
	Mean (SD)	Mean (SD)	P-value			
Upper limbs	0.707 (0.079)	0.707 (0.089)	0.992	---	---	---
Spine	0.907 (0.121)	0.930 (0.171)	0.599	---	---	---
Lower limbs	1.112 (0.136)	1.062 (0.118)	0.184	---	---	---
Whole body	1.014 (0.088)	1.013 (0.103)	0.963	---	---	---
BMD (g/cm²)	**Mean (95% CI)**	**Mean (95% CI)**	**Effect size determined through ANCOVA (eta-squared [ES-r])**			
Upper limbs	0.676 (0.648 to 0.704)	0.740 (0.712 to 0.786)	0.144*	0.008	0.619*	0.099*
Spine	0.851 (0.802 to 0.901)	0.986 (0.937 to 1.035)	0.198*	0.005	0.643*	0.030
Lower limbs	1.056 (1.017 to 1.095)	1.119 (1.080 to 1.158)	0.081*	0.025	0.699*	0.024
Whole body	0.966 (0.932 to 1.000)	1.062 (1.028 to 1.096)	0.207*	0.063	0.599*	0.003

*Denotes covariate with P-value < 0.05.
SD = standard deviation; 95% CI = 95% confidence interval; PHV = peak height velocity; LST = lean soft tissue.

Comparison of BMD accrual over the nine-month period between the boys and girls (**Table 4**) showed that the gains were similar between the boys and girls and that BMD accrual was not significantly affected by sex. On the other hand, baseline LST was the variable that most showed statistically significant differences, in the upper limbs (ES-r = 0.396, i.e. a high effect size) and whole body (ES-r = 0.107, i.e. a moderate effect size).

DISCUSSION

The aim of the present study was to identify determinants of sex-related BMD differences between male and female adolescents, and to identify the role of sports participation in this phenomenon. The findings suggest that the quantity of lean soft tissue is the most relevant determinant of bone-related differences between boys and girls, while sports participation indirectly affects bone density, in the sense that the more sports practice that was performed, the greater the gain in lean soft tissue would be.

In the present study, the most relevant variable relating to sex-specific differences in bone density was lean soft tissue (both baseline values and gains over nine months). Previous studies have identified a positive relationship between muscle mass and bone variables among adolescents.[20,21] The strengthening and bone remodeling that are stimulated by muscle contraction seems to be explained by the daily tension that muscles exert on the bone structure.[12,22,23] In agreement with our findings, the literature shows evidence that muscle development is an important factor for bone adaptation.[16] Expanded muscle mass contributes towards greater muscle strength and, subsequently, increased

Table 3. Comparisons of bone mineral density (BMD) after nine months of follow-up, between the boys and girls (n = 48)

BMD (g/cm²)	Boys (n = 24)	Girls (n = 24)	Sex	PHV	LST	Sport
	Mean (SD)	Mean (SD)	P-value			
Upper limbs	0.766 (0.122)	0.747 (0.095)	0.175	---	---	---
Spine	0.968 (0.145)	1.001 (0.176)	0.238	---	---	---
Lower limbs	1.163 (0.139)	1.110 (0.118)	0.481	---	---	---
Whole body	1.058 (0.100)	1.053 (0.105)	0.535	---	---	---
BMD (g/cm²)	**Mean (95% CI)**	**Mean (95% CI)**	**Effect size determined through ANCOVA (eta-squared [ES-r])**			
Upper limbs	0.724 (0.967 to 0.750)	0.790 (0.764 to 0.817)	0.171*	0.001	0.807*	0.045
Spine	0.900 (0.850 to 0.950)	1.070 (1.020 to 1.121)	0.275*	0.019	0.681*	0.053
Lower limbs	1.106 (1.062 to 1.151)	1.168 (1.123 to 1.212)	0.059	0.028	0.616*	0.016
Whole body	1.006 (0.974 to 1.038)	1.106 (1.074 to 1.139)	0.241*	0.070	0.681*	0.005

*Denotes covariate with P-value < 0.05.

SD = standard deviation; 95% CI = 95% confidence interval; PHV = peak height velocity; LST = lean soft tissue.

Table 4. Comparisons of bone mineral density (BMD) percentage accruals after nine months of follow-up, between the boys and girls (n = 48)

BMD (g/cm²)	Boys (n = 24)	Girls (n = 24)	Sex	PHV	LST	Sport
	Mean (SD)	Mean (SD)	P-value			
Upper limbs	7.9 (7.7)	5.6 (4.1)	0.062	---	---	---
Spine	6.6 (5.0)	7.8 (4.2)	0.741	---	---	---
Lower limbs	4.7 (3.7)	4.5 (2.6)	0.186	---	---	---
Whole body	4.2 (2.2)	3.9 (2.2)	0.819	---	---	---
BMD (g/cm²)	**Mean (95% CI)**	**Mean (95% CI)**	**Effect size determined through ANCOVA (eta-squared [ES-r])**			
Upper limbs	7.0 (4.3 to 9.7)	6.5 (3.8 to 9.3)	0.001	0.018	0.396*	0.036
Spine	5.8 (3.2 to 8.4)	8.6 (6.0 to 11.2)	0.037	0.010	0.018	0.012
Lower limbs	4.8 (3.0 to 6.6)	4.4 (2.6 to 6.1)	0.002	0.003	0.065	0.004
Whole body	4.0 (2.8 to 5.2)	4.2 (2.9 to 5.4)	0.000	0.001	0.107*	0.001

*Denotes covariate with P-value < 0.05.

SD = standard deviation; 95% CI = 95% confidence interval; PHV = peak height velocity; LST = lean soft tissue.

mechanical stress in the bone, thus stimulating bone adaptation.[24] Although bone undergoes constant adaptation through the processes of modeling and remodeling, mechanical tension stimulates physiological mechanisms that can influence bone formation. Therefore, mechanical stresses can trigger a cascade of events through mechanotransduction.[20]

Regular participation in weight-bearing sports during adolescence is linked to bone density gains.[9] Stronger bones reduce the likelihood of pathological fractures.[11] Although our findings did not reveal that sport had any direct role in the bone mineral density results, sports participation is beneficial for gain and maintenance of muscle mass.[25] Muscle mass has been shown to be the main pathway through which physical exercise/sports participation can improve part of the osteogenic process.[26,27] However, there are other pathways, such as physical loading and the ground reaction force generated by the activity.

In fact, regarding sex-related bone differences, sports participation and muscle mass acted independently in the upper limbs, spine and whole body, and the stress component may explain this. Recently, Ito et al.[16] found that judo participation increased BMD accrual in the spine more than was seen among their control group, but only among boys. This is interesting because, in our study, after excluding the impact of muscle mass and sports participation, the girls presented higher values in the spine than the boys (both at the baseline and at the follow-up), thus denoting the significant participation of both muscle mass and sports participation in this phenomenon. Moreover, judo, karate and swimming are sports in which the upper limbs are highly required,[16] which helps to explain the significant impact of these sports on this body segment. Similarly, Agostinete et al.[16] suggested that the potentially harmful impact of swimming on bone formation in adolescents would be attenuated by its effect on the upper limbs, given the high amount of muscle force produced in this body segment.

In the pre-pubertal and pubertal periods, hormonal and maturational factors seem to promote greater bone accrual attributable to physical exercise among boys than among girls.[16] The independent impact of sports participation on sex-related BMD differences appears to agree with the assumption that both the effects of exercise and sex-related effects offer greater bone growth in boys than in girls. Taking that into consideration, the low magnitude of the effect attributable to sports participation may be related to the sports category divisions used in the present study. Therefore, to better understand this important issue, future studies should identify sex-related BMD differences in specific sports, instead of combining sports with different impacts into a single group.

In the present study, we found that somatic maturation did not have any impact on the models. It has been hypothesized that biological maturation affects bone mineral density in both sexes.[28,29] However, given that the subjects in the present study had a mean chronological age of 12 years, the girls were mostly within the somatic maturation band, while the boys were still around one year away from the peak. Thus, the differences between the sexes could explain part of the variation in somatic maturation. Moreover, because we also adjusted for lean soft tissue, which is affected by biological maturation in both sexes,[30,31] it is plausible that somatic maturation affects lean soft tissue and that lean soft tissue affects BMD. In this manner, somatic maturation might still act as a mediator, which would thus restore its effect.

Although the present study presented positive points such as its longitudinal design, matching of the sample according to sex and age and analysis of BMD using DEXA, some limitations of this study need to be recognized. The first relates to the absence of measurement of bone geometry (a concept that characterizes both bone mineral density and bone mineral content), which would have significantly complemented the bone density measurements. Likewise, follow-ups longer than nine months would have been interesting, with the aim of observing greater potential differences between boys and girls, as well as for identifying manifestations of maturational events. The absence of analyses regarding hormones needs to be recognized, given the impact of hormones on bone formation in both genders.

Moreover, estimates using the somatic maturation indicator may present some bias, although previous studies have pointed out that the optimal chronological age for estimating PHV is between 10 years and 14 years for girls and between 12 years and 16 years for boys,[32] which is concordant with what was done in our sample. In this regard, future studies should also use better methods for making predictions of biological maturation, such as skeletal age.[33]

Although the adolescents who were included in the control group were only attending school physical education classes and were not performing any type of sport, it needs to be borne in mind that there was a lack of information regarding these adolescents' habitual physical activity. In addition, unfortunately, we did not perform any sample size calculations for this study, which was based on a convenience sample from a larger cohort study by our group.

Lastly, measurements of calcium consumption and exposure to sunlight (vitamin D) would be interesting confounders to insert in the multivariate models presented here.

CONCLUSION

The present findings suggest that lean soft tissue is the most relevant determinant of the differences in BMD between boys and girls, while sports participation and somatic maturation potentially have indirect roles in sex-related differences in BMD over time. The main message from this study is that, through engagement in sports practice, female adolescents may present increases in lean soft tissue, which in turn positively influence their BMD gain, thus enabling BMD values similar to or greater than among males.

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What do Cochrane systematic reviews say about the management of irritable bowel syndrome?

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ABSTRACT

BACKGROUND: Irritable bowel syndrome (IBS) is a clinical disorder associated with high socioeconomic burden. Despite its importance, management of IBS remains difficult and several interventions have been hypothesized as beneficial for this condition. This study identified and summarized all Cochrane systematic reviews (SRs) about the effects of interventions for managing IBS patients.

DESIGN AND SETTING: Review of systematic reviews, carried out in the Discipline of Evidence-Based Medicine, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP).

METHODS: Review of Cochrane SRs addressing interventions for IBS.

RESULTS: We included six SRs assessing acupuncture, bulking agents, antispasmodics, antidepressants, herbal medicines, homeopathy, hypnotherapy and psychological therapy for IBS. The certainty of evidence ranged from unknown to moderate, mainly due to imprecision in the estimates and high risk of bias from the primary studies included. There was moderate certainty of evidence that acupuncture had no important benefit regarding improvement of symptoms and quality of life, compared with sham acupuncture. There was also very low certainty of evidence that homeopathic asafoetida, used alone or in association with nux, was better than placebo regarding self-reported overall improvement.

CONCLUSION: There was moderate certainty of evidence that acupuncture had no important benefit regarding improvement of symptoms and quality of life. Further well-designed and well-conducted randomized clinical trials are needed in order to reduce the uncertainties regarding the most commonly used interventions for patients with IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) is a frequent clinical disorder. Its prevalence has been estimated as 11% worldwide,[1] with a range from 3% to 15% according to the diagnostic criteria used.[2] The definition most commonly used is the one that was proposed by the Rome IV investigators, and this takes into account recurrent abdominal pain associated with other gastrointestinal symptoms, without a clear organic cause.[3] The classification systems used generally envisage three groups: IBS predominantly involving constipation, IBS predominantly involving diarrhea and mixed IBS.[3]

Although IBS is a common disease, the etiological and pathophysiological aspects of this condition remain unclear and a matter of controversy. In the past, it was hypothesized that IBS might be more commonly associated with other frequently observed conditions such as sleep disorders and psychological disorders, and that these could be considered to be triggers of this disorder.[4] Recent studies have suggested that the pathophysiology of this so-called brain-gut disorder is more complex and that it involves neurohormonal deregulation, bacterial overgrowth, food intolerance, inflammation, altered intestinal barriers, alterations to fecal flora, and genetic influence. This myriad of factors has been transforming recent knowledge of IBS.[5]

IBS gives rise to an important socioeconomic burden, due to its high prevalence and its impact on daily activities. In fact, occurrences of IBS have been correlated with considerable levels of healthcare demand and missing work days, thereby contributing towards higher direct and indirect costs in a variety of healthcare systems.[6-8]

Management of IBS remains a challenge. Several interventions have been used in clinical practice, including pharmacological, psychological, behavioral and complementary

interventions.[9] In some cases, practical recommendations are made on the basis of low levels of clinical evidence, relating only to hypothesized aspects of the pathophysiology of the condition.[9]

Since IBS is a highly prevalent condition associated with a heavy socioeconomic burden, systematic reviews addressing interventions for treating this condition are needed in order to guide decision-making. Cochrane systematic reviews are considered to provide reliable evidence and are a useful tool for healthcare providers and patients.

OBJECTIVE

To summarize and present the evidence from Cochrane systematic reviews assessing interventions for management of irritable bowel syndrome patients.

METHODS

Design and setting

This was a review of Cochrane systematic reviews (SRs) carried out in the Discipline of Evidence-based Medicine of Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP). This manuscript was prepared for the section "Cochrane Highlights" of the São Paulo Medical Journal. It forms part of a formal collaboration between the São Paulo Medical Journal and the Cochrane Collaboration, and it is supported by Cochrane Brazil. The aim of this initiative is to disseminate the evidence from Cochrane SRs.

Inclusion criteria

Types of studies

We included only the latest published version of Cochrane systematic reviews (SRs). We excluded all protocols, or any SR marked as "withdrawn" in the Cochrane Database of Systematic Reviews (CDSR).

Types of participants

We considered any participant who had been diagnosed with irritable bowel syndrome, as determined through the criteria of the original review authors. Reviews addressing irritable bowel syndrome and also other clinical situations were included only if the subset of data relating to irritable bowel syndrome participants was provided separately.

Types of intervention

We considered any pharmacological or non-pharmacological intervention for therapeutic purposes, compared with placebo, no intervention or any other intervention.

Type of outcomes

We considered the clinical and laboratory outcomes that had already been considered by the SR authors. When multiple outcomes were presented, we chose the primary safety and effectiveness outcomes or the most clinically relevant outcomes, to present in the current review.

Search for reviews

We performed a systematic search in the Cochrane Database of Systematic Reviews (via Wiley) on December 4, 2018. The search strategy is fully depicted in **Table 1**.

Selection of systematic reviews

The selection process was performed by two authors, who independently screened all titles and abstracts retrieved through the electronic search. The authors checked whether the abstracts thus retrieved fulfilled the inclusion criteria and decided whether to include or exclude them. Any disagreements in the selection process were resolved through reaching a consensus.

Presentation of the results

We produced a synthesis and presented the following characteristics relating to the reviews that were included: PICOs (population, intervention, comparator and outcomes), objectives, methods, main results, risk of bias from the original studies and certainty of evidence through the GRADE approach;[10] along with the conclusions from the authors of the SRs that were included.

RESULTS

Search results

The initial search retrieved 78 abstracts of systematic reviews (SRs). After the selection process, six SRs were found to fulfill our inclusion criteria and were included in the analysis.[11-16]

Results from systematic reviews

The six SRs included assessed the effects of conventional interventions (bulking agents, antispasmodics and antidepressants) and non-conventional interventions (acupuncture, herbal medicines, homeopathy, psychological therapy and hypnotherapy) for participants with irritable bowel syndrome

Table 1. Search strategy

#1 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees
#2 (Syndrome, Irritable Bowel) or (Syndromes, Irritable Bowel) or (Colon, Irritable) or (Mucous Colitides) or (Colitis, Mucous) or (Irritable Bowel Syndromes) or (Mucous Colitis) or (Irritable Colon) or (Colitides, Mucous)
#3 #1 or #2
Filters: in Cochrane Reviews; *in Title, Abstract, Keywords*

(IBS). The main findings from the SRs included, and the quality of the evidence (based on the GRADE approach),[10] are detailed in **Table 2**. A brief summary of each SR is presented below.

1. Acupuncture

It has been hypothesized that acupuncture may have effects on the visceral system through stimulating the somatic system, thereby improving symptoms in patients with IBS. This SR[11] assessed the effects of acupuncture on IBS and included 17 randomized clinical trials (RCTs) with 1806 participants. Acupuncture was compared with no intervention, sham intervention (placebo for acupuncture) and pharmacological interventions.

1.1. Acupuncture versus sham acupuncture

- Symptom severity: no differences between the groups, as assessed using the IBS severity scoring system[17] (IBS-SSS), in which lower values are better (standardized mean difference, SMD -0.11; 95% confidence interval, CI -0.35 to 0.13; four RCTs; 281 participants; moderate certainty of evidence).
- Quality of life: no difference between the groups, as assessed using the IBS quality of life scale[18] (IBS-QOL), in which higher values are better (SMD -0.03; 95% CI -0.27 to 0.22; three RCTs; 253 participants; moderate certainty of evidence).

1.2. Acupuncture versus pharmacological treatment

- Proportion of participants with symptom improvement: higher for acupuncture group (risk ratio, RR 1.28; 95% CI 1.12 to 1.45; 5 RCTs; 449 participants; low certainty of evidence). This outcome was assessed through dichotomization of the scales considered in each RCT, in which a cutoff point was established to decide whether participants had experienced an "improvement". Likewise, the SR authors found an improvement in this same outcome favoring acupuncture over no specific treatment (RR 2.11; 95% CI 1.18 to 3.79; two RCTs; 118 participants).

Adverse events were reported in nine RCTs. In one RCT, it was reported that one participant had withdrawn due to syncope, while in eight RCTs, no serious adverse events were reported.

The authors of this SR concluded that acupuncture did not provide any benefit for treating IBS patients, compared with sham treatment. Acupuncture seemed to be better than pharmacological interventions or no intervention, but this finding would need to be interpreted with caution and would need to be explored through further RCTs. The fact that the trials were not blinded increased the risk of bias in subjective outcomes such as "symptom improvement". For further details and to access all the analyses, refer to the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005111.pub3/full.

2. Bulking agents, antispasmodics and antidepressants

This SR[12] included 56 RCTs (3725 patients) that assessed bulking agents (fiber supplements) (12 RCTs; 621 participants), antispasmodics (29 RCTs; 2333 participants) and antidepressants (15 RCTs; 922 participants).

Table 2. Characteristics, main results and quality of evidence of the systematic reviews included

Intervention	Comparison	Main findings	Evidence certainty (GRADE)*
Acupuncture	Acupuncture versus sham	*No difference*	
		• Symptom severity	Moderate
		• Quality of life	Moderate
	Acupuncture versus pharmacological treatment	*Benefits*	
		• Proportion of participants with symptom improvement	Moderate
Antispasmodic drugs	Antispasmodic drugs versus placebo	*Benefits*	
		• Improvement of abdominal pain	NA
		• Overall assessment	NA
		• Symptom score	NA
Antidepressants	Antidepressants versus placebo	*Benefits*	
		• Improvement of abdominal pain	NA
		• Overall assessment	NA
		• Symptom score	NA
Bulking agents	Bulking agents versus placebo	*No difference*	
		• Improvement of abdominal pain	NA
		• Overall assessment	NA
		• Symptom score	NA

Continue...

Table 2. Continuation.

Intervention	Comparison	Main findings	Evidence certainty (GRADE)*
Herbal medicines	Standard Chinese herbal formulation versus placebo	*Benefits* • Overall symptom improvement • Bowel symptom scale, as rated by gastroenterologist	NA NA
		No difference • Bowel symptom scale, as rated by participant	NA
	Individualized herbal formulation versus placebo	*No difference* Overall symptom improvement Bowel symptom scale	NA NA
	Herbal medicines versus conventional therapy	65 RCTs assessed 51 different herbal medicines. Data were very heterogenous and not pooled**	NA
	Herbal medicines plus conventional therapy versus conventional therapy alone	9 RCTs assessed herbal medicine in combination with conventional therapy versus conventional therapy alone. Data were very heterogenous and not pooled**	NA
Homeopathy	Asafoetida versus placebo	*Benefits* • Self-reported overall improvement	Very low
	Asafoetida associated with nux versus placebo	*No difference* • Self-reported overall improvement	Very low
	Homeopathic consultation plus target treatment versus usual care	*No difference* • Wellbeing outcome	NA
Hypnotherapy	Hypnotherapy versus waiting list	*Benefits* • Composite primary symptom reduction score • Proportions of hard/watery bowel movements *No difference* • Frequency of bowel motions (12 months) • Proportion of subjects with bloating • Frequencies of bowel motion and abdominal pain	NA NA NA NA NA
	Hypnotherapy plus pharmacological treatment versus pharmacological treatment alone.	*Benefits* • Abdominal pain (3 months) • Composite primary IBS symptom *No difference* • Quality of life (12 months) • Constipation score (3 and 12 months) • Diarrhea score (3 and 12 months) • Overall symptom score (12 months) • Abdominal pain (12 months)	NA NA NA NA NA NA NA NA
	Hypnotherapy versus psychotherapy plus placebo	*Benefits* • Abdominal pain • Bowel habit • Abdominal distension • General wellbeing	NA NA NA NA

Continue...

Table 2. Continuation.

Intervention	Comparison	Main findings	Evidence certainty (GRADE)*
Psychological interventions	Psychological interventions as a group versus usual care	*Benefits*	
		• Symptom score improvement (2 and 3 months)	NA
		• Abdominal pain improvement (2 and 3 months)	NA
		• Quality of life (2 months)	NA
		No difference	
		• Quality of life (3 months)	NA
	Psychological interventions as a group versus placebo	*Benefits*	
		• Symptom score improvement (2 months)	NA
		No difference	
		• Symptom score improvement (3 months)	NA
		• Abdominal pain improvement (3 months)	NA
	Cognitive behavioral therapy versus usual care	*Benefits*	
		• Symptom score improvement (3 months)	NA
		• Quality of life (2 and 3 months)	NA
		No difference	
		• Symptom score improvement (2 months)	NA
		• Abdominal pain improvement (2 and 3 months)	NA
	Cognitive behavioral therapy versus placebo	*No difference*	
		• Symptom score improvement (2 and 3 months)	NA
		• Abdominal pain improvement (2 and 3 months)	NA
		• Quality of life (3 months)	NA
	Interpersonal psychotherapy versus usual care	*Benefits*	
		• Relief of symptoms	NA
		No difference	
		• Symptom score improvement	NA
	Relaxation/stress management versus usual care	*Benefits*	
		• Symptom score improvement (2 months)	NA
		No difference	
		• Abdominal pain improvement	NA

*GRADE (Grading of Recommendations Assessment, Development and Evaluation) has the aim of assessing the certainty of the body of evidence. From this, the outcomes are classified as having high certainty (high confidence that the estimated effect is close to the true effect); moderate certainty (likely that the estimated effect is close to the real effect, but there is a possibility that it is not); low certainty (limited confidence in the effect estimate) or very low certainty (the true effect is likely to be substantially different from the estimate effect). **For further information about specific types of herbal therapy, refer to the relevant text in the "Results" section of this paper.

IBS = irritable bowel syndrome; NA = not assessed; RCTs = randomized clinical trials.

2.1 Bulking agents versus placebo

It was found that bulking agents (including both insoluble and soluble fibers) did not have any beneficial effect in relation to placebo, regarding improvement of abdominal pain (MD 0.03; 95% CI -0.34 to 0.40; P = 0.874; 3 RCTs; 186 participants), overall assessment (RR 1.10; 95% CI 0.91 to 1.33; P = 0.32; 11 studies; 565 participants) or symptom score (MD -0.00; 95% CI -0.43 to 0.43; P = 1.00; 3 RCTs; 126 participants). The subgroup analyses relating to insoluble and soluble fibers were consistent with the main analysis.

2.2 Antispasmodics versus placebo

Antispasmodics had a beneficial effect in relation to placebo for improvement of abdominal pain (58% versus 46%; RR 1.32; 95% CI 1.12 to 1.55; P < 0.001; number needed to treat, NNT 7; 13 studies; 1392 participants), overall assessment (57% versus 39%; RR 1.49; 95% CI 1.25 to 1.77; P < 0.0001; NNT 5; 22 RCTs; 1983 participants) and symptom score (37% versus 22%; RR 1.86; 95% CI 1.26 to 2.76; P < 0.01; NNT 3; 4 RCTs; 586 participants). Subgroup analyses for different types of antispasmodics found that use of cimetropium/dicyclomine, peppermint oil, pinaverium and trimebutine presented statistically significant benefits.

2.3 Antidepressants versus placebo

Antidepressants had a beneficial effect in relation to placebo for improvement of abdominal pain (54% versus 37%; RR 1.49; 95% CI 1.05 to 2.12; P = 0.03; NNT 5; 8 studies; 517 participants), overall assessment (59% versus 39%; RR 1.57; 95% CI 1.23 to 2.00; P < 0.001; NNT 4; 11 RCTs; 750 participants) and symptom score (53% versus 26%; RR 1.99; 95% CI 1.32 to 2.99; P = 0.001; NNT 4; 3 RCTs; 159 participants). Subgroup analyses showed that the following presented statistically significant benefits: (a) selective serotonin releasing inhibitors (SSRIs) for improvement of overall assessment; and (b) tricyclic antidepressants (TCAs) for improvement of abdominal pain and symptom score. A separate analysis on studies with adequate allocation concealment found that antidepressants gave rise to significant benefits regarding improvement of symptom scores and overall assessment. Adverse events were not assessed. For further details and to access all the analyses, refer to the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003460.pub3/full.

3. Herbal medicines

Herbal therapies are commonly used for many clinical conditions and it has been hypothesized that these could have benefits for IBS patients. This SR[13] assessed the effects of herbal medicines on management of IBS and included 75 RCTs (7957 participants). The methodological quality of three RCTs was high, but the overall quality of the remaining RCTs was low. Seventy-one different herbal medicines were tested alone or in combination with conventional therapy, and were compared with placebo or conventional pharmacological therapy.

3.1 Herbal medicines versus placebo

In 6 RCTs, 12 different herbal medicines were tested in comparison with placebo. Overall, herbal medicines showed better improvement of overall symptoms.

- Standard Chinese herbal formulation
  - Overall symptom improvement: better with herbal formulation, as rated by the participants (RR 2.15; 99% CI 1.07 to 4.32) and by the gastroenterologist (RR 2.62; 99% CI 1.19 to 5.77).
  - Bowel symptom scale (BSS): no difference between groups after 16 weeks of treatment, as rated by the participants (weighted mean difference, WMD -43.90; 99% CI -92.16 to 4.36), but better with herbal formulation, as rated by the gastroenterologist (WMD -76.30; 99% CI -125.45 to -27.15). However, this effect was not statistically significant at 14 weeks of follow-up.
- Individualized herbal formulation
  - Overall symptom improvement: no difference between groups (one RCT; 116 participants).
  - Bowel symptom scale (BSS): no difference between groups after 16 weeks of treatment, as rated both by the participants (WMD -47.0; 99% CI -98.55 to 4.55) and by the gastroenterologist (WMD -46.8; 99% CI -106.07 to 12.47). This finding was sustained at 14 weeks after completion of the treatment (WMD -56.30; 99% CI -120.80 to 8.20).

3.2 Herbal medicines versus conventional therapy

In 65 RCTs in which 51 different herbal medicines were tested, 22 herbal medicines resulted in statistically significant symptom improvement and 29 herbal medicines were not significantly different from conventional therapy.

3.3 Herbal medicines combined with conventional therapy versus conventional therapy alone

In nine RCTs in which herbal medicine combined with conventional therapy was evaluated, six showed that there was additional benefit from the combination therapy, compared with conventional monotherapy.

No serious adverse events from the herbal medicines were reported. For further details and to access all the analyses, refer to the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004116.pub2/full.

4. Homeopathy

This SR[14] assessed the effects of homeopathy for treating IBS patients and included three RCTs (213 participants).

4.1 Asafoetida versus placebo

Asafoetida is a substance derived from the roots of perennial herbs. In two RCTs, use of this substance showed significant benefit regarding the number of patients who had self-reported overall improvements (RR 1.61; 95% CI 1.18 to 2.18; two RCTs; 129 participants; very low certainty of evidence).

4.2 Asafoetida associated with nux versus placebo

Nux is a substance derived from seeds that contain strychnine poison. In a single RCT, use of this substance did not show any difference regarding the number of patients who had self-reported overall improvements (RR 1.31; 95% CI 0.80 to 2.15; one RCT; 42 participants; very low certainty of evidence).

4.3 Homeopathic consultation plus target treatment versus usual care

In a single RCT, there was no difference in the wellbeing outcome (MD 0.03; 95% CI -3.16 to 3.22; one RCT; 20 participants).

The very low quality of evidence prevented any solid conclusion about homeopathy for IBS. The RCTs included were small and used non-validated outcomes. Future RCTs with adequate sample size and clinically oriented valid outcomes would need to be performed to reduce the uncertainty in the use of homeopathy for IBS patients. For further details and to access all the analyses, refer to the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009710.pub2/full.

5. Hypnotherapy

Hypnotherapy has been reported to have beneficial effects for managing symptoms. This SR[15] had the aim of assessing the effects of hypnotherapy for patients with IBS. Four RCTs (147 participants) were included, but no meta-analysis was performed, due to clinical and methodological heterogeneity between the studies.

5.1 Hypnotherapy versus waiting list

Hypnotherapy was superior regarding the composite primary symptom reduction (CPSR) score[19] (MD -0.87; 95% CI - 1.36 to -0.38) and the proportions of hard/watery bowel movements (MD -0.25; 95% CI -0.38 to -0.12) over the short term, among patients for whom standard medical therapy had failed (37 participants; 2 RCTs). No differences between the interventions were found in relation to frequency of bowel motions (12 months), proportion of subjects with bloating, frequency of bowel motion and abdominal pain.

5.2 Hypnotherapy plus pharmacological treatment versus pharmacological treatment alone

Combined therapy was superior regarding abdominal pain after three months (MD -14.4; 95% CI -24.69 to -4.11) and composite primary IBS symptoms (81 participants; one RCT). No differences between the interventions were found in relation to quality of life (after 12 months), constipation score (after 3 and 12 months), diarrhea score (after 3 and 12 months), overall symptom score (12 months) and abdominal pain (12 months).

5.3 Hypnotherapy versus psychotherapy plus placebo

There were benefits in the hypnotherapy group at three months in relation to abdominal pain, bowel habit, abdominal distension and general wellbeing (81 participants; one RCT). We entered into correspondence with the authors and found that the data were no longer available for analysis (their study was conducted more than 20 years ago).

No adverse events were reported in any of the trials. The results from these studies need to be interpreted with caution due to their poor methodological quality and small size. For further details and to access all the analyses, refer to the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005110.pub2/full.

6. Psychological interventions

Physiological factors appear to be related to one of the pathophysiological aspects of IBS manifestation. There have been some indications of an association between IBS and psychiatric disorders.

The objective of this SR[16] was to investigate the benefits and harm of any psychological treatments in this population. The SR included 25 RCTs that assessed psychological interventions as a group: cognitive behavioral therapy, interpersonal psychotherapy and relaxation/stress management.

6.1 Psychological interventions as a group versus usual care

- Symptom score improvement: better with psychological interventions at two months (SMD 0.97; 95% CI 0.29 to 1.65; six RCTs; 222 participants) and at three months (SMD 0.62; 95% CI 0.45 to 0.79; eight RCTs; 593 participants), compared with usual care. When compared with placebo, psychological interventions seemed superior at two months (standardized mean difference, SMD 0.71; 95% CI 0.08 to 1.33; two RCTs; 44 participants), but not at three months (SMD -0.17; 95% CI -0.45 to 0.11; three RCTs; 230 participants).
- Abdominal pain improvement: better with psychological interventions at two months (SMD 0.54; 95% CI 0.10 to 0.98; three RCTs; 90 participants) and at three months (SMD 0.26; 95% CI 0.07 to 0.45; ten RCTs; 727 participants), compared with usual care. In comparison with placebo, no difference was found at three months (SMD 0.31; 95% CI -0.16 to 0.79; five RCTs; 416 participants).
- Quality of life: better with psychological interventions at two months (SMD 0.47; 95% CI 0.11 to 0.84; two RCTs; 132 participants), but not at three months (SMD 0.31; 95% CI -0.16 to 0.77; three RCTs; 243 participants).

6.2 Cognitive behavioral therapy versus usual care

- Symptom score improvement: no difference through use of cognitive behavioral therapy, compared with usual care at two months (SMD 0.75; 95% CI -0.20 to 1.70; four RCTs; 133 participants). At three months, cognitive behavioral therapy was better than usual care (SMD 0.58; 95% CI 0.36 to 0.79; five RCTs; 378 participants). In comparison with placebo, there was no difference between the groups at two months (SMD 0.68; 95% CI -0.01 to 1.36; two RCTs; 44 participants) and at three months (SMD -0.17; 95% CI -0.45 to 0.11; three RCTs; 230 participants).
- Abdominal pain improvement: no difference through use of cognitive behavioral therapy, compared with usual care at two months (SMD 0.45; 95% CI 0.00 to 0.91; three RCTs; 80 participants) and at three months (SMD 0.22; 95% CI -0.04 to 0.49; seven RCTs; 359 participants). The results were similar in comparison with placebo at two months (SMD -0.41; 95% CI -1.30 to 0.48; one RCT; 20 participants) and three months (SMD 0.33; 95% CI -0.16 to 0.82; five RCTs; 395 participants).
- Quality of life: An improvement through cognitive behavioral therapy was observed in comparison with usual care at two months (SMD 0.44; 95% CI 0.04 to 0.85; two RCTs; 97 participants) and at three months (SMD 0.92; 95% CI 0.07 to 1.77; one RCT; 24 participants). In comparison with placebo, no difference was found between the groups at three months (SMD 0.16; 95% CI -0.22 to 0.54; one RCT; 129 participants).

6.3 Interpersonal psychotherapy versus usual care

- Relief of symptoms: better with psychotherapy than with usual care (RR 2.02; 95% CI 1.13 to 3.62; number need to treat, NNT 4; two RCTs; 254 participants).
- Symptom score improvement: no difference between the groups (SMD 0.35; 95% CI -0.75 to 0.05; two RCTs; 254 participants).

6.4 Relaxation/stress management versus usual care

- Symptom score improvement: better with relaxation/stress group than with usual care at two months (SMD 0.50; 95% CI 0.02 to 0.98; four RCTs; 123 participants).
- Abdominal pain improvement: no difference at three months (SMD 0.02; 95% CI -0.56 to 0.61; three RCTs; 158 participants).

Long-term follow-up results were scarce and there was no convincing evidence that treatment effects were sustained following completion of the treatment, for any treatment type. For further details and to access all the analyses, refer to the original abstract, available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006442.pub2/full.

DISCUSSION

This review included six Cochrane systematic reviews (SRs) that evaluated interventions for management of irritable bowel syndrome (IBS). The SRs addressed acupuncture, herbal medicines, homeopathy, hypnotherapy, psychological interventions, bulking agents, antispasmodics and antidepressants. The certainty of evidence ranged from unknown to moderate.

There was moderate certainty of evidence that acupuncture had no important benefit regarding improvement of symptoms and quality of life, compared with sham acupuncture. Additionally, one SR reported with very low certainty of evidence that homeopathic asafoetida, alone or in association with nux, was better than placebo regarding self-reported overall improvement. The other four SRs did not assess the certainty of evidence using the GRADE approach, and therefore future updates need to prioritize this assessment.

Our search strategy also retrieved four Cochrane SR protocols that might be included in a future update of this review.[20-23] The aims of these studies are to evaluate probiotic agents for diarrhea-predominant IBS,[20] probiotics for IBS in children,[21] biofeedback[22] and physical activity.[23] When published, these SRs will provide the current evidence from these increasingly used interventions for treating IBS and will help guide clinical practice. Also, the present review was restricted to data in the Cochrane Library. However, many SRs have been published by other scientific journals, and these may cover interventions that were not included here.

The fact that the RCTs included in each SR presented methodological and reporting limitations also reduced the certainty of the evidence found. Overall, heterogeneity relating to outcomes and low sample sizes were the most common shortcomings. These, respectively, prevented quantitative synthesis and magnified the imprecision of the findings.

Regarding practical implications, there were no solid conclusions that might reflect a strong recommendation for clinical practice. Healthcare providers and patients need to be aware that there is a lack of evidence from randomized clinical trials to support even the most commonly used interventions for treating IBS. Clinical practice may be individually guided through the results presented in **Table 2**, but future studies may change these results substantially.

Over the last few years, new classes of drugs have been introduced for management of those patients. However, few RCTs or SRs assessing their effects have been published. Linaclotide, which increases intestinal secretion through activation of guanylate cyclase C, is used for treating constipation and different presentations of diarrhea.[24] Eluxadoline, a mu-opioid receptor agonist, may likewise be useful for controlling abdominal pain, through regulating gastrointestinal motility, secretions and visceral sensation.[25] Although few studies have provided any support for a

role for special diets in treating IBS, FODMAP diets (based on restriction of fermentable oligosaccharides, disaccharides, monosaccharides and polyols) are frequently used in clinical practice and need to be considered in further studies.[26] Fecal transplantation is another controversial topic, and upcoming RCTs and SRs need to encompass assessment of this intervention in future analyses.[27]

In summary, it is not possible to provide full comprehension of IBS management through addressing only the published SRs. The major advances in drugs and alternative treatments that have been published recently make it imperative for updated and GRADE-guided[10] SRs to be produced. Future RCTs need to focus on the gaps in the evidence and consider clinically relevant outcomes. Core outcome sets need to be developed within IBS research, and trialists should include these in their analyses.

CONCLUSION

This review included six Cochrane systematic reviews that evaluated acupuncture, herbal medicines, homeopathy, hypnotherapy, psychological interventions, bulking agents, antispasmodics and antidepressants for treating irritable bowel syndrome (IBS). There was moderate certainty of evidence showing that use of acupuncture did not provide any important differences in symptom severity scores and quality of life, in comparison with sham acupuncture. Further well-designed and well-conducted randomized clinical trials are needed in order to reduce the uncertainties regarding several commonly used interventions for treating IBS.

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Intracranial aneurysm and arachnoid cyst: just a coincidence? A case report

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KEY WORDS:
Arachnoid cysts.
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Intracranial hemorrhages.

ABSTRACT

CONTEXT: Presence of an arachnoid cyst and a non-ruptured intracystic brain aneurysm is extremely rare. The aim of this paper was to describe a case of a patient with an arachnoid cyst and a non-ruptured aneurysm inside it. Clinical, surgical and radiological data were analyzed and the literature was reviewed.

CASE REPORT: A patient complained of chronic headache. She was diagnosed as having a temporal arachnoid cyst and a non-ruptured middle cerebral artery aneurysm inside it. Surgery was performed to clip the aneurysm and fenestrate the cyst.

CONCLUSIONS: This report raises awareness about the importance of intracranial vascular investigation in patients with arachnoid cysts and brain hemorrhage.

INTRODUCTION

Intracranial arachnoid cysts account for 1% of all brain lesions.[1] Most of them are located in the middle fossa.[1] Because neuroimaging has become more available, arachnoid cysts are becoming diagnosed more frequently, even when they are asymptomatic. This type is the most common presentation,[2] and constitutes an incidental finding. Patients with arachnoid cysts can also present with headache, nausea and vomiting, and with cranial nerve palsy.[1] These cysts are acquired lesions relating to abnormal splitting of subarachnoid layers, and they may reach huge dimension. In addition, they may be related to collagen disorder diseases.[1]

On the other hand, the etiology of brain aneurysms is a controversial topic in which genetic changes, smoking and arterial hypertension constitute predisposing factors.[1] The estimated overall prevalence of unruptured intracranial aneurysms in adults without comorbidities is about 3.2%.[3] Therefore, although they are common lesions that are often associated with collagen diseases such as Marfan syndrome and polycystic renal disease,[3] an association between an arachnoid cyst and brain aneurysm in the same patient is extremely rare.[4,5]

The aim of this paper was to report a case of a patient with a diagnosis of an arachnoid cyst and a non-ruptured intracystic brain aneurysm. The literature on this rare condition was also reviewed.

CASE REPORT

A 54-year-old female patient presented with a clinical complaint of a left chronic hemicranial headache with pulsatile pattern. In her past medical history, she had only had arterial blood hypertension. Her neurological examination was normal. She did not have any relevant family history.

Neurological investigation was performed through brain magnetic resonance imaging (MRI), which revealed a left temporal arachnoid cyst (**Figure 1**). There were no signs of intracranial bleeding. In addition, localized vascular dilatation at the left middle cerebral artery bifurcation (inside the cyst) was noticed, which was suggestive of saccular aneurysm. Because of this, cerebral angiography was performed, which confirmed the presence of a left middle cerebral artery aneurysm with dimensions of 9 mm x 6 mm and a neck of 3 mm (**Figure 1**).

Surgical treatment was proposed, consisting of left pterional craniotomy to clip the middle cerebral artery aneurysm. This procedure was implemented without complications. Fenestration

of the cyst was also performed to provide communication with the basal cisternae (**Figure 2**). Only a single clip was needed to achieve occlusion of the aneurysm. The patient presented good recovery, with complete exclusion of the aneurysm from the brain circulation and cyst volume reduction. She presented without neurological deficits and was discharged from hospital for ambulatory follow-up.

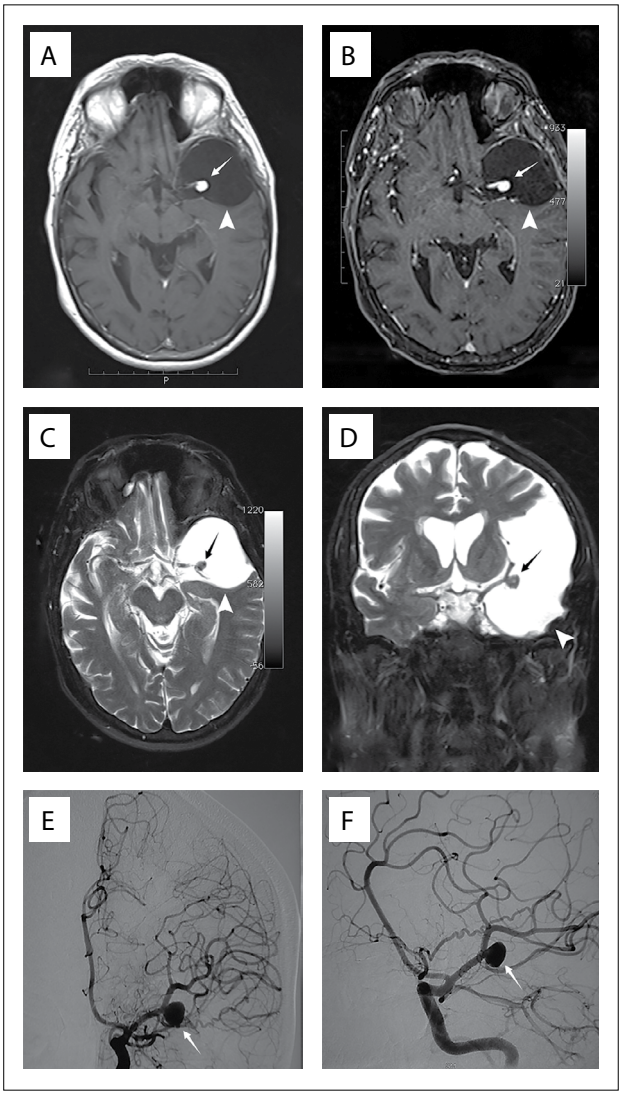

Figure 1. A) Axial T1-weighted non-contrasted magnetic resonance imaging (MRI) showing hypointense lesion at the middle fossa and nodule formation inside the cyst; B) Axial T1-weighted MRI showing hypointense lesion at the middle fossa with saccular dilation inside; C) Axial T2 MRI showing the cyst and the middle cerebral artery bifurcation with saccular dilation at this location; D) Coronal T2 MRI showing the temporal cyst and middle cerebral artery bifurcation with dilation; E) Cerebral arteriography showing aneurysm at the left middle cerebral artery bifurcation; F) Oblique-incidence cerebral angiography showing the aneurysm.

DISCUSSION

Arachnoid cysts are congenital lesions that may cause major neurological symptoms,[1] but which generally constitute an incidental finding. Because MRI and computed tomography (CT) have become more available, these cysts are becoming diagnosed more frequently. Regarding etiology, there are three main theories:

1. Embryonic dysgenesis during arachnoid cyst formation due to a primary defect of the mesenchyme adjacent to the neural tube;
2. Localized brain agenesis, atrophy or hypoplasia causing secondary expansion of the space for cerebrospinal fluid (CSF);
3. Localized disorder secondary to an inflammatory, infectious, traumatic or hemorrhagic lesion.[1]

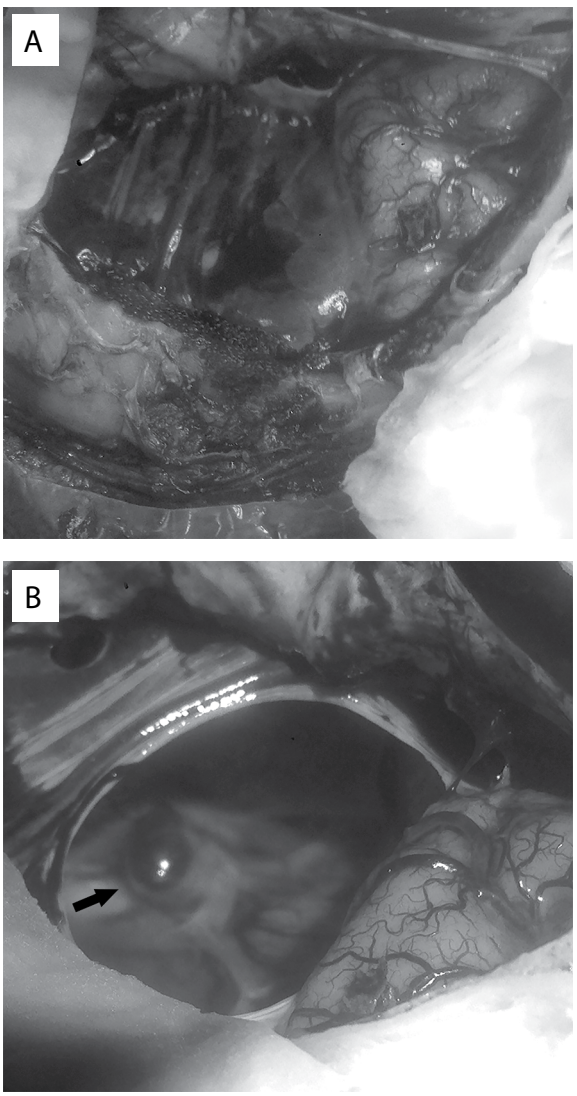

Figure 2. Microsurgical views: A) Before cyst wall opening; B) After cyst wall opening showing the aneurysm at the left middle cerebral artery bifurcation inside it.

Table 1. Search of the literature in medical databases for case reports on intracranial aneurysm and arachnoid cysts

Database	Search strategies	Papers found	Papers related (with ruptured aneurysm)	Papers related (with non-ruptured aneurysm)	Female	Male	Main neurological symptom
MEDLINE (via PubMed, on March 5, 2017)	"Arachnoid cysts" [MESH] AND "Intracranial aneurysm" [MESH] AND Case Reports[ptyp]	23	8	0	6	2	Headache
LILACS (via BVS, on June 1, 2017)	Arachnoid cysts [Palavras] and Intracranial aneurysm [Palavras]	3	2	0	1	1	Headache

Most authors have maintained that arachnoid cysts are congenital, and this theory has been accepted because of their association with other malformations such as corpus callosum agenesis, Marfan syndrome, type 1 neurofibromatosis and polycystic kidney disease.[1]

Similarly, the etiology of saccular brain aneurysms is not well established.[4] There is an association between collagen diseases and other forms of brain dysplasia, such as in Elhers-Danlos and Marfan syndromes and in polycystic kidney disease.[1]

The current prevalence of brain aneurysms in patients with polycystic kidney disease ranges from 4 to 12%, which is higher than in the general population (1-4%).[3] In these cases, the risk of rupture risk is higher: about five times greater than in patients without this disease.[3]

Romão et al.[3] evaluated 92 patients with polycystic disease and found that six of them had some form of intracranial lesion: three with aneurysms and three with arachnoid cysts. However, none of them had both lesions.[3] It is possible that arachnoid cysts and brain aneurysms are distinct disorders relating to a single dysembryogenesis.[2] Thus, it can be seen that an association between brain aneurysm and an arachnoid cyst, as in the case reported here (**Figures 1** and **2**), is very rare.

Arachnoid cysts of the middle fossa only rarely induce neurological symptoms.[5] These symptoms occur when there is increased pressure on the neighboring structures.[5] Neurological signs and symptoms may originate from bleeding inside the cyst. Intracystic hemorrhages are generally due to traumatic brain injury (TBI).[1] Even mild TBI can cause subdural hematomas or intracystic hemorrhage.[1,5]

Intracystic hemorrhage due to ruptured brain aneurysm is an extremely rare condition,[1] with few cases reported in the literature. In most cases, the aneurysm is attached to the cyst wall and its rupture gives rise to arachnoid membrane permeation, thus causing intracystic bleeding.[1] Intracystic hemorrhage is usually caused by rupture of aneurysms of posterior communicating arteries, internal carotid or middle cerebral bifurcations and anterior communicating arteries. These aneurysms may be adjacent to the cyst[1] and may evolve with intracystic or subarachnoid hemorrhage and subdural hematomas.[2]

An association between brain aneurysm and an arachnoid cyst is a very rare condition (**Table 1**). A review of the literature was performed through PubMed, searching for the terms "arachnoid cyst" and "intracranial aneurysm" and the few cases reported in the literature were found to describe patients with brain hemorrhage. Therefore, simultaneous arachnoid cyst and non-ruptured brain aneurysm is an even rarer situation.[2] In the present report, this diagnosis was an incidental finding. de Oliveira et al.[5] found associations between aneurysms and arachnoid cysts through a review of the literature in which only 10 cases were reported. In most of these cases, intracranial hemorrhage was the first manifestation.[5]

There has also been one report of multiple aneurysms associated with arachnoid cysts,[2] which evolved with rupture of the intracystic aneurysm, without typical subarachnoid hemorrhage.[1] All of these possibilities should be borne in mind during neuroimaging evaluations on patients with arachnoid cysts without symptoms and on those who present with intracranial hemorrhage.

CONCLUSION

There is no strong evidence in literature to correlate arachnoid cysts and brain aneurysms. However, for all patients with diagnoses of arachnoid cyst and brain hemorrhage, intracranial vascular investigation should be performed, because these conditions may be associated due to their common pathogenesis. The present unique case of non-ruptured brain aneurysm and arachnoid cyst also serves to raise awareness about the importance of proper vascular investigation, even in cases without intracranial hemorrhage.

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Coexistence of morphea and granuloma annulare: a rare case report

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KEY WORDS:
Granuloma annulare.
Collagen diseases.
Scleroderma, localized.

ABSTRACT

CONTEXT: Localized scleroderma (morphea) is characterized by fibrosis of skin and subcutaneous tissue. Granuloma annulare is a relatively common disease that is characterized by dermal papules and arciform plaques.

CASE REPORT: Here, we present the case of a 42-year-old woman who developed granuloma annulare on the dorsum of her feet and abdominal region, and morphea on the anterior side of her lower limbs. We also discuss the etiological and pathogenetic processes that may cause the rare coexistence of these two diseases.

CONCLUSION: Only a few cases in the literature have described coexistence of morphea and granuloma annulare.

INTRODUCTION

Morphea, also known as localized scleroderma, is characterized by fibrosis of skin and subcutaneous tissue. The increase in collagen production resulting from skin fibrosis can arise from endothelial cell injury, immunological factors (for example, relating to T lymphocytes) and inflammatory activation and dysregulation of collagen production.[1]

Granuloma annulare is a common cutaneous disorder that classically presents as annular skin-colored to erythematous papules without epidermal changes, which are located on the dorsum of hands and/or feet. There are many variants of the disease, which can occur in localized, generalized (including generalized annular, disseminated papular and atypical generalized granuloma annulare), subcutaneous, and perforating forms.[2] Generalized granuloma annulare is defined by simultaneous presence of at least ten skin lesions or by widespread annular plaques, and can occur in around 8-15% of patients with granuloma annulare. It is more likely to occur in middle-aged and elderly patients.[3]

Only a few cases in the literature have presented with coexistence of morphea and granuloma annulare. These are separate disorders according to the dermatological literature.[3,4]

Here, we present a case of morphea together with granuloma annulare, with the aim of discussing the etiological and pathogenetic processes that may cause the rare coexistence of these two diseases.

CASE

Our patient was a 42-year-old woman who developed sclerotic plaques with a violet-colored border and central depression, on the anterior side of her lower limbs, and also erythematous annular, arciform plaques on the dorsum of her feet and lower abdominal region. These conditions started concomitantly one year before we saw the patient (**Figures 1** and **2**).

Lyme IgM/IgG antibodies were investigated by means of Western blotting. An autoimmune panel (antinuclear antibodies and anti-ds-DNA) was produced. Fasting blood sugar levels, erythrocyte sedimentation rate, thyroid function and antibodies, immunoglobulin levels and protein electrophoresis were investigated. The patient was negative for *Borrelia* antibodies. There were no systemic symptoms. The laboratory findings were all within normal ranges.

Histopathological examination on the dorsum of the feet and abdominal region showed interstitial granulomatous infiltrate in the middle and upper dermis and moderately elevated mucin

deposits (**Figure 3**). A lower-limb specimen showed lymphoplasmacytic inflammatory infiltrates separating the collagen strands and surrounding eccrine coils in the deep dermis, and these findings were associated with loss of adipocytes around the eccrine apparatus (**Figure 4**). Histopathological examination also revealed morphea on the anterior side of the lower limbs and granuloma annulare on the dorsum of the feet and abdominal region.

We diagnosed this case as one of morphea plaque and generalized granuloma annulare, in interstitial form with these clinical and histopathological findings. The patient was started on topical steroid ointment therapy. The morphea lesions slowly regressed and the granuloma annulare lesions healed, although the dorsum of the feet continues to present pigmentation for two years.

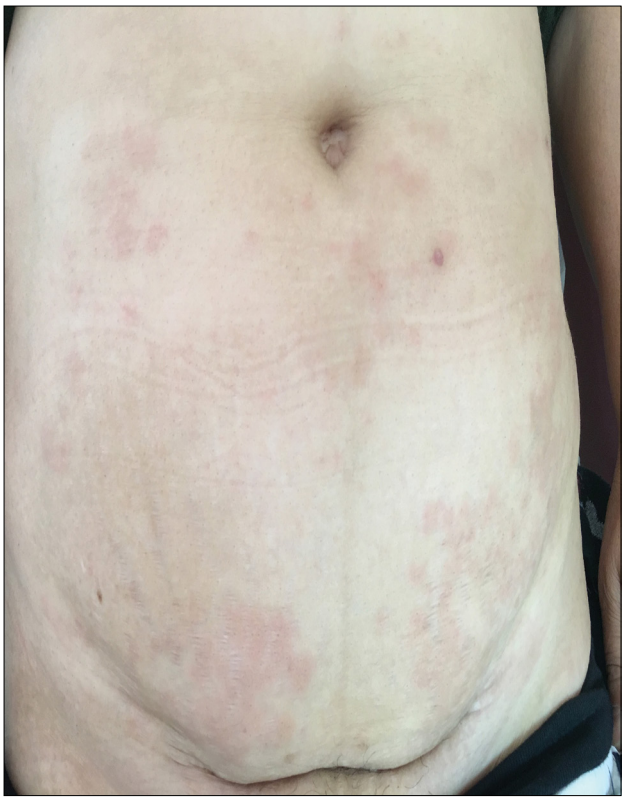

Figure 1. Erythematous annular, arciform plaques on the lower abdominal region.

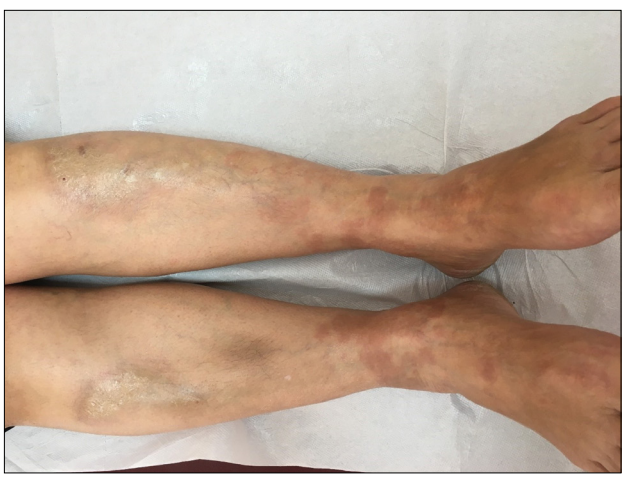

Figure 2. Sclerotic plaques with violet-colored border and central depression on the anterior side of lower limbs.

DISCUSSION

Granuloma annulare is a benign, self-limited cutaneous inflammatory condition that usually presents as a ring of multiple skin-colored to erythematous papules, often on the acral surfaces. Exposure to sunlight, insect bites, viral infection and trauma have all been postulated as causes. In the generalized form of granuloma annulare, there may be an association with diabetes

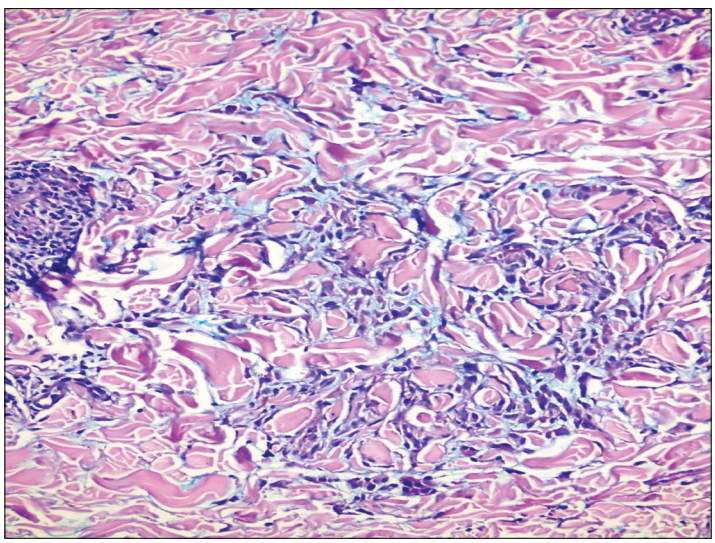

Figure 3. Histiocytic cell infiltration with interstitial distribution between coarse collagen fibers in dermis (hematoxylin and eosin, x 100).

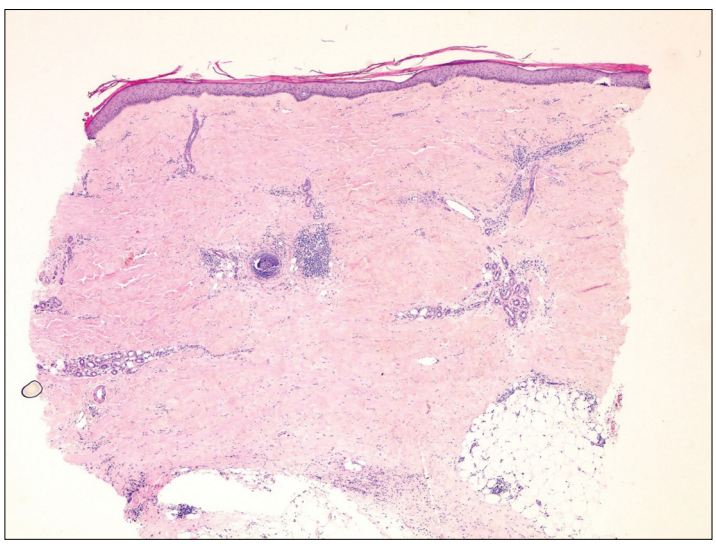

Figure 4. Lymphoplasmacytic inflammatory infiltrate separating collagen strands and surrounding eccrine coils in deep dermis (hematoxylin and eosin, x 40).

mellitus.[1,2] Histological evaluations have revealed foci of degenerative collagen associated with palisaded granulomatous inflammation. Granuloma annulare is further classified according to lesion morphology, into four subtypes with overlapping features: localized, macular, patch and atypical.[1-3]

Morphea is characterized by reddened edematous areas. In its chronic phase, it forms a sclerotic indurated plaque with an ivory-colored center. Histologically, in the acute phase, lymphohistiocytic infiltrate is present between swollen and eosinophilic collagen bundles. In the chronic phase, the inflammatory infiltrate becomes minimal and only homogeneous sclerotic hyalinized collagen bundles remain. T lymphocytes appear to be the major agent involved in induction of the disease.[1,5]

Sarcoidosis, granuloma annulare and forms of granulomatous vasculitis such as Churg-Strauss syndrome (CSS) and Wegener's granulomatosis (WG) are the most common granulomatous disorders that occur in immunocompromised cutaneous regions. These may share common pathogenic mechanisms.[6] Like some other authors,[4-6] we suggest that a common etiological link might explain this association.

Histologically, both granuloma annulare and morphea, show perivascular and interstitial lymphohistiocytic infiltrate and collagen, immune-mediated vasculitis or nonimmune vascular injury. It remains unclear whether dysregulation of control over fibroblast function by T-cell derived cytokines might be the common event in the pathogenesis of these two diseases.

Both diseases have been correlated with Lyme disease.[4,5] However, most studies based on polymerase chain reaction (PCR) have not confirmed any etiological role for *Borrelia burgdorferi* infection regarding localized scleroderma and granuloma annulare. Our patient did not have antibodies for *Borrelia*. Therefore, *Borrelia burgdorferi* infection could not have been the common etiopathogenetic agent for this case, either.

There are no more than 10 case reports in the available literature (**Table 1**). The lesions followed each other in all of those patients. On the other hand, the lesions in the present case appeared simultaneously.

Morphea and granuloma annulare cause inflammation of blood vessels and may lead to alterations in collagen. Autoimmune or infectious disease etiology has been proposed for both morphea and granuloma annulare, and we cannot rule out the possibility that this may be the true causal link.

In 1983, Holmes and Meara[5] reported the first case of biopsy-proven morphea in association with granuloma annulare. Tajima et al.[7] reported two cases with scleroderma and perforating granuloma annulare . Ben-Amitai et al.[4] reported three cases (**Table 2**). In all of these cases, the illnesses developed in succession. However according to our patient's reports, the two illnesses started together. The two cases with scleroderma that were reported[7] were at the same location, while all the other cases were at different locations.

Table 1. Results from search carried out on July 11, 2017

	Search strategy	Full results	Related references
MEDLINE (via PubMed)	("Scleroderma, Localized"[Mesh]) AND ("Granuloma annulare"[Mesh])	9	3
LILACS (via BVS)	mh:"Sleroderma localized) AND mh:"Granuloma anmulare"	0	0

MEDLINE = Medical Literature Analysis and Retrieval System Online; LILACS = Literatura Latino-americana e do Caribe em Ciências da Saúde; BVS = Biblioteca Virtual em Saúde.

Table 2. Ages in years at onset of diseases of granuloma annulare and morphea among patients reported in the literature

Number of cases reported (year)	Patient age - initial disease	Patient age - secondary disease	Authors
1 case (1983)	5 - GA	46 - M	Holmes and Meara[5]
2 cases (1996)	30 - SS	33 - GA	Tajima et al.[7]
	22 - SS	39 - GA	
3 cases (1999)	61 - GA	66 - M	Ben-Amitai et al.[4]
	51 - M	63 - GA	
	46 - M	73 - GA	

GA = granuloma annulare; SS = systemic scleroderma; M = morphea.

There have been a few reports of morphea developing at a healed previous site of herpes zoster. Therefore, there may be some common mechanisms for morphea and granuloma annulare developing at a previous site of injury, whatever the cause of this injury may be.

However, in the case presented here, the coexistence of these two disorders did not fit with the concept of an immunocompromised cutaneous region. Autoimmune etiology has also been proposed for both morphea and granuloma annulare.[4] No autoimmune positivity was detected in this case.

CONCLUSION

There are only a few cases in the literature describing coexistence of morphea and granuloma annulare. Here, we reported a case of simultaneous presentation of both diseases, and we have discussed the etiological and pathogenetic processes that cause this rare coexistence.

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Hypoglycemia caused by co-secretion of insulin from lung tumor and cardia cancer: first case report

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KEY WORDS:
Hyperinsulinism.
Adenocarcinoma of lung.
Diazoxide.

ABSTRACT

CONTEXT: Non-islet-cell-tumor-induced hypoglycemia (NICTH) is caused on rare occasions by secretion of insulin from tumor cells that are reported to have a single tissue origin.

CASE REPORT: A 67-year-old male patient had cardia adenocarcinoma and concomitant lung adenocarcinoma with extensive metastases and repeated episodes of intractable hypoglycemia. Immunohistochemical staining for insulin showed that lung adenocarcinoma stained positive and gastric cardia adenocarcinoma stained weakly positive. These results indicate that tumor cells of different tissue origins co-secreted insulin.

CONCLUSIONS: This is the first report on intractable hypoglycemia due to co-secretion of insulin from two kinds of primary tumor cells in a single patient.

INTRODUCTION

Non-islet-cell-tumor-induced hypoglycemia (NICTH) is a rare paraneoplastic syndrome characterized by repeated episodes of hypoglycemia. NICTH is commonly associated with excessive secretion of immature insulin-like growth factor (IGF)-2 precursor or IGF-1, by mesenchymal or epithelial tumor cells. Several studies have also reported that NICTH is related to excessive secretion of insulin from some tumors originating from a single tissue. Here, we report the first case of intractable hypoglycemia due to co-secretion of insulin from gastric cardia adenocarcinoma (GCA) and lung adenocarcinoma (LA), as confirmed by immunohistochemical staining for insulin. We obtained approval from our institution's ethics committee to report this case and the patient's family consented to the publication.

CASE REPORT

A cardia mass was found in a 67-year-old male patient in May 2012, and surgical resection was performed. Postoperative pathological examination showed moderately to poorly differentiated ulcerative gastroesophageal junction (GEJ) adenocarcinoma. In March 2015, the patient complained of frequent dizziness in the mornings, which improved after eating. On the morning of May 4, 2015, he presented limb convulsion unconsciously and could not be awakened. The patient's blood glucose level was 0.9 mmol/L. Five minutes after 50% glucose treatment, he recovered consciousness. Positron emission tomography-computed tomography (PET-CT) showed pulmonary, adrenal, intracranial, intrahepatic, retroperitoneal and thoracic vertebral lesions.

On May 11, the patient underwent CT-guided biopsy of a lesion in the left lung (**Figure 1**). Pathological examination showed lung adenocarcinoma (LA), and he received stereotactic radiotherapy in the whole brain, lungs and abdominal cavity. He and his family refused chemotherapy and further surgery. During the treatment, hypoglycemia occurred many times. At first, extra meals could maintain normal blood glucose. Later, continuous intravenous infusion of glucose injection was required, while the glucose concentration and infusion rate progressively increased. To prevent hypoglycemia, the maximum infusion rate for 50% glucose injection was 100 ml per hour. Dynamic enhanced MRI did not show any clear lesion in the pancreas. Adrenocorticotropic hormone, cortisol, growth hormone, glucagon and five thyroid function parameters were within normal ranges. An insulin autoantibody test was negative.

IGF-1 was 222 (96-212 ng/ml) and IGF-2 was significantly lower than normal according to western blotting. The patient was unresponsive to diazoxide (125 mg, three times a day for 10 days), and at that time, his blood diazoxide concentration was 13.4 μg/ml. The treatment was subsequently changed to tacrolimus capsules (10 mg, once a day), but the patient died five days later. The patient's family refused to allow an autopsy.

Immunohistochemical staining for insulin showed that LA samples were stained positive (**Figure 2B**) and GCA samples weakly positive (**Figure 3B**). The results from immunohistochemical staining on GEJ adenocarcinoma were as follows: CgA (+), syn (+), GPG9.5 (+) and MAP2abc (+) (**Figure 3 C-F**).

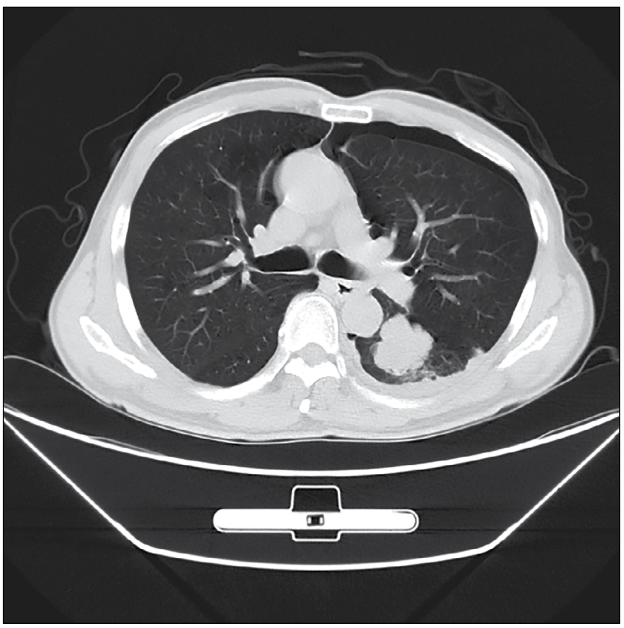

Figure 1. Computed tomography scan showing a mass in lung window.

DISCUSSION

In NICTH, there are mainly three mechanisms leading to hypoglycemia: tumor cells secrete excessive high-molecular-weight IGF-2 precursor, IGF-1, and insulin.[1] Previous studies have reported that insulin-secreting non-islet-cell tumors can originate in any germ layer, and that all of them have a single tissue origin. In the present study, the patient had two kinds of tumors that originated from the endoderm, i.e. GCA and LA, and both of them secreted insulin.

When hypoglycemia occurred in our patient, both serum C-peptide and insulin levels increased. The patient had hypoglycemia due to endogenous hyperinsulinism. Drug-induced hypoglycemia and insulin autoimmune syndrome were ruled out. Our patient had GCA and concomitant LA, thus suggesting the possibility of ectopic secretion of insulin from non-islet-cell tumors. Immunohistochemical staining for insulin showed that LA stained positive and GCA stained weakly positive, thus indicating that high levels of endogenous insulin were secreted from both GCA and LA. The control tumor tissue was stained negative for insulin (**Figure 4**). Additionally, GCA was stained positive for neuroendocrine cell-specific markers (syn and CgA), which showed that GCA belongs to neuroendocrine cells and further supports the notion that GCA secreted insulin. Thus far, ectopic secretion of insulin has been reported in only a few non-islet-cell tumors, and all of these had a single tissue origin in different germ layers. Immunohistochemical staining on a pulmonary lesion showed CKAE1/AE3 (+++), CK7 (+++), TTF-1 (+++), napsin-A (++) and Ki67 labeling

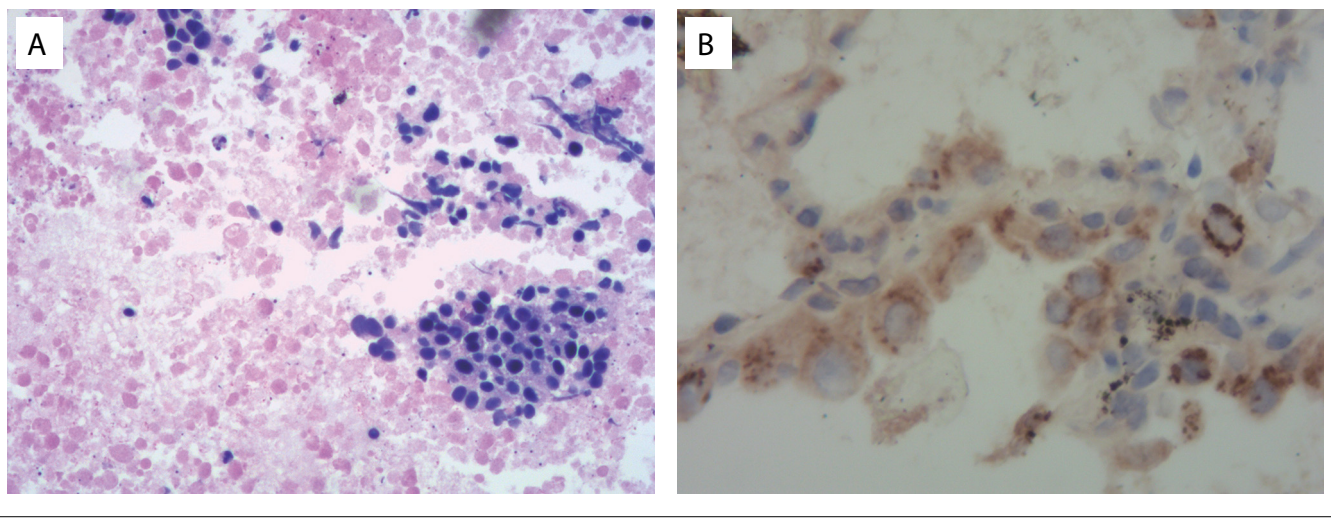

Figure 2. Immunohistochemical staining on lung adenocarcinoma in our patient: (A) hematoxylin-eosin staining on lung adenocarcinoma (× 200); and (B) tumor cells of lung adenocarcinoma with positive staining for insulin (× 200).

index of 10%. TTF-1 and napsin-A-positive results showed that the pulmonary lesion was not metastatic GCA, but was a primary LA. Thus, our patient was diagnosed as having tumors from two kinds of tissue cells of endodermal origin. Hence, our patient's high insulin levels came from tumors of two different tissue origins. This is the first reported case of NICTH caused by co-secretion of insulin from multiple primary carcinomas.

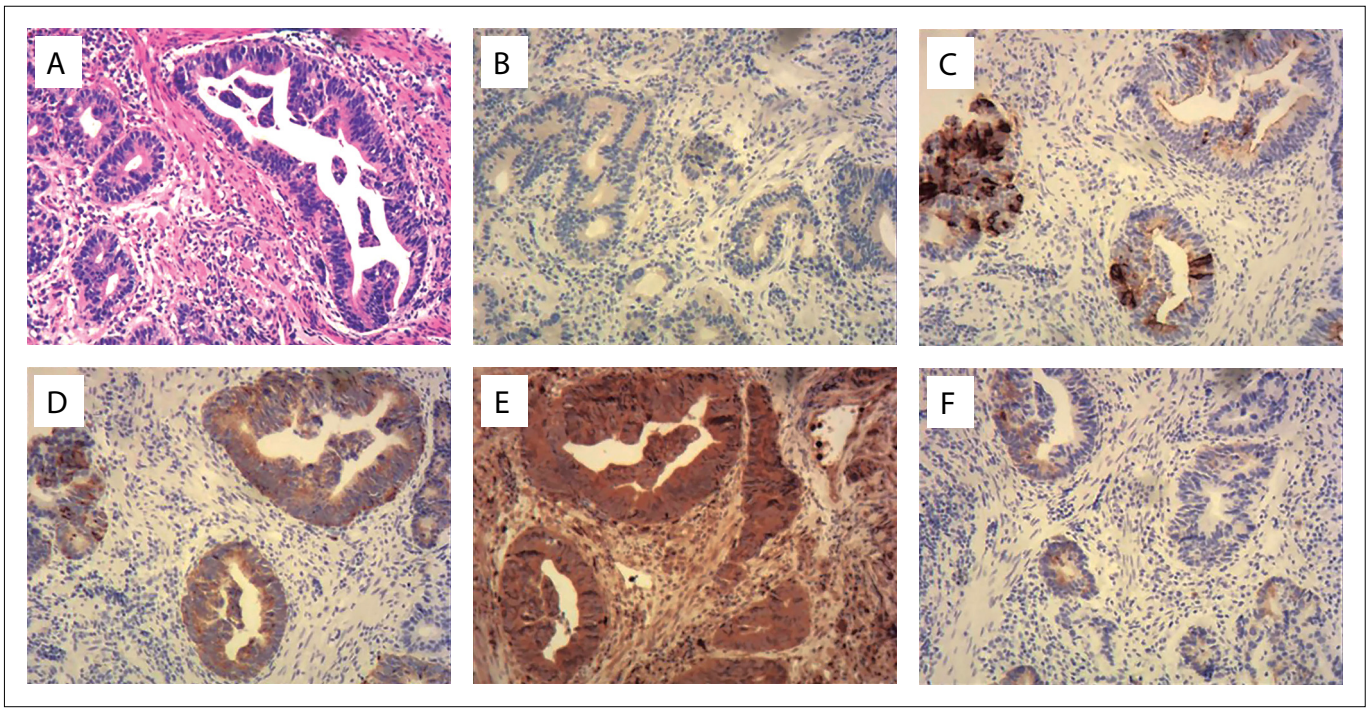

Figure 3. Immunohistochemical staining on gastroesophageal junction adenocarcinoma in our patient: (A) hematoxylin-eosin staining on gastroesophageal junction tumor cells (× 100); (B) tumor cells stained weakly positive for insulin (× 100); and (C–F) tumor cells stained positive for CgA, syn, GPG9.5 and MAP2abc (× 100).

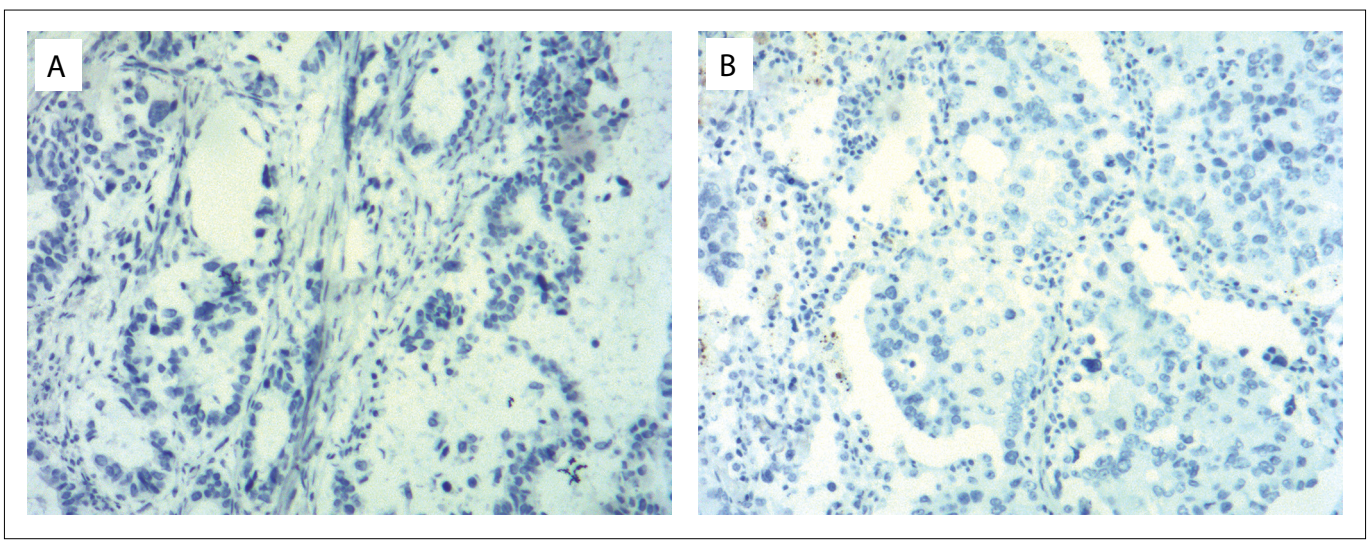

Figure 4. Immunohistochemical staining on gastroesophageal junction adenocarcinoma and lung adenocarcinoma in the control: (A) tumor cells of gastroesophageal junction adenocarcinoma with negative staining for insulin (× 100); and (B) tumor cells of lung adenocarcinoma with negative staining for insulin (× 100).

Table 1. Search of the literature in medical databases for case reports on insulin secretion from lung carcinoma and cardia carcinoma. The search was conducted on June 10, 2017

Database	Search strategy	Full result	Similar case report
MEDLINE (via PubMed, June 10, 2017)	#1 ("Cardia Neoplasms"[Mesh]) OR "Lung Neoplasms"[Mesh]) #2 "Hyperinsulinism"[Mesh]) #3 "Hypoglycemia"[Mesh] #4 #1 AND #2 AND #3	3	0
Embase (via Embase, June 10, 2017)	#1 ('Cardia carcinoma'/exp/mj) OR ('Lung carcinoma'/exp) #2 'Hyperinsulinism'/exp/mj #3 'Hypoglycemia'/exp/mj #4 #1 AND #2 AND #3	0	0

Diazoxide can inhibit secretion of insulin and ease the condition of hypoglycemia. In 1979, Fajans used diazoxide for the first time to treat insulinoma.[2] Diazoxide was also later used to treat hypoglycemia caused by high levels of insulin secreted from inoperable extrapancreatic malignancies. Gill et al.[3] found that the mean dose of diazoxide for treating islet cell tumors was 267 ± 138 mg/day (range 100–600), with a response rate of 97.5%. Our patient had absolute indications for taking oral diazoxide tablets (125 mg, three times a day). However, this did not relieve his hypoglycemia. His plasma concentration of diazoxide was 13.4 μg/ml, which showed that diazoxide did not work. Shames et al.[4] reported on a patient with bronchial carcinoid tumors who had severe hypoglycemia relating to hyperinsulinism. The efficacy of treatment with diazoxide injection was poor. The authors speculated that this was associated with unusual autonomy of insulin secretion by tumor cells. In addition to this, we speculate that the molecular mechanism through which non-islet-cell tumors secrete insulin probably differs from that of islet cell tumors. Our patient's treatment was then changed to tacrolimus capsules. Tacrolimus has been reported to inhibit hyperglycemia-stimulating insulin gene expression with an inhibition rate of up to 70%. However, our patient's condition deteriorated sharply and he died after five days of treatment with tacrolimus.

We reviewed the literature in MEDLINE and EMBASE using the English keywords "Hyperinsulinism", "Hypoglycemia", "Cardia neoplasms" and "Lung neoplasms" (**Table 1**). No other similar case was found.

CONCLUSION

In summary, this is the first reported case of hypoglycemia associated with co-secretion of insulin by LA and GCA. Regardless of the type of tumor tissues, NICTH should be taken into consideration for some nonspecific symptoms of hypoglycemia in tumor patients, such as dizziness, convulsions, hallucinations and coma. Early diagnosis and timely treatment are recommended for these patients, to improve their quality of life.

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A rare mediastinal occurrence of neuroblastoma in an adult: case report

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KEY WORDS:
Mediastinum.
Neuroblastoma.
Adult.

ABSTRACT

CONTEXT: Neuroblastoma is the most common extracranial malignant solid tumor that occurs during childhood. It arises from primitive cells and is seen in the adrenal medulla and sympathetic ganglia of the sympathetic nervous system.

CASE REPORT: We present a rare case of a 40-year-old man who was diagnosed with the onset of neuroblastoma arising in the mediastinum. He was treated by means of surgical resection in the superior mediastinum after neoadjuvant chemotherapy. The patient's surgical outcome was satisfactory.

CONCLUSION: There are still no standard treatment guidelines for adult neuroblastoma patients. Although they have a poor prognosis, the main treatment option should be complete surgery at an early stage. This situation may become clarified through biological and genetic studies in the future.

INTRODUCTION

Neuroblastomas are the most common extracranial malignant solid tumors that occurs during childhood. They arise from primitive cells and are seen in the adrenal medulla and sympathetic ganglia of the sympathetic nervous system. These aggressive cells begin to grow uncontrollably. Neuroblastomas may lead to signs such as swelling in the face, neck, arms and upper chest, headaches, dizziness, changes to consciousness, drooping eyelids and small pupils. They may also lead to signs of paraneoplastic syndromes that include constant diarrhea, fever, high blood pressure (causing irritability), rapid heartbeat, flushing of the skin and sweating. Because neuroblastomas consist of embryonic cells, they are especially common among small children: up to 90% of the patients are younger than six years old. On the other hand, neuroblastomas are only rarely seen in older children and adults. Incidence rates of one case per 100,000 children per year and one case per 10 million adults per year have been reported.[1,2] The most common locations in adults are the chest, pelvis and neck.[2] Approximately 20% of the cases occur in the mediastinum.[2]

Multimodal treatments are used, including surgery, chemotherapy and radiotherapy. No standard treatment protocol has been developed for adults. Thus, the same protocol is used for adults and children. In adults, the disease presents much more aggressively than in children.[2] Here, we present a rare case of neuroblastoma in an adult, which was treated by means of neoadjuvant chemotherapy and surgery.

CASE REPORT

A 40-year-old male patient was hospitalized with complaints of anorexia, fatigue, headache and weight loss. Physical examination and routine blood tests were unremarkable. Chest x-ray detected a right paratracheal lesion. The following tumor markers were all negative: carcinoembryonic antigen, carbohydrate antigen 19-9, alpha fetoprotein and vanillylmandelic acid, as also were urine tests. Lactate dehydrogenase and neuron-specific enolase blood levels were also within normal limits. Catecholamine metabolites were not found to be elevated in 24-hour urine collection. Chest computed tomography (CT) examination revealed a mass of lobulated outline between the lower border of the superior vena cava and the subcarinal area (**Figure 1A** and **1B**). Adjacent vascular and mediastinal structures had been invaded. Its size was 5 cm x 4 cm. In positron-emission tomography (PET)-CT images, the standardized uptake value was 19.5.

Therefore, he underwent mediastinoscopy for diagnostic purposes. The histopathological findings revealed the presence of a neuroblastoma. The morphology comprised small round cells. The absence of ganglion cells and state of maturation determined that the neuroblastoma was of poorly differentiated stroma-poor Schwannian subtype. The Ki-67 proliferation rate was 70%. The tumor cells showed a diffuse strong reaction with neuron-specific enolase. A bone marrow biopsy confirmed that this had not become infiltrated by tumor cells.

The patient was diagnosed as having stage III unresectable neuroblastoma. The multidisciplinary oncology council decided to implement three cycles of neoadjuvant chemotherapy. These three cycles, which were repeated every 14 days, consisted of a regimen of ifosfamide (day 1; 5000 mg/m^2), carboplatin [day 1; optimized to achieve the area under the curve (AUC) dose calculation = 5; maximum of 800 mg] and etoposide (days 1-3; 100 mg m^2) (ICE regimen).

Contrast-enhanced chest CT was performed after chemotherapy and revealed that the tumor had almost completely regressed. Therefore, an operation was planned (**Figure 2A**). Muscle-sparing right posterolateral thoracotomy was performed. The tumor was found to have become attached to the mediastinal structures, especially the superior vena cava and trachea. Nonetheless, it was possible to completely resect the tumor by means of blunt and sharp dissection without causing any complications. Lymph node dissection was added to the surgery.

Histopathological examination showed the presence of necrotic tumor tissue. Metastasis was only detected in hilar lymph nodes. No complications were encountered during the postoperative period. A chest CT scan performed three months later did not show any recurrence (**Figure 2B**).

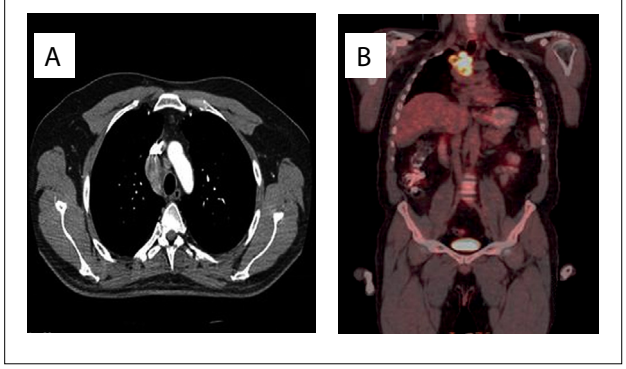

Figure 1. A) Computed tomography (CT) scan showing that the anterior mediastinal tumor invaded the major mediastinal structures. B) Positron-emission tomography (PET)-CT scan showing an aggressive mediastinal mass with high 18-FDG (fluorodeoxyglucose) affinity.

DISCUSSION

Neuroblastoma is a very common childhood disease, but it is rarely detected in adolescents and adults. The most important clinically relevant factors that influence survival among these patients are stage, age, histology and tumor grade. Young age and low stage with timely diagnosis are two important favorable prognostic features.[3] Whereas five-year overall survival is 85% for infants, it is only 36% for adults.[2]

Currently, there are no standard treatment guidelines for patients with adult neuroblastoma. Thus, attempts to adapt treatment protocols developed for children have been made, for use in adult cases.[4] Different treatments are required according to different stages of the disease. Localized tumors are treated by means of primary surgery if possible (stages 1 and 2). Neoadjuvant chemotherapy (NCT) is recommended in cases of inoperable

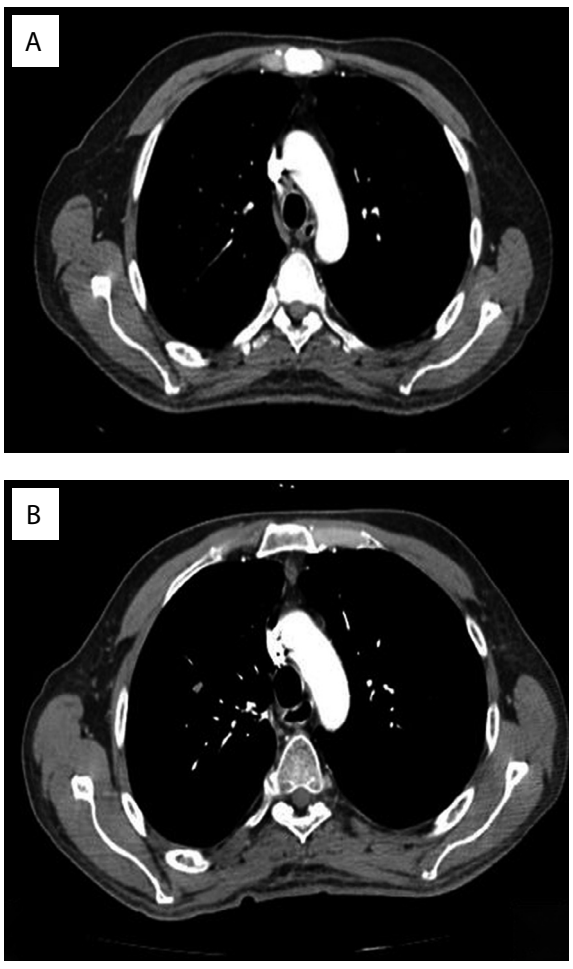

Figure 2. A) Computed tomography (CT) scan after neoadjuvant chemotherapy, showing that the tumor had almost completely regressed. B) CT scan showing absence of recurrence three months after surgery.

Table 1. Search of the literature in medical databases for case reports on neuroblastoma, neuroblastoma in adults and mediastinal neuroblastoma treated by means of thoracic surgery. The search was conducted on May 22, 2017

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	((((Neuroblastoma AND Neuroblastoma in adult) AND Mediastinal neuroblastoma) AND "case reports" [Publication Type]	6	2
Embase (via Elsevier)	((((Neuroblastoma AND Neuroblastoma in adult) AND Mediastinal neuroblastoma) AND "case reports" [Publication Type]	8	0
LILACS (via Bireme)	((Neuroblastoma AND Neuroblastoma in adult) AND Mediastinal neuroblastoma) AND "case reports" [Publication Type]	4	1

stage 3 neuroblastoma. Local radiotherapy may be indicated for aggressive tumors, with or without total resection of the primary tumor. Metastatic neuroblastoma (stage 4) requires neoadjuvant chemotherapy followed by surgery of the primary tumor, if possible. Stage 4S may regress spontaneously. However, half of these cases need chemotherapy and radiotherapy because of tumor progression. Some localized or stage 4S tumors may even show spontaneous regression without any treatment.[3,4] Our case was diagnosed as having stage 3 neuroblastoma. It was unresectable. However, it became possible to completely resect the tumor after it regressed, through NCT.

Tumors categorized as neuroblastoma have been further divided into three subtypes: undifferentiated, poorly differentiated and differentiated, based on their degree of neuroblastic differentiation.[4] Presence of Schwannian stroma in neuroblastomas is related to patient prognosis. Our case was identified as the poorly-differentiated stroma-poor Schwannian subtype.

Conter et al.[5] compared neuroblastoma cases in 118 adults (mean age of 47 years) and 112 children (mean age of 5 years). For all stage-matched categories, the prognoses for the adult patients were not statistically different from those of the pediatric neuroblastoma patients.

A search of the literature in major medical databases for case reports on neuroblastoma, neuroblastoma in adults and mediastinal neuroblastoma is presented in **Table 1**.

CONCLUSION

The diagnosis of neuroblastoma in adults has been reported in few case reports. There are still no standard treatment guidelines for adult neuroblastoma patients. The main treatment option should be complete surgery at an early stage. At advanced stages, multimodal oncological treatment can be performed, followed by surgery, if this is possible. It is unclear why these patients have a poor prognosis. This situation may become clarified through biological and genetic studies in the future.

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Acknowledgements and funding

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Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

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Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

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Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the

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Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

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For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

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