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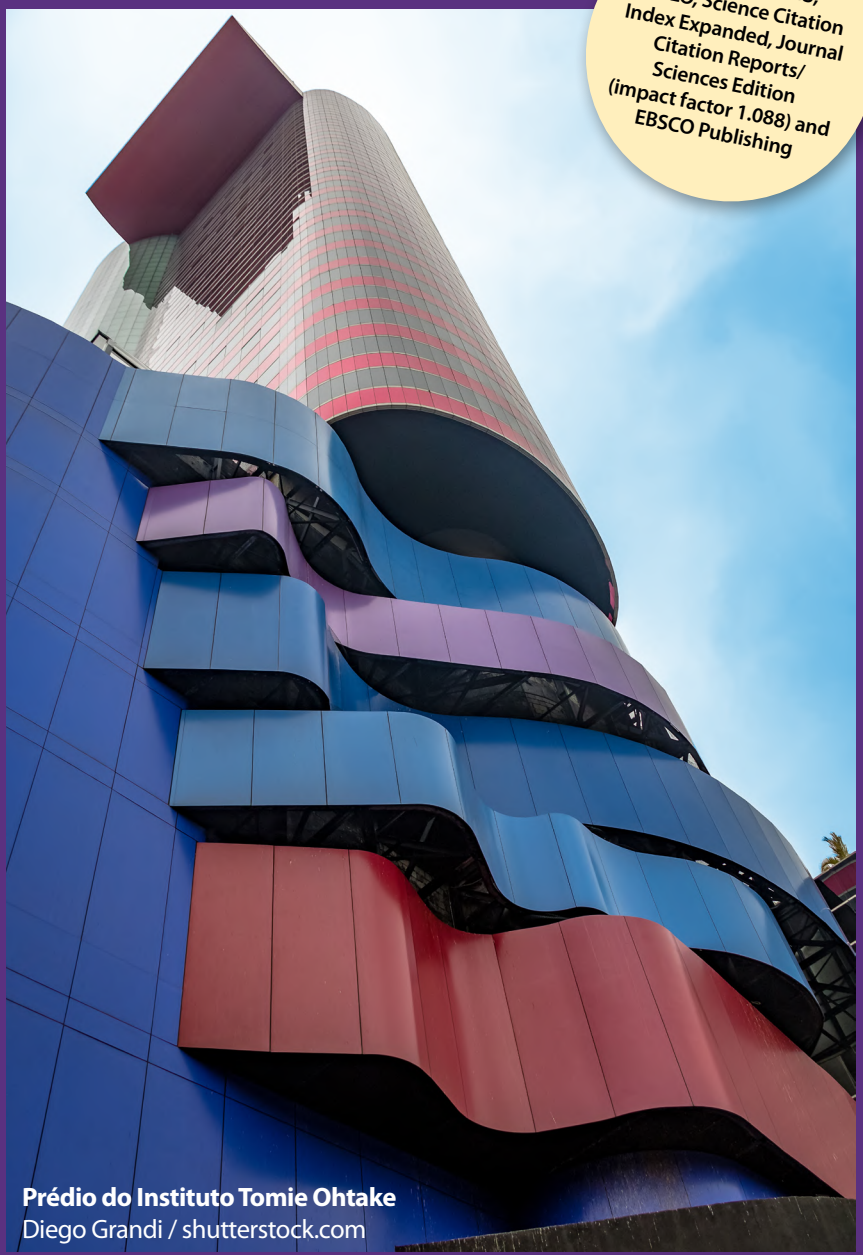

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Cardiovascular and cancer mortality in Brazil from 1990 to 2017

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The profile of mortality in Brazil has changed over the last three decades. Deaths due to infections, nutritional diseases and maternal causes accounted for 25% of all occurrences in 1990. In 2017, they represented approximately 10%. Injuries are now the cause in almost 20% of deaths among men and 5% among women. Hence, non-communicable diseases are proportionally increasing as the cause of death for both sexes (**Figure 1**). This nosological category encompasses cardiovascular, respiratory, digestive, neurological and renal diseases, along with cancer. The most frequent components are cardiovascular diseases and cancer, both worldwide and in Brazil.[1-2]

Recently, an analysis conducted at the Center for Diseases Control and Prevention revealed that cancer may be about to surpass heart diseases as the leading killer in the United States.[3] I analyzed the trends of both cancer and cardiovascular diseases (including heart and cerebrovascular diseases) in Brazil using data from the Global Burden of Diseases study 2017, which are available online (http://ghdx.healthdata.org/gbd-results-tool). This description follows three steps: first, the total number of deaths and the proportional mortality; second, rates according to the population each year; and third, age-standardized rates.

Figure 2 displays four moments over these decades (1990-2017). It shows that the number of deaths due to cardiovascular diseases was higher than the number due to cancer, but that a significant change took place over this period. In 1990, the number of deaths due to circulatory disorders was 140% higher than the number due to cancer; but in 2016, the number due to cardiovascular diseases was 60% greater than the number due to cancer. The proportional mortality due to circulatory disorders remained unchanged, but it increased significantly for death due to cancer. Among men, the proportional mortality increased from 10.6% (1990) to 17.4% (a relative increase of 65%). Among women, the proportional mortality increased from 12.7% (1990) to 19.2% (a relative increase of 50%).

Figure 3 shows the trends in the numbers of deaths divided by the population of each year (crude rates). Visually, it is possible to speculate that cardiovascular rates are declining or flattening; in contrast, the rates due to cancer increased monotonically during this period. After adjustment for the difference in age strata over this period, as shown in **Figure 4**, it is easy to understand that the patterns for the risks of death due to circulatory disorders and cancer are different. The decline in age-standardized death rates due to cardiovascular diseases is steeper than that of the cancer rates. **Table 1** presents the annual percentage change in the age-standardized death rates and shows that the decline in circulatory diseases over the period from 1990 to 2017 occurred at a faster pace. However, for both categories and both sexes, the rate of declining slowed down over the last five years of observation (2013-2017).

Concluding, in contrast to what has been described in the United States, cancer deaths in Brazil are not surpassing fatal cases due to cardiovascular diseases. In this country, the number of deaths due to cardiovascular diseases and the risk of death due to these diseases, independent of aging, are higher than the numbers and risks relating to cancer, for both sexes. A more detailed explanation according to the types of circulatory disorders and types of cancer will be presented in forthcoming issues of the *São Paulo Medical Journal*.

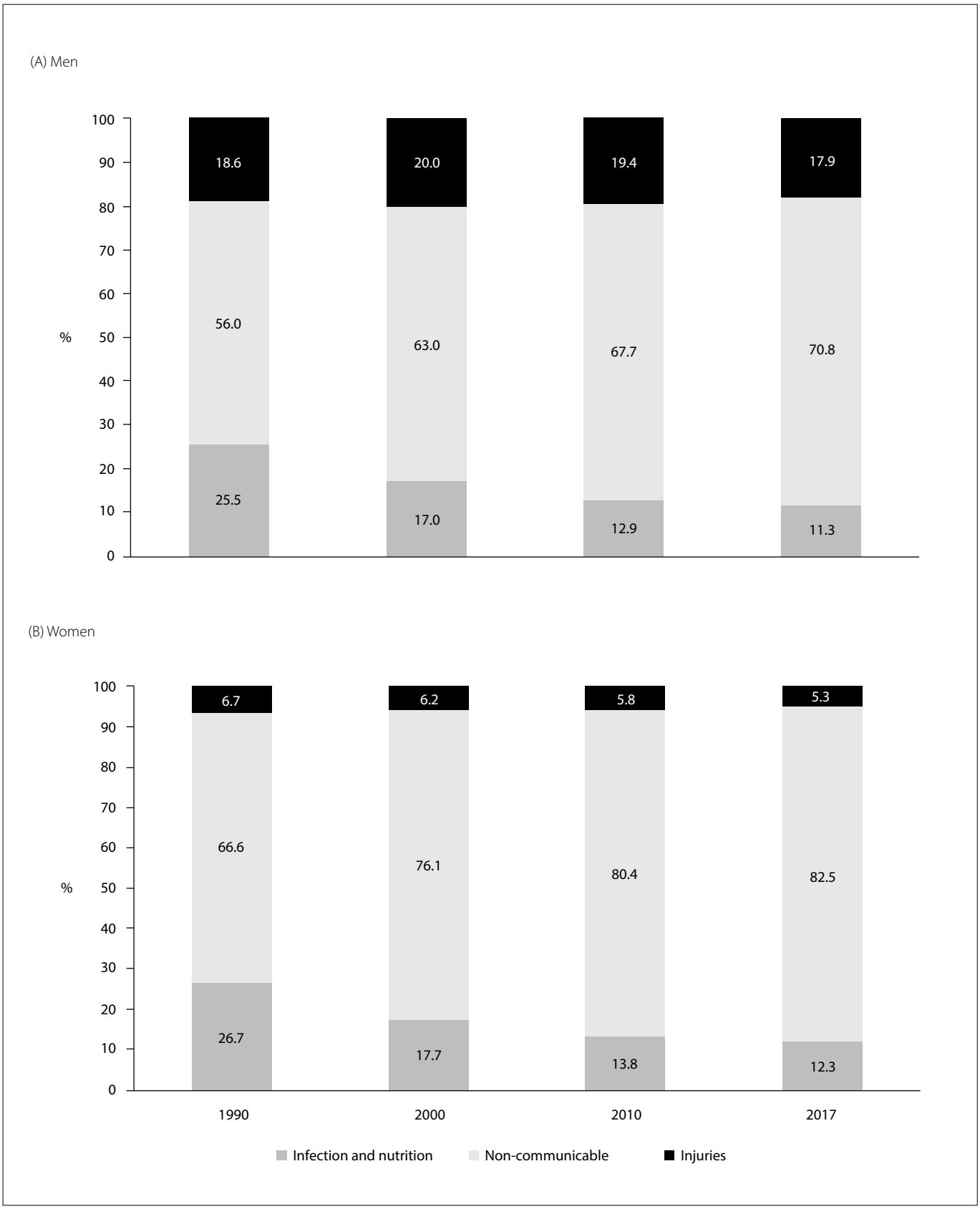
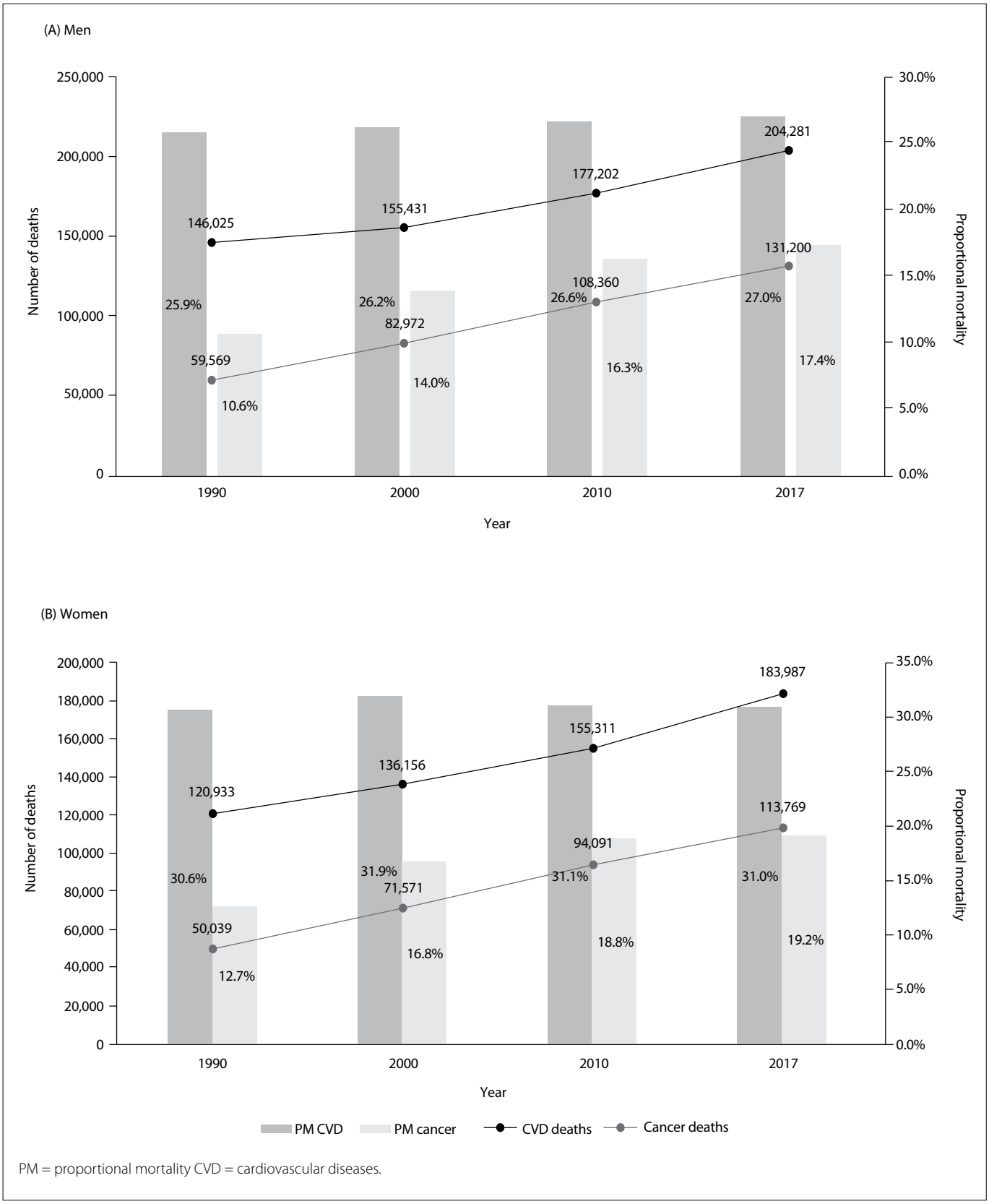
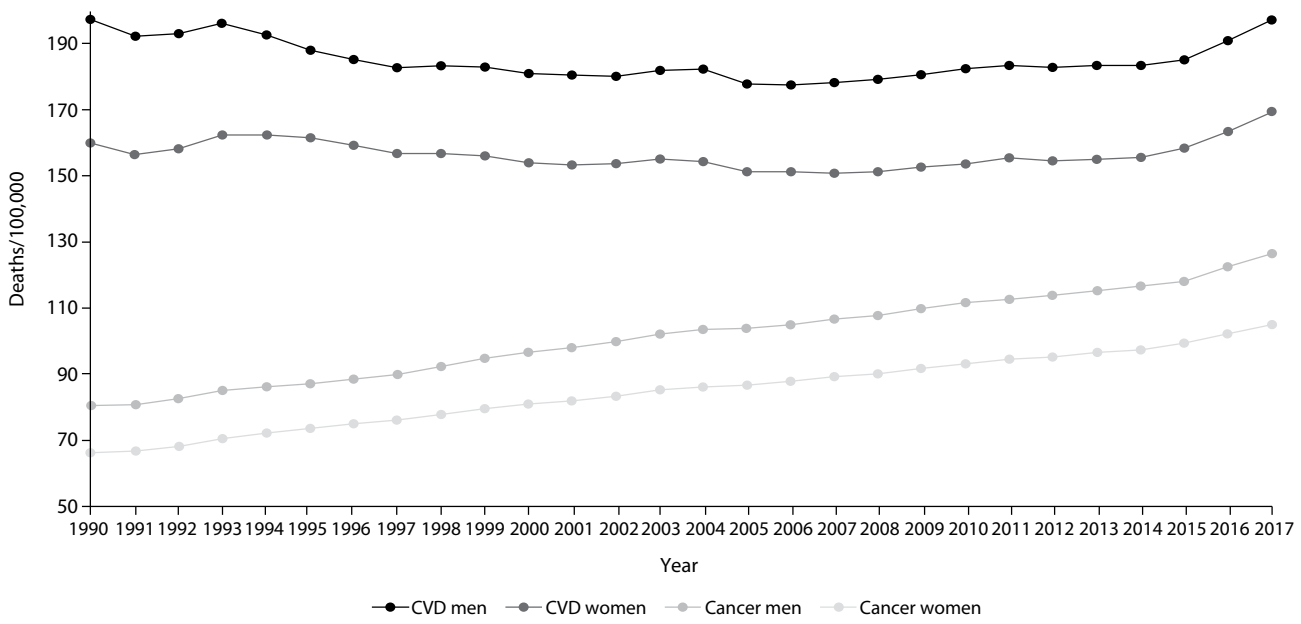


Figure 1. Evolution of proportional mortality relating to all causes for men (A) and women (B), due to infectious and nutritional diseases, non-communicable disorders and injuries in Brazil.



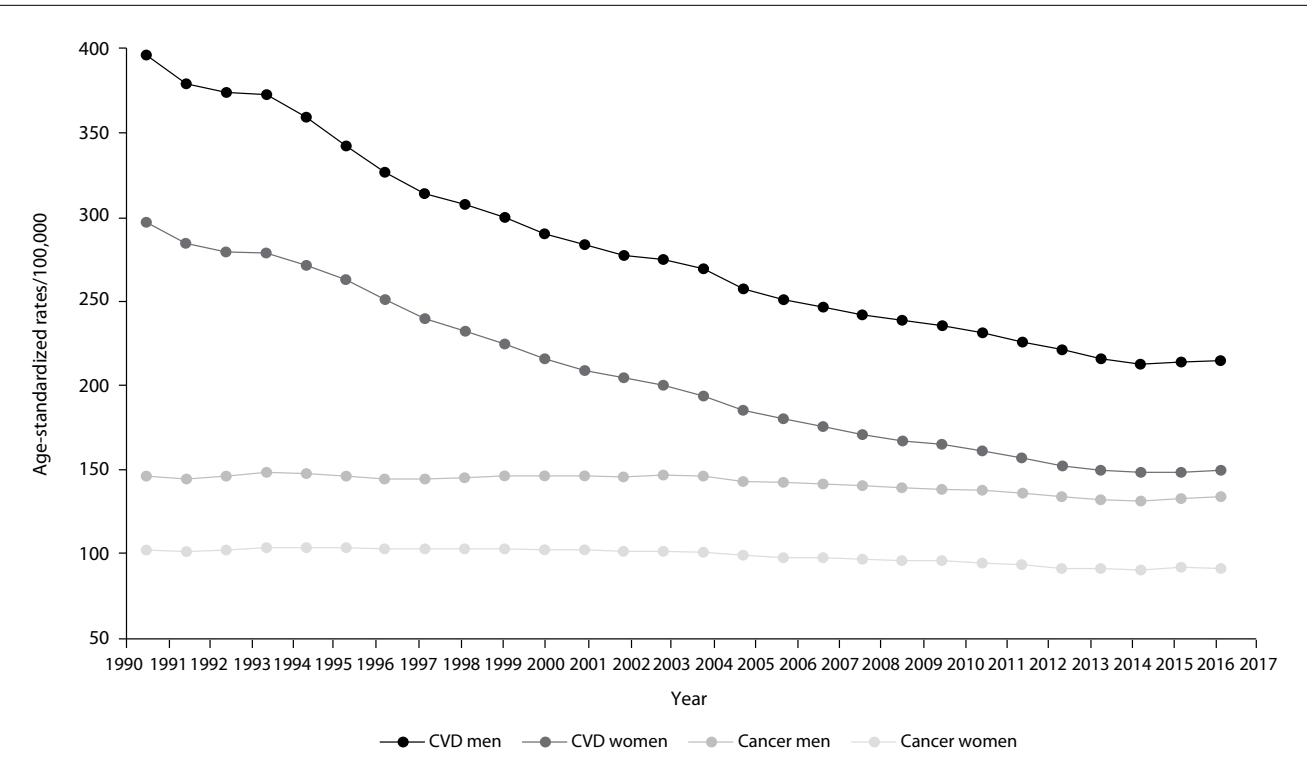
PM = proportional mortality CVD = cardiovascular diseases.

Figure 2. Evolution of number of deaths and proportional mortality relating to all causes for men (A) and women (B), due to cardiovascular diseases and cancer in Brazil.



CVD = cardiovascular diseases.

Figure 3. Crude death rates due to cardiovascular diseases and cancer in Brazil from 1990 to 2017.



CVD = cardiovascular diseases.

Figure 4. Age-standardized death rates due to cardiovascular diseases and cancer in Brazil from 1990 to 2017.

Table 1. Annual percentage change in age-standardized death rates due to cardiovascular diseases and cancer in Brazil from 1990 to 2017, and over the last ten years (2008-17) and last five years (2013-17) of observation

	Cardiovascular diseases		Cancer	
	Men	Women	Men	Women
1990-2017	-2.26	-2.55	-0.32	-0.41
Last 10 years	-1.32	-1.46	-0.53	-0.57
Last 5 years	-0.71	-0.52	-0.10	-0.17

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Effect of changes to the formal curriculum on medical students' motivation towards learning: a prospective cohort study

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KEY WORDS:
Motivation.
Learning.
Curriculum.
Students, medical.
Education, medical.

ABSTRACT

BACKGROUND: One of the factors known to influence performance in the learning process is student motivation. In turn, students' motivation can be regulated by a large number of variables relating to the individual (such as sex, age and socioeconomic status) or to aspects of the academic life.

OBJECTIVE: The primary aim of this study was to evaluate the influence of curriculum changes involving reduction in content overload and increased early exposure to clinical settings, on motivation towards learning among Year 1 medical students. Secondarily, the aim was to ascertain whether this influence on motivation remained stable until the undergraduate program ended (Year 6).

DESIGN AND SETTING: Prospective study on two student cohorts at a Brazilian state-owned university.

METHODS: Two consecutive student cohorts were assessed: one with a traditional curriculum (n = 87) and the other with a reformed curriculum (n = 63), at the same medical school. Participants in both cohorts gave responses on four scales in Years 1 and 6: the Academic Motivation Scale, containing subscales for autonomous and controlled motivation, and lack of motivation towards learning; Beck's Anxiety and Depression Inventories; Spielberger's State-Trait Anxiety Inventory; and the Social Adjustment Scale. In Year 6, 68% of the initial sample (66 students with the traditional curriculum and 36 with the reformed curriculum) was reassessed.

RESULTS: No differences between Year 1 cohorts were found regarding demographic and social background, social adjustment, depression or anxiety. Students with the reformed curriculum scored significantly higher regarding autonomous and controlled motivation than those with the traditional curriculum. Comparison between Year 6 and Year 1 showed increases in controlled motivation only for the traditional curriculum cohort.

CONCLUSION: Curriculum changes were associated with increased motivation towards learning in Year 1, which persisted until Year 6.

INTRODUCTION

Learning is influenced by different factors, and learners' engagement is primordial among these factors. In turn, engagement is affected by students' motivation and their perception of the relevance of the aims and features of the learning process.[1] Consequently, well-motivated students seem to have more favorable study behavior and higher quality of learning.[1,2]

According to the self-determination proposition,[2] motivation can be understood as a propensity to move or to do something. Motivation comprises a continuum that goes from absence of motivation at one end to extrinsic motivation and onwards to intrinsic motivation at the other end. In educational activities, extrinsic motivation is oriented towards the outcomes of the learning process, whereas intrinsic motivation is based on inherent interest in or pleasure with the process itself. Intrinsic motivation is associated with higher learning quality, increased persistence and better psychosocial adjustment.[2]

Motivation towards learning is regulated by and can itself regulate several aspects of academic life. Concerning medical education, motivation seems to influence study behavior, choice of specialty, intention to continue studying and academic success.[3] Motivation can also be influenced by factors at the individual level that are independent of the academic environment, such as sex, age, ethnicity, socioeconomic status and personality traits.[3]

Although the influence of affective aspects of the learning process has been recognized, students' motivation has not been a predominant driver in medical curricular planning or reform.[4] Moreover, the effects of curricular changes on students' motivation are not entirely understood.

We previously reported[5] that as students went through their first year in a traditional medical school, they showed significantly decreasing intrinsic motivation. These decreases were not correlated with academic performance, as measured mainly through grades in final exams. On the other hand, these students also showed higher anxiety and maladjustment of their leisure and social life at the end of the year, compared with its beginning. Potentially, these results may have been influenced by features of the formal curriculum, which was predominantly teacher-centered, with lack of awareness regarding content overload and lack of concern about clarifying the medical relevance of the scientific concepts taught, thus possibly frustrating students' expectations.

In the light of our earlier report,[5] the curriculum described then was reformed, guided by the SPICES model.[6] The reform reduced the content and introduced learning activities and medical scenarios, many of them within the community, during Years 1 and 2. These activities had higher authenticity and took into consideration medical practices in the national healthcare services. The existence of two consecutive cohorts of medical students, one following a traditional curriculum and the other, a reformed curriculum, provided an opportunity to assess their possible impacts on motivation towards learning.

Therefore, the aim of this study was to evaluate whether the curriculum reform was associated with any changes in the motivation towards learning among first-year students. We also tested whether the students' levels of motivation towards learning that had been observed in Year 1 remained stable until the end of the undergraduate program.

METHODS

Setting and ethics

This study was carried out at the Ribeirao Preto Medical School, a state-owned school affiliated to the University of São Paulo, in southeastern Brazil, which has an intake of 100 new students every year. The local undergraduate program committee and ethics committee approved the study (protocol 1753/2007). Some of the procedures involved here were described previously.[5] The participants signed informed consent forms.

Educational context

The traditional curriculum at this institution comprised didactic teaching of basic biomedical sciences (Years 1 and 2) and clinical sciences (Years 3 and 4), followed by internship training in clinical placements (Years 5 and 6). This curricular design was strongly influenced by the Flexnerian model.[7] During the first two years, disciplines such as anatomy, physiology, genetics and biochemistry were taught using teaching and learning strategies that were based mainly on lectures and traditional laboratory activities.

The curriculum reform was restricted to Years 1 to 3, and it focused on content reduction, fostering of interdisciplinary integration and promotion of early contact with clinical activities, with increased use of the primary and secondary levels of the public national healthcare system as learning scenarios. However, the reform did not envisage any changes among academic staff members; instead, the teachers were encouraged to use active learning methods and to replace formal lectures with small-group discussions around medically relevant topics. Time was made available in the curriculum in Year 3 for teacher-student discussions of basic biomedical topics within the context of clinical activities with real patients, thus lessening the border between the basic and clinical cycles. This reform also had the aims of stimulating early engagement in discussions on issues relating to health promotion and providing a broader humanistic perspective for healthcare. Lastly, a full morning or afternoon was reserved for leisure or extra-curricular activities, in order to reduce the overload of the weekly timetable.

Participants

Initial data were collected at the end of the academic years 1 and 6 of the two cohorts. All Year 1 medical students enrolled in the last edition of the traditional curriculum and in the first edition of the reformed curriculum were invited to participate as volunteers and asked to give responses to the instruments in a single session. Five years later, at the end of the undergraduate program (Year 6), all students who had previously taken part in the study were once again invited to respond to the self-report instruments, upon agreement through a new consent form. To preserve confidentiality, an assistant researcher who was not directly involved in the study anonymized the surveys.

Instruments

The sociodemographic profile of the sample was assessed through a questionnaire that had been developed specifically for our previous study.[5]

The students' social adjustment to and satisfaction with academic life, leisure activities, family relationships and financial situation were evaluated through the Social Adjustment Scale Self-Report (SAS-SR).[8–10] This consists of 54 items that are rated from 0 to 5, with higher scores attributed to lower adjustment. Symptoms of depression and anxiety were evaluated using Beck's Depression Inventory (BDI)[11,12] and Anxiety Inventory (BAI).[13,14] These comprise 21 items each, with scores ranging from 0 to 3. These three scales were used in their Brazilian versions, which have been shown to have good performance in reliability and validity analyses.[10,12]

In addition, in order to estimate anxiety on a trait scale, the subjects gave responses to Spielberger's State-Trait Anxiety Inventory (STAI-T),[15] in its version validated for use in Portuguese.[16] The scores were classified as high if they were more than one standard deviation (SD) above the mean or low if they were more than one SD below the mean.[17]

Motivation towards learning was assessed on the Academic Motivation Scale (AMS),[18] which has been translated into Portuguese and has been shown to have good psychometric properties.[18,19] Each of its 28 items can be given a score between 1 (no match) and 7 (full match). These items were originally divided into seven subscales:

1) **amotivation**, corresponding to absence of recognition of the connection between one's own actions and the outcome;
2) **extrinsic motivation by external regulation**, when the learning behavior is guided through environmental reinforcements or restrictions;
3) **extrinsic motivation by introjection**, which occurs through internalization of external rules;
4) **extrinsic motivation by identification**, when the external reasons for learning are perceived as coming from one's own choices;
5) **intrinsic motivation to experience things**, guided by satisfaction that is provided through the stimulating sensations experienced during the learning processes;
6) **intrinsic motivation to accomplish things**, which comes from the satisfaction of acquiring new competencies to do things; and
7) **intrinsic motivation to know things**, corresponding to the pleasure or satisfaction in acquiring new knowledge.[18,20]

We also summarized this scale into three dimensions,[19,21] which were named:

1) **amotivation**;
2) **autonomous motivation** (the **intrinsic** subscales plus **extrinsic motivation by identification**); and
3) **controlled motivation** (the two additional **extrinsic motivation** subscales). The coefficient of reliability (Cronbach's alpha) was 0.83 for **autonomous** motivation and 0.86 for **controlled** motivation.[19,21]

Statistical analysis

The statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 20.0 (Armonk, NY, 2011). Categorical variables were analyzed using Pearson's chi-square test (χ^2), and using Fisher's exact test when appropriate. Ordinal variables were evaluated using Student's t test. The assumed normality of the data was confirmed through the Shapiro-Wilk test.

With the aim of ascertaining changes over the time, the motivation scores were subjected to repeated-measurement multivariate analysis of variance (MANOVA) (Hotteling's trace), considering the curricula (traditional and reformed) as "between factor" and time (Years 1 and 6) as "within factor". Post-hoc analysis comparisons between curricula were conducted using an independent t test, and the paired Student's t test in cases of comparison between years.

We estimated the effect size using Cohen's d test and considered values ≤ 0.20 to be small; values > 0.20 to 0.80 to be medium, and values higher than 0.80 to be large.[22]

P-values $P < 0.05$ were considered significant.

RESULTS

Demographics, anxiety and depression

The sample was composed of 150 students: 87 (58.0%) enrolled in the traditional curriculum, and 63 (42.0%) in the reformed curriculum. The majority was male (61.3%), aged between 17 and 29 years (mean = 20.0; standard deviation, SD = 1.7).

As shown in **Table 1**, no significant differences were found between the students following the traditional and reformed curricula, regarding demographic, social, economic and family education background. The majority of the students classified their ethnicity as white (77.9%), had attended private high schools (89.3%) and had experienced one year or more of preparatory course for the university admission exam (71.1%). The majority of their parents (fathers 70.7%; mothers 74.0%) had attended university, and 58.8% of the students reported that their annual family income was higher than the equivalent of United States dollars (US$) 36,000.

In general, the participants in both curriculum groups reported having satisfactory levels of social adjustment and low levels of depressive symptoms, but had high levels of anxiety complaints (P-values ≥ 0.090; **Table 2**).

Table 1. Demographic and socioeconomic background of first-year medical students enrolled in a traditional curriculum (n = 87) and in a reformed curriculum (n = 63)

	Curriculum			χ^2	P
	Traditional n (%)	Reformed n (%)	Total n (%)		
Male	58 (66.7)	34 (54.0)	92 (61.3)	2.48	0.115
White ethnicity	67 (77.9)	49 (77.8)	116 (77.9)	1.56	0.668
Private high school	79 (89.7)	56 (88.9)	134 (89.3)	5.24	0.264
≥ 1 year of preparatory course	63 (73.3)	43 (68.3)	106 (71.1)	0.44	0.506
Father attended university	57 (65.5)	49 (77.8)	106 (70.7)	2.65	0.104
Mother attended university	61 (70.1)	50 (79.4)	111 (74.0)	1.63	0.202
Annual family income > US$ 36,000	48 (56.5)	39 (61.9)	87 (58.8)	0.44	0.507

χ^2 = Pearson's chi-square test; US$ = United States dollars.

Through converting the BDI scores into severity classes, 89.7% of the traditional-curriculum students and 80.0% of the reformed-curriculum students were classified as having minimal presence of depression (Fisher's exact test; P = 0.81).

Regarding the BAI classes, 70.1% and 71.0% of the students in these respective groups showed moderate presence of anxiety symptoms (Fisher's exact test; P = 0.529). The remainder of the students in both groups showed severe anxiety symptoms (respectively 29.9 and 29.0%).

No difference in the distribution of anxiety traits was observed between the cohorts. Among the students following the traditional curriculum and reformed curriculum, 12.6% and 17.5%, respectively, were classified as having high levels of anxiety traits ($\chi^2 = 0.70$; degrees of freedom = 2; P = 0.704). The correlation between BAI and STAI-T scores was moderate (r = 0.542; P < 0.001).

We were able to reassess 68% of the initial samples when they reached Year 6: 66 students who were following the traditional curriculum (75.9%) and 36 who were following the reformed curriculum (57.1%). These students did not differ from the participants who had dropped out, regarding social characteristics (P ≥ 0.201) and the mean scores for social adjustment, anxiety and the seven motivation subscales (P ≥ 0.098). However, at the time when the students who were evaluated twice had entered the study, they presented fewer depressive complaints (BDI reassessed mean = 5.65, SD = 4.63, versus not reassessed mean = 7.57, SD = 6.90; P = 0.049, d = 0.33) and better academic adjustment (academic life reassessed mean = 1.87, SD = 0.46, versus not reassessed mean = 2.23, SD = 0.66; P < 0.001, d = 0.63).

Motivation

Students enrolled in the reformed curriculum had higher mean scores on five of the motivation subscales (**intrinsic motivation to know, to accomplish things and to experience**; and **extrinsic motivation by identification** and **by introjection**) than did those following the traditional curriculum (**Table 2**). In other words, students enrolled in the reformed curriculum reported significantly higher scores in relation to both **autonomous motivation** (T = 3.77; P < 0.001; d = 0.63) and **controlled motivation** (T = 2.65; P = 0.009; d = 0.44) than did those following the traditional curriculum. There was no significant difference regarding the **amotivation** index.

Repeated-measurement MANOVA confirmed the differences according to curriculum that were observed during Year 1 [time and curriculum interaction, F (1,100) = 7.02; P = 0.009]. In general, students enrolled in the reformed curriculum reported higher levels of motivation, both in Year 1 and in Year 6, in comparison with students following the traditional curriculum. However, the groups of students behaved differently in Year 6 of the medical school [F (1,100) = 7.57; P = 0.007]. MANOVA applied separately to each group showed that changes to the motivation indexes

Table 2. Comparison of social adjustment, psychiatric symptoms and types of motivation between Year 1 medical students enrolled in a traditional curriculum (n = 87) and in a reformed curriculum (n = 63)

	Curriculum		P	d
	Traditional Mean (SD)	Reformed Mean (SD)		
Social adjustment (SAS-SR)				
Academic life	1.92 (0.54)	2.07 (0.56)	0.090	0.27
Leisure	1.83 (0.42)	1.99 (0.82)	0.122	0.25
Family life	1.49 (0.80)	1.71 (0.65)	0.084	0.30
Finances	1.34 (0.61)	1.36 (0.66)	0.824	0.03
Symptoms				
Anxiety (BAI)	29.6 (8.0)	28.3 (8.9)	0.485	0.21
Depression (BDI)	6.5 (6.0)	6.2 (5.1)	0.932	0.05
Intrinsic motivation (AMS)				
to know	19.7 (5.4)	22.2 (5.0)	**0.005**	0.48
to accomplish	15.3 (5.3)	18.8 (5.0)	**< 0.001**	0.67
to experience	15.4 (5.4)	17.9 (4.9)	**0.003**	0.50
Extrinsic motivation (AMS)				
by identification	21.7 (4.9)	23.5 (3.6)	**0.017**	0.41
by introjection	11.1 (5.3)	13.9 (5.7)	**0.002**	0.51
by external regulation	18.9 (5.9)	20.3 (5.6)	0.164	0.23
Motivation (AMS)				
Amotivation	6.6 (3.6)	7.1 (4.3)	0.447	0.13
Autonomous	72.1 (17.4)	82.4 (15.2)	**< 0.001**	0.63
Controlled	30.0 (9.3)	34.2 (9.7)	**0.009**	0.44

SD = standard deviation of the mean; SAS-SR = Social Adjustment Scale Self-Report; BAI = Beck's Anxiety Inventory; BDI = Beck's Depression Inventory; AMS = Academic Motivation Scale; P = Student's t test; d = Cohen's d test for effect size.

occurred among the students enrolled in the traditional curriculum [F(1,65) = 7.32; P = 0.009], but not among those enrolled in the reformed curriculum [F(1,35) = 2.53; P = 0.121]. Post-hoc analyses showed that there was an increase in the **controlled** motivation of the students enrolled in the traditional curriculum (T = 2.83, P = 0.006, d = 0.39, **Table 3**).

DISCUSSION

The aim of this study was to assess whether changes in the early years of the formal undergraduate medical curriculum that were intended to reduce content overload and to increase early exposure to clinical and community healthcare activities, might have an impact on students' motivation. We found that the curriculum changes were associated with increased **autonomous** and **controlled** motivations towards learning at the end of the first year, without affecting other subjective measurements, such as social adaptation, anxiety and depressive symptoms. The results further showed that the motivation levels associated with the reform in the early years were preserved throughout the program, from Year 1 to Year 6, among the students enrolled in the reformed curriculum. In contrast, we found that there was an increase in the level of **controlled** motivation measured in Year 6 among the students enrolled in the traditional curriculum, such that it became similar to what had already been seen in Year 1 among the students enrolled in the reformed curriculum.

The demographic profiles of the medical students included in our study were similar to what had previously been reported in our medical school[23] and in other medical schools in Brazil.[19,24] In Year 1, both groups showed satisfactory levels of social adjustment and low levels of depressive symptoms, but showed levels of anxiety complaints that ranged from moderate to high, along with anxiety traits. These levels were observed independently of the curriculum that was followed. It is likely that this finding can be explained by the fact that the measurements were made at the end of the academic year, when students are usually concerned about the proximity of the final exams.

The pattern of motivation towards learning among our medical students was also similar to what was obtained using the same instrument in another Brazilian medical school, 10 years earlier.[19] The highest score was obtained on the subscale **extrinsic motivation by identification** followed by the score for **intrinsic motivation to know**; whereas **amotivation** showed the lowest score, followed by the score for **extrinsic motivation by introjection**. However, the mean scores obtained from our sample were lower than those described previously,[19] particularly among the students enrolled in the traditional curriculum.

The higher levels of motivation observed among the students enrolled in the reformed curriculum can be correlated with some of its new features, which fitted into Harden's SPICES model.[6] In the new curriculum, greater student-centeredness was achieved through reductions in content overload and the encouragement that was given for teachers to use small-group discussions instead of formal lectures. Greater integration between fields was pursued through merging traditional disciplines into broader modules, such as "general morphology", covering anatomy, histology and embryology. Early clinical experience for students was planned to occur predominantly within community healthcare settings.

Because the reform touched several dimensions of the SPICES model, it is not possible to identify key elements that would be particularly associated with increased student motivation. All of the improvements were likely to have contributed towards increasing the motivation towards learning. For instance, a review of earlier literature on the psychological basis of problem-based learning (PBL), an educational strategy that encompasses many of the SPICES model components, found indirect evidence of increased "intrinsic interest in the subject matter", which is clearly a construct relating to motivation.[25] Another review on PBL outcomes found evidence of increased student satisfaction with their learning processes and environment.[26] Along the same lines, another study showed that students enrolled in a PBL curriculum were more likely to have intrinsic motivation, whereas those following a traditional curriculum tended to express extrinsic motivation, particularly in the first years of the medical school.[27] Furthermore, a systematic review showed that there were associations between early experience for students in clinical and community settings, which was a major feature of the reform reported here, and a number of positive outcomes, including increased student motivation, through "**reminding them of their vocation to be a doctor and reinforcing it**" and therefore enhancing learning using a variety of mechanisms.[28]

Table 3. Results regarding motivation towards learning among medical students, expressed as mean (with standard deviation, SD), with two assessments: at the end of the first year and at the end of the sixth year of the medical school

Motivation	Traditional curriculum (n = 66)				Reformed curriculum (n = 36)			
	Year 1 Mean (SD)	Year 6 Mean (SD)	P	d	Year 1 Mean (SD)	Year 6 Mean (SD)	P	d
Amotivation	6.3 (3.0)	6.8 (3.6)	0.276	0.15	7.4 (4.8)	6.5 (3.1)	0.274	0.22
Controlled	30.3 (8.4)	33.8 (9.2)	**0.006**	0.39	34.5 (9.2)	33.3 (7.9)	0.362	0.14
Autonomous	73.3 (16.7)	77.7 (14.2)	0.060	0.28	83.1 (16.8)	80.9 (14.9)	0.344	0.14

SD = standard deviation of the mean; P = paired Student's t test; d = Cohen's d coefficient.

One perspective that is complementary to this is that newly admitted Year 1 medical students may have perceived the curriculum changes as evidence of institutional commitment to their education. This is one of the most important factors determining students' success, according to Tinto and Pusser's model.[29] This model was developed to reach better understanding of the factors involved in students' attrition, persistence and success, but the motivational component was implicit in many of its considerations. Moreover, students' perceptions relating to the quality of the course, in terms of the meaning and value of the educational experience, have also been regarded as linked to autonomous motivation.[2]

Among the students who followed the traditional curriculum, **controlled** motivation increased significantly from Year 1 to Year 6. This can be explained by the fact that learning activities during Years 3-6 were almost exclusively carried out within healthcare settings, thus fulfilling student expectations. On the contrary, there were no significant changes over the course of time on any of the motivation subscales, among the students following the reformed curriculum. Since the changes associated with the curricular reform predominantly affected the first two years of the undergraduate medical program, with only minor changes in Year 3 and no impact on Years 4-6, it is unlikely that the students' motivation towards learning would have continued to increase. Nevertheless, these findings, taken overall, indicate that the learning activities in each of the years (Year 2 to Year 6) were able to sustain the students' increased level of motivation towards learning that were associated with the curricular reform.

Some caveats should be considered before generalizing the findings from this study. Our results need to be analyzed cautiously taking into account the small size of the samples and the use of a single school as the recruitment context for the volunteers who were studied. Particularly regarding the follow-up, there may also have been some bias towards presumably better adapted individuals, since the students who we reassessed in Year 6 were the same who had better academic adjustment and lower scores for depressive complaints at the end of Year 1. Indeed, regarding this last point, despite the lower scores, no volunteer was classified as having more than a minimal level of presence of depressive symptoms. Furthermore, other than a trend relating to anxiety, which seems to influence motivation,[30] personality traits and other markers of psychological stress and indicators of academic performance were not assessed. Thus, the implications of these factors for changes in motivation could not be determined. Nevertheless, our study provides a contribution given that, so far, few studies have studied the impact of curricular changes on motivation towards learning among medical students, using validated instruments and a prospective design.

In summary, our results indicate that a curriculum reform that was designed mainly to reduce content overload and provide early medical experiences in community settings was associated with increased motivation towards learning among freshman medical students. Our data also suggest that changes to the curriculum in the early years of the undergraduate program may bring forward the higher motivation levels that would otherwise only be reached later. These findings should be considered when making decisions on the changes to be included in curriculum reform within more traditional undergraduate medical programs.

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Risk factors and relationship between screening periodicity and risk of cervical cancer among nurses and midwives. A cross-sectional study

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Nurse midwives.
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Papanicolaou test.

ABSTRACT

BACKGROUND: If nurses and midwives undergo cervical cancer screening regularly, they can become role models for other women regarding this screening.

OBJECTIVES: The aims here were (i) to determine factors associated with undergoing cervical cancer screening; and (ii) to examine the association of cervical cancer screening periodicity with cervical cancer risk levels among nurses and midwives.

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

METHODS: 466 nurses and midwives participated in this study. The relationships between undergoing Pap smear screening and sociodemographic characteristics, cervical cancer risk factors, perception of cervical cancer risk and calculated cervical cancer risk levels were examined. Cervical cancer risk levels were determined using the "Your Disease Risk" assessment tool (Washington University).

RESULTS: 35% of the nurses and midwives had undergone Pap smear testing at least once in their lifetimes. The odds of having undergone Pap smear testing were higher among smokers (odds ratio, OR: 2.08; 95% confidence interval, CI: 1.24-3.48) and among those who perceived their risk of cervical cancer to be high (OR: 3.60; 95% CI: 1.36-9.51). The frequency of undergoing Pap smear testing at least once in a lifetime was higher among primiparae (OR: 17.99; 95% CI: 6.36-50.84) and secundiparae (OR: 41.53; 95% CI: 15.01-114.91) than among nulliparae. No relationship was found between Pap smear test periodicity and calculated risk level.

CONCLUSION: There is a need to assess motivational barriers that might lead to low levels of Pap smear screening among nurses and midwives who are role models for women regarding cervical cancer prevention.

INTRODUCTION

Cervical cancer screening using Pap smear tests is a cost-effective method for preventing cancer.[1,2] Diagnosing and treating cervical cancers at the premalignant stage will decrease both incidence and mortality.[1] In the United States, Finland, Sweden, Denmark and Norway, the incidence of cervical cancer has been significantly reduced through the use of Pap smear test screening.[3,4]

However, in developing countries such as Turkey, the incidence of cancer is gradually increasing.[5] This increase reveals that there is a need for effective application of cancer screening programs. The American Cancer Society has recommended that all women should start to undergo cervical cancer screening from the age of 21, and that women aged 30-65 years should undergo Pap smear screening once every three years.[6] In Turkey, Pap smear test screening is recommended for women aged 30-65 years within the scope of the National Cancer Control Program.[7] If a person has a high risk of cervical cancer, it is recommended that testing should be done from an early age.[4]

Nurses and midwives work at every stage of the healthcare system and are the professionals who come into direct contact with society. Nurses and midwives' lifestyles relating to cervical cancer and the degree to which they self-apply methods for early diagnosing of this condition are indicative of their individual awareness within this field. Positive attitudes and behavior regarding Pap smear testing among healthcare professionals may contribute towards prevention of cervical cancer both for themselves and for the community.[8]

Despite the role of nurses and midwives in cervical cancer screening, there is little knowledge about Turkish nurses and midwives' own cervical cancer screening behavior. Studies conducted

among healthcare professionals in Turkey have focused more on the frequency of screening.[9-13] Only two of these studies examined the factors affecting whether individuals choose to undergo Pap smear tests. It was determined that age affected screening behavior,[9] and that having information on risk factors did not affect screening behavior.[12] However, we did not find any studies in which cervical cancer risk levels among midwives and nurses were examined.

OBJECTIVES

The aims of this study were (i) to determine factors associated with undergoing cervical cancer screening; and (ii) to examine the association of cervical cancer screening periodicity with cervical cancer risk levels among nurses and midwives working in two Turkish public hospitals.

METHODS

The potential participants for this cross-sectional study comprised female nurses and midwives working in two different hospitals located in the province of Balıkesir in Turkey (n = 680). These hospitals are the largest public hospitals in this province, and the highest numbers of nurses and midwives work in these institutions. No sample selection was conducted for this study: the aim was to reach the entire potential population.

Prior to undertaking the study, written permissions were obtained from the Balıkesir University Ethics Committee for Non-Interventional Studies and from the managements of the two hospitals. Participants gave their informed consent to be included in this study.

Research data were collected between January 2016 and September 2017. The data were collected through a survey that was created by the present researchers taking into consideration information from the literature within this field. The survey questionnaires were distributed to all midwives and nurses at the institutions where they worked, in closed envelopes. The questionnaire consisted of questions to determine the survey participants' educational background, marital status, cervical cancer risk perception and frequency of undergoing Pap smear tests. It also included questions taken from the "Your Disease Risk" program,[14] which were used to calculate the level of cervical cancer risk.

There were 202 nurses and midwives who refused to participate in the study. A further 12 midwives and nurses were excluded from the study because they did not complete the survey. Thus, a total of 466 nurses and midwives fully filled out the questionnaire. The response rate was therefore 68.5%.

In order to determine the cervical cancer risk level, the risk assessment tool "Your Disease Risk", published by the Washington University School of Medicine, was used.[14] In the risk calculation software, assessments were made according to the following features: age; histories of cancer, human immunodeficiency virus (HIV), hysterectomy, smoking and sexually transmitted diseases (STDs); number of sexual partners; age at the time of initial sexual intercourse; use of condoms; number of children delivered; and whether any Pap smear tests had been undertaken over the last three to five years. The questions asked through this software were added to the questionnaire.

In the risk calculation model for cervical cancer, there were seven risk categories: very much below average, much below average, below average, average, above average, much above average and very much above average. In our study, the cervical cancer risk among the participants was found to be "average", "below average" or "much below average". These three groups were analyzed in the chi-square test. In examining the relationship between risk levels and experience of having undergone Pap smear tests, the cervical cancer risk levels "below average" and "much below average" were combined into a single group, named the "low" group, and in the logistic regression analysis, the assessment was thus made in terms of two groups, named the "average" and "low" groups.

For analytical purposes in the chi-square test, the following variables were dichotomized: marital status (currently married versus unmarried); smoking status (currently smoking versus non-smoker); and having given birth (having given birth versus not having given birth). The following variables were analyzed as three groups: age (20-29 years versus 30-39 versus ≥ 40); cervical cancer risk perception (high versus low versus unknown); and calculated cervical cancer risk level (average versus below average versus much below average). In the logistic regression analysis, age (≥ 30 years versus < 30) and calculated cervical cancer risk level (average versus low) were dichotomized. The number of births was divided into four groups (no births, one birth, two births or three births). The frequency of having Pap smear screening was assessed in four groups (first time, once a year, once every 2-3 years or at irregular intervals) and the latest Pap smear screening was assessed in four groups (within one year, 1-3 years ago, 4-5 years ago or more than five years ago).

The data were analyzed through the Statistical Package for the Social Sciences (SPSS) for Windows 20.0 statistical software. Continuous variables were presented as means and standard deviations; and categorical variables were presented as numbers and percentage distributions. The characteristics of participants who had undergone Pap smear testing once in their lifetimes and those who had not been screened were compared using the chi-square test for categorical variables and using Fisher's exact test for categorical variables with small cell counts. To investigate factors associated with screening for cervical cancer, we used simple and adjusted logistic regression models. The variables that were found to be statistically significant through the chi-square test were included in the logistic regression model. The statistical significance level was taken to be $P < 0.05$.

RESULTS

The mean age of the participants was found to be 33.3 ± 7.4 (minimum = 22; maximum = 55). 35.0% of the participants had undergone Pap smear testing at least once in their lifetimes. The most common reason for not having undergone Pap smear testing was found to be negligence (**Table 1**).

The characteristics of the participants according to screening status are shown in **Table 2**. The incidence of having undergone Pap smear testing at least once in a lifetime was higher among subjects who were older, who were smokers, who had given birth, who had histories of STD, who had histories of chronic diseases, who perceived their risk to be high and who had average risk of cervical cancer **(Table 2)**. These significant variables were examined together in the logistic regression model.

The incidence of having undergone Pap smear testing was higher among smokers than among non-smokers (odds ratio, OR: 2.08; 95% confidence interval, CI: 1.24-3.48) and among those who stated that they perceived their risk of cervical cancer to be high, compared with those who perceived their risk to be low (OR: 3.60; 95% CI: 1.36-9.51). The frequency of having undergone Pap smear testing at least once in a lifetime was higher among participants who had given birth once (OR: 17.99, 95% CI: 6.36-50.84) and among participants who had given birth twice (OR: 41.53, 95% CI: 15.01-114.91) than among those who had never given birth (**Table 3**).

Ninety-four percent of the participants were found to have a low level of cervical cancer risk. No relationships were detected between Pap smear test periodicity and the calculated risk level (**Table 4**).

DISCUSSION

This study determined the association between having undergone Pap smear testing and cervical cancer risk levels among female nurses and midwives who were providing services in two hospitals. In this study, about one-third of the participants had undergone Pap smear testing at least once in their lifetimes. The most common reason for not having undergone Pap smear testing was found to be negligence. The incidence of having undergone Pap smear testing once in a lifetime was higher among smokers. This rate was higher among the individuals who stated that they perceived their risk of cervical cancer

Table 1. Proportions of nurses and midwives who had and had not undergone Pap smear testing and reasons for not undergoing any tests

	Number	%
Pap smear test		
Done	163	35.0
Not done	303	65.0
Reasons for not having undergone Pap smear testing		
Not knowing that it is necessary	14	4.6
Neglect	199	65.7
Afraid of undergoing a smear test	17	5.6
Ashamed of undergoing a smear test	13	4.3
Afraid of cervical cancer	2	0.7
Being single	58	19.1

Table 2. Comparison of characteristics between participants who had been screened once in their lifetimes and participants who had not (n = 466)

Characteristics	Pap smear test				P
	Done		Not done		
	Number (n = 163)	%	Number (n = 303)	%	
Age group (years)					
20-29	45	27.6	123	40.6	**0.001**
30-39	64	39.3	152	50.2	
≥ 40	54	33.1	28	9.2	
Educational status					
High school	25	15.3	51	16.8	0.326
Associate's degree*	64	39.3	98	32.3	
Bachelor's degree	74	45.4	154	50.9	
Marital status					
Married	140	85.9	183	60.4	**0.001**
Unmarried	23	14.1	120	39.6	
Smoking status					
Smoker	65	39.9	67	22.1	**0.001**
Non-smoker	98	60.1	236	77.9	
Childbirth					
Having given birth	155	95.1	139	45.9	**0.001**
Not having given birth	8	4.9	164	54.1	
Live birth count					
1 birth	38	24.5	59	42.2	**0.004**
2 births	99	63.9	70	50.4	
3 births	18	11.6	10	7.2	
Regular use of condom in sexual intercourse					
User	19	11.7	27	8.9	0.343
Non-user	144	88.3	276	91.1	
History of STDs					
Present	7	4.3	1	0.3	**0.003**
None	156	95.7	302	99.7	
History of chronic diseases					
Present	24	14.7	23	7.6	**0.015**
None	139	85.3	280	92.4	
Response to the question: "Do you think you have a high risk of cervical cancer?"					
"Yes"	38	23.3	25	8.3	**0.001**
"No"	12	7.4	40	13.2	
"Don't know"	113	69.3	238	78.5	
Calculated cervical cancer risk					
Average	16	9.8	12	4.0	**0.001**
Below average	49	30.1	60	19.8	
Much below average	98	60.1	231	76.2	

STD = sexually transmitted disease.

*Associate's degree programs take two years. High school graduates can qualify for associate's degree programs.

to be high, compared with those who perceived their risk to be low. The frequency of having undergone Pap smear testing at least once in a lifetime was higher among those who had given birth once or twice, compared with those who had never given birth. The majority of the participants had low risk levels.

Table 3. Factors associated with screening for cervical cancer among midwives and nurses (n = 466)*

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P
Age group			0.753
Age ≥ 30	1.79†† (1.18-2.72)	1.08 (0.65-1.79)	
Age < 30**	1.00	1.00	
Marital status			0.170
Married	3.98†† (2.44-6.65)	0.54 (0.22-1.29)	
Unmarried**	1.00	1.00	
Smoking status			**0.005**
Smoker	2.33†† (1.53-3.53)	2.08 (1.24-3.48)	
Non-smoker**	1.00	1.00	
Response to the question: "Do you think you have a high risk of cervical cancer?"			
Yes	4.99†† (2.22-11.68)	3.60 (1.36-9.51)	**0.010**
Don't know	1.58 (0.81-3.24)	1.40 (0.62-3.10)	0.414
No**	1.00	1.00	
Cervical cancer risk level			
Average	2.63†† (1.20-5.85)	1.00 (0.64-0.74)	0.999
Low**	1.00	1.00	
Number of births			
1 birth	13.06 (5.93-31.47)	17.99 (6.36-50.84)	**0.001**
2 births	28.67 (13.75-66.34)	41.53 (15.01-114.91)	**0.001**
3 births	35.37 (12.68-107.02)	1.40 (0.23-0.41)	0.900
Not having given birth**	1.00	1.00	

*A model was created based on age, marital status, number of births, smoking status, risk perception and calculated cervical cancer risk level; **Reference value. OR = odds ratio; CI = confidence interval.

Table 4. Comparison of incidence of Pap smear testing according to cervical cancer risk level (n = 163)

	Cervical cancer risk level				P*
	Average		Low		
	Number (n = 16)	%	Number (n = 147)	%	
Frequency of undergoing Pap smear testing					
First time	5	31.3	34	23.1	0.534
Once a year	1	6.2	27	18.4	
Once every 2-3 years	4	25.0	30	20.4	
Irregular intervals	6	37.5	56	38.1	
Latest Pap smear screening					
Within last year	7	43.8	67	45.6	0.946
1-3 years ago	4	25.0	42	28.6	
4-5 years ago	3	18.8	13	8.8	
More than 5 years ago	2	12.5	25	17.0	

*Fisher exact test.

No relationships were found between Pap smear test periodicity and the calculated risk level.

Thirty-five percent of the nurses and midwives who participated in this study had undergone Pap smear testing at least once in their lifetimes. The frequency of having undergone Pap smear testing at least once in a lifetime was found to range from 10.2% to 83.7% in studies conducted in Turkey and Serbia among women.[15,16] This rate was found to range from 23.7% to 45.2% among healthcare professionals in Turkey.[9-13] In studies conducted among nurses in different countries, the incidence of Pap smear testing at least once in their lifetimes ranged from 3.4% to 72.6%.[17-22] The frequency of having undergone Pap smear testing was higher in our study than in some studies[17-20] and lower than in other studies.[21,22] In addition to factors such as age, education and presence of a screening program in a given country, it has been shown that the level of development of countries also has an effect in relation to cervical cancer screening.[8] Studies in which the incidence of Pap smear testing was lower than in our study were conducted in underdeveloped or developing countries.[17-20]

About two-thirds of the nurses and midwives who participated in this study stated that they had never undergone Pap smear testing. In this study, it was determined that for most of the nurses and midwives who had not undergone Pap smear testing, this was due to their own negligence (65.7%), according to their responses to the questionnaire. In other studies among nurses and midwives, the most common reasons that they stated for not having undergone such tests were factors such as not considering themselves to be at risk,[18,19] thinking that screening was not necessary for themselves[11,23] and negligence.[13] Encouragement by the partner, regular examination by a gynecologist and suggesting a Pap smear test by these experts are effective measures in increasing the regular undertaking of the Pap smear test.[22,24] In-service training can be given to nurses and midwives regarding the importance of cervical cancer risk factors and of undergoing Pap smear tests.

In the present study, it was found that the incidence of undergoing Pap smear testing was higher among smokers. Higher levels of carcinogenic substances were found in the cervical mucus of smokers than in the mucus of non-smokers. It is thought that these substances may be effective in aiding development of cervical cancer through causing damage to the deoxyribonucleic acid (DNA) of cervical cells.[4] In some studies conducted among healthcare professionals, the levels of information regarding the fact that smoking is a risk factor for cervical cancer were found to be low.[11,13] On the other hand, in other studies, although these levels were found to be high, only low levels of screening were occurring.[12,23] In our study, the odds of undergoing Pap smear testing were higher among smokers. This significant finding may have been caused by the fact that because of their profession, the research group of this study knew about the fact that smoking is an important risk factor for cervical cancer.

In the study group, the odds of having undergone Pap smear testing were higher among participants who perceived themselves to be at risk in terms of cervical cancer. Women's perceptions of risk relating to cervical cancer are an important subjective finding: this perception leads them to maintain a healthy lifestyle and take advantage of early diagnostic methods. Perception of high risk of cervical cancer leads women to increase their frequency of undergoing screening.[25] 13.5% of the nurses and midwives who participated in the present study perceived their own risk of cervical cancer as high. In a study conducted among nurses working in a hospital in Turkey, 31.8% of them indicated that they perceived themselves to be in the at-risk group in terms of cervical cancer.[13] The proportion of nurses in a study conducted in Singapore who perceived that they had a high level of individual cervical cancer risk was lower than what was found in the present study.[22] In a study conducted in a group undergoing treatment for high-grade cervical intraepithelial neoplasia, it was found that 64% of these women perceived themselves to be at high risk and 30% at low risk.[26]

Multiparity has been linked with higher risk of cervical cancer in women.[2] In the present study, the frequency of having undergone Pap smear testing at least once in a lifetime was higher among participants who had given birth once or twice than among those who had never given birth. In a study conducted among nurses in India, it was also found that multiparity increased the frequency of Pap smear testing.[27] However, no relationship was found between the frequency of having undergone Pap smear testing and the number of births, in studies conducted in the general population in India.[25,28] In the present study, in univariate analysis (chi-square test), it was determined that the incidence of having undergone Pap smear testing increased significantly with increasing age among the nurses and midwives. However, this relationship was not observed in the logistic regression analysis. Among nurses, the incidence of having undergone Pap smear testing was found to be highest in the 40 to 44-year age group in Australia,[21] in the 35 to 49-year age group in Singapore[22] and in the group aged 40 years and over in Turkey.[9]

It is quite difficult to calculate the risk of cervical cancer in absolute terms. However, calculating the individual risk of cervical cancer using the risk calculation models that have been developed may provide a guide in terms of both cervical cancer prevention and early diagnosis.[29] Nevertheless, it is important to accurately compile risk factors from women in determining the risks. In the present study, the calculated level of cervical cancer risk was low in 94% of the nurses and midwives, while only 6% of them had an average level of risk. In a study conducted among women aged 35-69 years, it was calculated that 8% of them had a high level of cervical cancer risk, while 22% of them had an average level of risk and 70% of them had a low level of risk.[15] In that study, the higher level of risk found among the participants may have resulted from the older age of the participants in that study, compared with those of the present study, along with the higher level of risky behavior among the participants in that study. The low risk presented by the majority of the present study group was due to its young age, with relatively few risky behavioral characteristics. The number of women undergoing treatment for STDs was minimal in the present study.

The risky behavior among the participants that needed to be taken into account in calculating the cervical cancer risks originated from smoking and failure to undergo Pap smear testing over the past three years. About a third of the women in the present study continued to smoke. Açıkgöz et al. found that the incidence of undergoing Pap smear testing decreased as the level of cervical cancer risk increased.[15] However, in the present study, in the univariate analysis (chi-square test), as the level of cervical cancer risk increased, the incidence of having undergone Pap smear testing increased significantly. On the other hand, this relationship was not observed in the logistic regression analysis. Regardless of which part of society women belong to or at which age they are, it needs to be ensured that they can undergo regular Pap smear testing and that their risky behavior is reduced.

The strengths of the present study include the fact that, although several knowledge-attitude-behavior studies on cervical cancer among nurses and midwives in Turkey were found to be available through our review of the literature, there were none in which the level of cervical cancer risk was determined among nurses and midwives. For the first time in Turkey, nurses and midwives' cervical cancer risk levels were identified using risk level determination software.

The limitations of our study relate mainly to data collection. We collected self-reported data. Although self-reporting is an acceptable method of data collection in public health studies, it is associated with the potential for recall bias. Therefore, the results regarding the women's risk levels may have been determined in different manners. The results from this study cannot be generalized to all nurses and midwives. Since the participants did not respond to any question regarding how many partners they had had, the cervical cancer risk level among these individuals may have been lower than the true level because they were considered to be monogamous.

It is undeniable that healthcare professionals have a role to play in raising awareness about cervical cancer within the community. It is necessary to conduct studies aimed at ascertaining what the motivational barriers are that lead to such low levels of Pap smear test screening among nurses and midwives who are role models for women regarding prevention of cervical cancer. Correct information about cervical cancer risk factors and the importance of Pap smear test screening is needed not only for women in the at-risk group but also for nurses and midwives. In this way, socially more effective results regarding prevention of cancer and use of early diagnostic and treatment methods will be obtained.

CONCLUSION

It was found that the incidence of having undergone Pap smear testing at least once in a lifetime among nurses and midwives was low in this study. Smokers, participants with a high perception of cervical cancer risk and those who had given birth presented higher levels of having undergone Pap smear testing at least once. Most of the nurses and midwives presented low cervical cancer risk levels. No relationships were found between Pap smear test periodicity and the calculated cervical cancer risk level.

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Cardiovascular risk assessment using the lipid accumulation product index among primary healthcare users: a cross-sectional study

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KEY WORDS:
Obesity.
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Primary health care.
Waist circumference.

ABSTRACT

BACKGROUND: The lipid accumulation product (LAP) index is an abdominal adiposity marker.

OBJECTIVE: The aim of this study was to describe the cardiovascular risk of primary healthcare users through the LAP index and correlate it with anthropometric and biochemical indicators.

DESIGN AND SETTING: Cross-sectional study in primary care units in a city in northeastern Brazil.

METHODS: The subjects responded to a structured questionnaire that contained questions about their sociodemographic condition, and then underwent an anthropometric nutritional assessment. The LAP index values were expressed as three degrees of cardiovascular risk intensity: high risk (above the 75th percentile), moderate risk (between the 25th and 75th percentiles) and low risk (below the 25th percentile).

RESULTS: The median LAP index was 52.5 cm.mmol/l (range: 28.2-86.6), and there was no statistically significant difference between the sexes: 57.7 cm.mmol/l (24.5-91.1) and 49.5 cm.mmol/l (29.8-85.2) for females and males, respectively (P = 0.576). Among all the subjects, 67.2% were overweight and there was a statistically significant difference in mean LAP index between those who were and those who were not overweight. Statistically significant differences in anthropometric and biochemical markers for cardiovascular risk were observed among individuals who had higher LAP index values. There were significant correlations between the LAP index and all of the biochemical variables.

CONCLUSIONS: These significant correlations between the LAP index and the traditional biochemical risk markers may be useful within conventional clinical practice, for cardiovascular risk screening in primary healthcare.

INTRODUCTION

Cardiovascular diseases (CVD) are considered to be one of the most serious public health problems because of their multidimensional nature and all the consequences that they have for the individuals affected, their families and the healthcare system.[1] Obesity is becoming a global epidemic and, additionally, the prevalence of CVD risk is increasing. Therefore, it is important to know the magnitude of CVD risk factors in order to implement healthcare planning such that effective intervention in this reality becomes possible.[2] Hence, to predict CVD risk, it is necessary to sum the factors and analyze how synergisms between them may influence the development of coronary events.[3]

Body mass index (BMI) is the recommended indicator for diagnosing and classifying obesity.[2] However, it determines overall obesity and does not have the capacity to identify how body fat is distributed. Thus, it has limitations with regard to distinguishing excess fat and lean mass, and with regard to determining the anatomical locations or functions of different fat deposits, especially because fat accumulated in the abdominal region is more associated with metabolic diseases than is the BMI alone.[4,5] Therefore, it is important to also use other cardiovascular risk indexes, in order to improve screening accuracy.

The lipid accumulation product (LAP) is one of these indexes. It is based on a combination of two safe and inexpensive measurements: waist circumference and serum triglycerides.[6] These tend to increase with age, which suggests that overaccumulation of lipids occurs over time.[7] The LAP index may thus constitute an abdominal adiposity marker that correlates with central lipid accumulation.[8]

Since the LAP index was first proposed, in Kahn's pioneering study,[9] many researchers have used it to predict cardiovascular risk in different populations, such as among patients with type 2 diabetes[6] or insulin resistance,[10] women with polycystic ovarian syndrome[10,11] and hospital outpatients[12] and inpatients.[7] However, no studies have evaluated the use of this index among patients attending primary care units.

While all adults and elderly people should have their cardiovascular risk assessed, this is not practical in many developing countries. In such countries, decision-making about whom to screen and when to do this is resource-dependent.

According to the European guidelines on cardiovascular disease prevention in clinical practice,[13] opportunistic screening for cardiovascular risk is a form of screening that is done when the opportunity arises. For example, such opportunities may arise when individuals attend consultations with their general practitioners for some other reason, as occurs in primary care units. In Brazil, the aim in primary care units is to resolve up to 80% of the population's health problems, without the need for referral to hospitals.

OBJECTIVE

Thus, the objective of this study was to describe the CVD risk of primary healthcare users through the LAP index and correlate this with anthropometric and biochemical indicators for cardiovascular risk.

METHODS

Study population and sampling procedure

This was a cross-sectional study on a population of adults and elderly people of both sexes who were living in a city in northeastern Brazil and attending primary healthcare units. The exclusion criteria of the study were that the subjects should not be pregnant women and should not be adults or elderly people with the any of the following conditions: liver disease, ascites, acquired immune deficiency syndrome, malnutrition or renal replacement therapy.

During the data collection period, the researchers invited all users who were present at the healthcare unit and who met the inclusion criteria to participate in the study. After these individuals had voluntarily agreed to participate in the study, they signed an informed consent statement in duplicate.

This research project had previously been approved by the ethics committee of the Federal University of Rio Grande do Norte (Universidade Federal do Rio Grande do Norte, UFRN), under protocol no. 284,437 and ethics committee no. CAAE 13148313.1.0000.5568, on May 26, 2013. All the procedures used were in accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration.

The total population of the city and the prevalence of high LAP index that was found in a previous study in Brazil[4] were taken into consideration in calculating the sample size. The study power was set at 80% and the significance level at 5%. The required minimum number of patients was found to be 384 individuals.

Data collection

Data collection took place between July 2014 and October 2015, during the mornings. Firstly, the patients answered a structured questionnaire that asked for information about their housing, socioeconomic condition and lifestyle. Their economic class was evaluated using the ABEP (Brazilian Association of Polling Companies) methodology,[14] which takes into account the numbers of material goods and monthly-paid employees in the household and the educational level of the main income earner. From this, the subjects were clustered into economic classes A1/A2, B1/B2, C1/C2, D and E, which were subsequently regrouped into: A/B (better condition), C (intermediate condition) and D/E (worse condition). Economic classes D and E are predominant, according to the ABEP.

Body mass measurements were obtained using a properly calibrated professional mechanical scale with stadiometer (model 110 CH, Welmy, Brazil) with a capacity of up to 150 kg. The subjects were asked to remove their shoes and heavy clothing, such that they were then weighed while only wearing minimal clothing. For height measurements, the subjects stood barefoot at the center of the equipment, with their feet together and arms extended down the sides of the body, and the Frankfurt horizontal plan was used. BMI was then calculated and nutritional status was then ranked in accordance with the cutoffs recommended by the World Health Organization (WHO).[2]

Waist circumference (WC) was measured using an inelastic tape at the midpoint between the lower costal margin and the iliac crest. The cutoff for excess abdominal adiposity was set at 102 cm for men and 88 cm for women, as recommended by the National Cholesterol Education Program (NCEP/ATP III, 2001).[15] Hip circumference was measured with the measuring tape positioned at the point of greatest circumference in the gluteal region. The waist-to-hip ratio (WHR) was then calculated by dividing waist circumference by hip circumference. The WHR cutoff points established by WHO[2] were implemented, such that values of > 1 and > 0.85 represented the risk of developing cardiovascular disease among men and women, respectively.

The biochemical test results were collected from the patients' records. Results from tests that had been performed within 30 days prior to the anthropometric evaluation were accepted. Total cholesterol and fractions, triglycerides and blood glucose, all measured in a fasting state, were recorded. The LAP index was determined through the equation proposed by Kahn,[9] according to sex.

For women, this was defined as [(waist circumference in cm – 58) x (triglycerides in mmol/l)]; while for men, this was [(waist circumference in cm – 65) + (triglycerides in mmol/l)]. High cardiovascular risk was ranked according to the LAP index, such that the 75th percentile (P75) was taken to be the cutoff for data distribution. Triglyceride measurements in mg/dl were converted to mmol/l.

Statistical analysis

The data were organized in the Microsoft Excel software and were then exported to the Statistical Package for the Social Sciences (SPSS) software version 20.0 for Windows, for analysis. The normality of the distribution of the quantitative variables was tested using the Shapiro-Wilk test. LAP index values were expressed in quartiles using three degrees of cardiovascular risk intensity: high risk (above the 75th percentile), moderate (between the 25th and 75th percentiles) and low (below the 25th percentile). The categorical variables were correlated using the chi-square test, and quantitative variables were compared using the t test for independent samples, or the Mann-Whitney test for nonparametric data. Correlations were tested using the Pearson correlation test. $P \leq 0.05$ was considered significant for all analyses.

RESULTS

The subjects were aged 18-90 years, and their mean age was 48.4 ± 15.9 years. **Table 1** shows the description of the sample data. Predominance of females and married, retired and sedentary individuals were observed. Sedentarism was defined as < 150 minutes of moderate-intensity physical activity per week. The subjects' economic class was consistent with populations that are attended through the public healthcare system, in that these subjects presented lower levels of financial resources (economic classes D and E).

The median LAP index in the general population was 52.5 cm.mmol/l (range: 28.2-86.6), and there was no statistically significant difference between the sexes: 57.7 cm.mmol/l (24.5-91.1) and 49.5 cm.mmol/l (29.8-85.2) for females and males, respectively ($P = 0.576$). Among all the subjects, 293 were overweight (67.2%), and there was a statistically significant difference in mean LAP index between those who were and those who were not overweight: 99.03 ± 74.76 cm.mmol/l and 48.86 ± 50.60 cm.mmol/l, respectively ($P < 0.01$).

Table 2 provides an overview of cardiovascular risk prevalence using different anthropometric methods and the LAP index. From the data presented, it can be seen that these subjects showed significant cardiovascular risk. The indicator that pointed towards the highest cardiovascular risk for both sexes was the WHR, and this was also higher among men. Among women, the LAP index was the indicator that identified the highest prevalence of cardiovascular risk. In comparing the sexes, the prevalence of cardiovascular risk factors was only different between the sexes regarding increased WC and WHR.

Table 3 summarizes the correlation analysis on the BMI, WHR and LAP index, in relation to the traditional biochemical parameters of cardiovascular disease. The LAP index showed statistically significant correlations with all the biochemical parameters analyzed. This was better than was seen regarding WHR and BMI, which showed significant correlations with only three and two biochemical variables, respectively. These results demonstrate that the LAP index presented higher power for screening individuals with metabolic abnormalities than did BMI. However, specifically in relation to glycemia, the WHR was the indicator that showed

Table 1. Sociodemographic description of the sample

Variable	n = 437	%
Sex		
Male	115	26.3%
Female	322	73.7%
Occupation		
Retired	93	21.3%
Housework (unemployed)	69	15.8%
Farmer	47	10.9%
Self-employed	37	8.5%
Teacher	11	2.5%
Domestic worker	19	4.3%
Other	155	35.5%
Marital status		
Married	275	62.9%
Single	118	27%
Widower	26	5.9%
Divorced	18	4.1%
Economic class		
A/B	0	0%
C	198	45.3%
D/E	239	54.7%
Active physically		
Yes	141	31.3%
No	296	67.7%
Smoker		
Yes	67	15.6%
No	312	71.4%
Former smoker	57	13%

Table 2. Comparison of prevalence of cardiovascular risk parameters between sexes

	Total	Male	Female	P-value*
Obesity	133 (30.5%)	38 (33%)	95 (29.6%)	0.834
High waist circumference	84 (19.2%)	42 (36.5%)	42 (13.0%)	< 0.01
High waist-to-hip ratio	202 (64.1%)	74 (84.1%)	128 (56.4%)	< 0.01
High lipid accumulation product index (P75)	109 (24.9%)	34 (31.2%)	75 (23.3%)	0.182

*P-values obtained using the chi-square test.

the strongest correlation. The strongest correlation for high-density lipoprotein (HDL)-cholesterol was with BMI.

Lastly, **Table 4** shows a comparison between biochemical test values and BMI among people who were classified as presenting high cardiovascular risk (≥ P75) and low cardiovascular risk (< P75) according to the LAP index. With the exception of total cholesterol and low-density lipoprotein (LDL) cholesterol, there were statistically significant differences in relation to all the variables tested, thus demonstrating that people with higher LAP index values also showed negative changes in other cardiovascular risk parameters.

DISCUSSION

Although most guidelines recommend a mixture of screening measures to identify people who are at relatively high risk of CVD, the pre-existing tools are not particularly effective for reducing the risk of cardiovascular events.[13] The results from the present study showed that the LAP index presented good correlations with the metabolic profile and anthropometric variables. This emphasizes the hypothesis that it is an easy-to-use and practical tool for detecting interactions between excess adiposity and cardiovascular risk. It may therefore be useful within primary healthcare services that face financial constraints that hinder access to cardiovascular risk markers of greater sophistication.

Many cardiovascular risk assessment systems are available for use among apparently healthy individuals, including Framingham,[16] SCORE,[17] CUORE[18] and others. In practice, most risk estimation systems perform rather similarly when applied to populations that are recognizably comparable to those from which the risk estimation system was derived. However, these tools sometimes are not useful in situations in which it is necessary to ascertain a greater number of cardiovascular risk variables (including anthropometric and biochemical values), and in which the time available for assessing the individual is limited.

Thus, the LAP index is a useful tool because it only includes two variables, which are usually available cheaply in a wide variety of healthcare services. Recently, Xie et al.[19] evaluated cardiovascular risk among Chinese patients with growth hormone deficiency, using the Framingham score and LAP index. In comparison with healthy controls, they found that the LAP index was higher among adult growth hormone deficiency patients, but that these higher LAP indexes were not associated with Framingham risk. This was probably observed because there was no common factor between the LAP index and Framingham risk score.

Only a few studies have aimed to evaluate the LAP index in different populations. Some of these studies have proposed a cutoff point using a receiver operator characteristic (ROC) curve.[6,20,21] Wakabayashi and Daimon[6] evaluated 10,170 Japanese workers (35-40 years old) and proposed cutoff values for the LAP index of 21.1 cm.mmol/l and 37.2 cm.mmol/l for women and men, respectively. These values were lower than those observed in the present study because our sample had a higher mean age (48.4 years) and was stratified into nutritional status categories (overweight or not overweight). However, our results also showed that women had lower LAP index values than those of men. Nascimento et al.[21] found a high cutoff point through using an ROC curve in a cross-sectional study conducted on 78 women aged 18 to 42 years who presented polycystic ovarian syndrome and were attended at a university hospital in Brazil. Except for HDL levels, logistic regression showed that all cardiovascular risk markers presented a higher chance of being altered when the LAP index was above the cutoff value of 37.9 cm.mmol/l. This higher value may have been found because women with polycystic ovarian syndrome already present higher cardiovascular risk than that of

Table 3. Correlations of body mass index, waist-to-hip ratio and lipid accumulation product (LAP) index with biochemical parameters

	Body mass index	Waist-to-hip ratio	LAP index
Glycemia	r = 0.106 P = 0.03	r = 0.249 P ≤ 0.01	r = 0.183 P ≤ 0.01
Total cholesterol	r = 0.013 P = 0.79	r = 0.112 P = 0.05	r = 0.248 P ≤ 0.01
HDL-cholesterol	r = -0.314 P ≤ 0.01	r = -0.295 P ≤ 0.01	r = -0.296 P ≤ 0.01
LDL-cholesterol	r = 0.040 P = 0.52	r = 0.096 P = 0.13	r = 0.151 P ≤ 0.01

P-values obtained using the Pearson correlation test.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 4. Comparison between biochemical test values and body mass index, in terms of high cardiovascular risk (above P75) and low cardiovascular risk (below P75) according to the lipid accumulation product (LAP) index

Variables	LAP percentile 75	Mean ± SD	P-value
Triglycerides (mg/dl)	Below P75	136.87 ± 56.36	< 0.01[a]
	Above P75	297.17 ± 146.50	
Total cholesterol (mg/dl)	Below P75	197.18 ± 45.29	0.19[b]
	Above P75	222.0 ± 54.575	
HDL-cholesterol (mg/dl)	Below P75	51.22 ± 13.98	< 0.01[b]
	Above P75	42.10 ± 10.03	
LDL-cholesterol (mg/dl)	Below P75	118.75 ± 39.61	0.17[a]
	Above P75	125.80 ± 42.84	
Glycemia (mg/dl)	Below P75	101.09 ± 38.37	< 0.01[a]
	Above P75	120.46 ± 57.35	
Body mass index (kg/m^2)	Below P75	27.31 ± 5.68	< 0.01[b]
	Above P75	32.88 ± 5.35	

[a]P-value obtained through Mann-Whitney test; [b]P-value obtained through independent t test.
LAP = lipid accumulation product; SD = standard deviation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; P75 = percentile 75.

the general population. Lastly, in a regional hospital in southern Taiwan, Chiang and Koo[20] evaluated 513 individuals and showed that the optimal cutoff for the LAP index was 28.4 cm.mmol/l, for both sexes.

Our results showed a difference in the distribution of the LAP index between people who were overweight and those who were not overweight, thus showing that the index had good discriminatory power regarding cardiovascular risk. Other studies have also shown a correlation between higher LAP values and the risk of cardiovascular events in clinical populations.[19-21] This has also been observed in some subgroups of normal-weight subjects who were metabolically obese.[9]

In a longitudinal study, Du et al.[22] evaluated 3,552 subjects with normal weight and showed that through using an ROC curve, the LAP index was more effective than were anthropometric parameters for identifying normal and metabolically obese individuals, thus demonstrating the power of the LAP index for determining the presence of cardiovascular risk.

In another study, Xia et al.[23] evaluated a representative sample of 2,524 Chinese non-diabetic individuals. Comparison with the results from using BMI and WC showed that use of the LAP index had a greater impact on the insulin resistance index. Moreover, in multivariate analysis, the LAP index had a greater impact on homeostatic model assessment (HOMA) than did BMI and WC. These results showed that the LAP index really discriminated among biochemical markers, regardless of general adiposity.

Some limitations of our study should be considered in interpreting the results. We did not evaluate insulin resistance and we did not have any medical diagnosis for diabetes or other cardiovascular diseases among our cases. Furthermore, we did not use any imaging technique to detect body compartments, especially with regard to overall and visceral fat, to correlate with all the anthropometric indexes. Thus, it was not possible suggest any cutoff point for screening for these diseases through analyzing an ROC curve, for example. We suggest that future studies should evaluate insulin resistance or diabetes in such patients, given that the association between cardiovascular risk and diabetes is well-established.

CONCLUSION

Through using the LAP index, a notable number of people presenting cardiovascular risk factors could be identified among primary healthcare users in Brazil. High cardiovascular risk according to the LAP index seemed to be associated with anthropometric and biochemical cardiovascular risk markers. These significant correlations between the LAP index and the traditional biochemical risk markers may be useful within conventional clinical practice, for cardiovascular risk screening in primary healthcare.

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A novel simplified scoring system for predicting mortality in emergency colorectal surgery: prediction model development

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ABSTRACT

BACKGROUND: Despite advances in surgical approaches, emergency colorectal surgery has high mortality and morbidity.

OBJECTIVE: We aimed to create a simple and distinctive scoring system, for predicting mortality among patients undergoing emergency colorectal surgery.

DESIGN AND SETTING: Prediction model development study based on retrospective data-gathering.

METHODS: Patients who underwent emergency colorectal surgery between March 2014 and December 2016 at a single tertiary-level referral center were included in our study. Patient demographics, comorbidities, type of surgery, etiology and laboratory and radiological findings were collected retrospectively and analyzed. A new clinical score (named the Numune emergency colorectal resection score) was constructed from the last logistic regression model, in which one point was assigned for the presence of each predictive factor.

RESULTS: 138 patients underwent emergency colorectal surgery. These comprised 64 males (46.4%) and 74 females (53.6%), with a mean age of 64 years. Multivariate analysis revealed that blood urea nitrogen level > 65 mg/dl (odds ratio, OR: 8.03; 95% confidence interval, CI: 2.16-15.77), albumin level < 0.7 mg/dl (OR: 4.43; 95% CI: 1.96-14.39) and American Society of Anesthesiologists score ≥ 3 (OR: 3.47; 95% CI: 0.81-9.18) were associated with postoperative complications. The Numune score was graded from I to III. The risk of mortality was found to be 63.2% in the group with grade III, which accounted for 35.2% of the subjects. There were 37 postoperative deaths.

CONCLUSIONS: Surgeons need scoring systems, especially to predict postoperative mortality. We propose the Numune emergency colorectal resection score for emergency surgical procedures as a practical, usable and effective system for predicting postoperative morbidity.

INTRODUCTION

Despite advances in surgical approaches, emergency colorectal surgery has high mortality and morbidity.[1] The mortality rates after emergency colorectal surgery range from 2.3% to 80%.[2,3] This wide range is secondary to the expertise of the surgical center and the patients' comorbidities. Colorectal emergency situations such as diverticulitis, trauma and ischemia may be related to either benign or malignant etiologies.[3]

Colorectal cancer is the reason behind colorectal emergencies in 85% of the cases, with colonic obstruction in 11%-43% of all presentations.[4] Perforation and obstruction of the colon and rectum are important factors leading to postoperative mortality in patients with emergency admissions.[5] The comorbidities that cannot be managed adequately in emergency colorectal surgery and which cause highest mortality are cardiopulmonary, renal and thromboembolic diseases.[6]

Scoring systems for use in predicting postoperative mortality after surgical procedures already exist. The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) and the Portsmouth-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (p-POSSUM) are two examples of such scoring systems. Both of these use physiological and operative parameters.[7] Through use of these systems, it was realized that advanced age and high frequency of emergency procedures within colorectal surgery made these two scores inadequate. Thus, after omission of certain parameters, a new model was devised for colorectal surgery, which was named the colorectal-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (cr-POSSUM).[8]

The cr-POSSUM system consists of multiple variables and defines a physiological score and an operative score. Following this, predictive values can be found through logarithmic equations. Computer software needs to be used in order to calculate predictive scores. The cr-POSSUM system can accurately predict postoperative complications, but unfortunately it is not practical, especially in emergency situations.

OBJECTIVE

To propose a scoring system for predicting mortality among patients undergoing emergency colorectal surgery.

METHODS

Local ethics board approval was obtained for this study, through registration number E-18-1938 (date: April 25, 2018). The patients included in this study underwent emergency colorectal surgery between March 1, 2014, and December 30, 2016, at a single tertiary-level referral center. The sociodemographic features, comorbidities, American Society of Anesthesiologists score, etiology, laboratory and radiological findings, blood transfusions, operative time, indications for surgery and type of surgery of the 138 patients thus included were analyzed retrospectively. Twenty-six patients whose data were incomplete were excluded from the study. Postoperative complications and mortality rates were also analyzed.

The following data were collected and used in the analyses as independent variables: age, gender, results from liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase and total and direct bilirubin), renal function tests, albumin level, complete blood cell count, type of surgery, presence of ostomy, operative time and blood transfusion. The primary endpoint (dependent variable) was postoperative mortality.

Continuous data were presented as the mean value ± standard deviation. Differences in continuous variables were analyzed using the Mann-Whitney U test. The Shapiro-Wilk test was used to assess normality of data distribution. Categorical variables were analyzed using chi-square tests. Logistic regression was used to identify the factors associated with mortality. The results from the multivariate analysis were presented as odds ratios with 95% confidence intervals. Receiver operating characteristic curve analyses were used to determine the optimal cutoff values for continuous variables.

A new clinical score (named the Numune emergency colorectal resection score) was constructed from the final logistic regression model, in which one point was assigned for the presence of each predictive factor. Model discrimination was measured as the area under the receiver operating characteristic curve. The discrimination of the prognostic model was considered perfect if the area under the curve was 1, good if the area under the curve was > 0.8, moderate if the area under the curve was 0.6-0.8 and poor if the area under the curve was < 0.6.[1] Specificity, sensitivity, positive predictive value, negative predictive value, negative likelihood ratio and positive likelihood ratio were also calculated.

RESULTS

During the study period, emergency colorectal surgery was performed on 138 patients. These comprised 64 males (46.4%) and 74 females (53.6%), with a median age of 64 years (minimum: 23; maximum: 91).

The patients were classified according to their American Society of Anesthesiologists (ASA) score. Among them, 4 (2.90%) were classified as presenting ASA score I, 40 (28.99%) as ASA score II, 55 (39.86%) as ASA score III and 39 (28.26%) as ASA score IV. Twenty-three patients (16.7%) received blood transfusions during their surgery.

The most frequent surgical site was the right colon, followed in sequence by the sigmoid colon, the descending colon and the rectum. The average operative time was 147 ± 29 minutes (**Table 1**). The most common indication for the surgery was obstruction, and the other indications were perforation and ischemia. The most common etiologies were colorectal cancer in 76 patients (55.07%), ischemic colitis in 27 patients (19.5%) and volvulus in 11 patients (7.97%) (**Table 1**).

All the operations were performed by general surgeons. Regarding the type of surgery, right hemicolectomy was conducted in the cases of 64 patients (46.9%), followed by left hemicolectomy in 21 (15.2%), low anterior resection in 15 (10.9%), anterior resection in 13 (9.4%), total abdominal colectomy in 5 (3.6%) and subtotal abdominal colectomy in 4 (2.9%). A preventive ostomy was created in 86 patients (62.3%).

Thirty-seven postoperative deaths occurred (26.8% of the patients). The main reason for mortality was sepsis, which occurred in the cases of 17 patients (11.6%). The other reasons for mortality comprised multiple organ failure in 12 patients (8.2%), pneumonia in 6 (4.1%) and pulmonary thromboembolism in 2 (1.4%) (**Table 1**). There were 38 occurrences of minor complications among the patients. Surgical wound infection was the most common minor complication (15.9%). Other reasons for occurrences of wound infection included bleeding in 3 patients (2.1%), anastomotic leakage in 7 (4.8%), necrosis of ostomy in 3 (2.1%) and postoperative ileus in 1 (0.7%).

In univariate analyses, age greater than 65 years, American Society of Anesthesiologists score greater than or equal to 3, blood urea nitrogen level higher than 65 mg/dl, creatinine higher than 1.2 mg/dl, albumin level lower than 2.7 mg/dl, aspartate aminotransferase level higher than 50 u/ml and indication for resection were found to be statistically associated with postoperative mortality (**Table 1**).

Multivariate risk prediction model and prediction score

All of the variables that could be assessed before the operation were included in the multivariate model. Three variables

were found to be significant in this analysis: blood urea nitrogen level > 65 mg/dl (odds ratio, OR: 8.03; 95% confidence interval, CI: 2.16-15.77); albumin level < 0.7 mg/dl (OR: 4.43; 95% CI: 1.96-14.39); and American Society of Anesthesiologists score ≥ 3 (OR: 3.47; 95% CI: 0.81-9.18) (**Table 2**).

A probability score was calculated by adding together the number of points assigned to each variable. Although the regression coefficients ranged from 1.24 to 2.08, one point was assigned to each of these risk factors, for simplicity. The resulting Numune emergency colorectal resection score (composed of the blood urea nitrogen level, albumin level and American Society of Anesthesiologists score) was graded on a range from I to III.

Table 1. Demographic and clinical characteristics of patients

Variable	Survivors (n = 101)	Non-survivors (n = 37)	P
Mean age (years)	61 ± 14	72 ± 12	**< 0.0001**
Gender, male/female	53/48	12/25	**0.0109**
White blood cell count (/mm³)	13.07 ± 5.69	13.88 ± 7.44	0.0634
Aspartate aminotransferase (U/l)	20 (17-27)	139.63 (18-52)	**0.005**
Alanine aminotransferase (U/l)	14 (11-20)	148 (10-32)	0.718
Blood urea nitrogen (mg/dl)	39 (30-53)	70 (50-113)	**< 0.0001**
Creatinine (U/l)	0.97 (0.80-1.14)	1.33 (1.19-1.99)	**< 0.0001**
Albumin (mg/dl)	3 (2.6-3.4)	2.55 (2.1-2.8)	**0.003**
American Society of Anesthesiologists score ≥ 3	60	25	**< 0.0001**
Etiology			
Colorectal cancer	66	10	**< 0.0001**
Ischemia	8	19	
Volvulus	8	3	
Diverticulitis	6	1	
Other	13	4	
Type of surgery			
Right hemicolectomy	47	17	0.613
Left hemicolectomy	16	5	
Low anterior resection	10	5	
Sigmoid resection	10	4	
Transvers colectomy	2	0	
Anterior resection	11	2	
Total colectomy	2	3	
Subtotal colectomy	3	1	
Operation time	149 ± 27	140 ± 29	0.5
Preventive ostomy +/-	57/44	29/8	0.028
Reason for mortality			
Sepsis	0	17	
Multiple organ failure	0	12	
Pneumonia	0	6	
Pulmonary thromboembolism	0	2	

Three groups of patients were defined based on the Numune emergency colorectal resection score. The first group, with a score graded as I, comprised 64.8% of the patients, and their mortality rate was 7.1%. The second group included patients with a score graded as II, who had a mortality rate of 26.6%; this group comprised approximately 28% of the cohort. The third group, which comprised approximately 35.2% of the patients, included those with a Numune emergency colorectal resection score graded as III, and their mortality rate was 63.15% (**Table 3**).

The specificity, sensitivity, positive predictive value, negative predictive value, negative likelihood ratio and positive likelihood ratio for the Numune emergency colorectal resection grades of II or III were 64.36%, 86.49%, 47.06%, 92.86%, 0.21 and 2.43, respectively. The area under the receiver operating characteristic curve was 0.794 (95% CI: 0.704-0.885) for the Numune emergency colorectal resection score (**Figure 1**).

DISCUSSION

Prediction of postoperative mortality after emergency colorectal surgery is an ongoing field of research. In this study, we defined a new scoring system, the Numune emergency colorectal resection score. The simplicity of our calculation is quite apparent, as it uses only three variables, among which two are part of the routine serum biochemistry evaluation: blood urea nitrogen level, albumin level and American Society of Anesthesiologists score.

Several scoring systems are used within colorectal surgery to predict postoperative morbidity and mortality. The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) was designed by Copeland et al. in order to evaluate postoperative morbidity and mortality.[9] The Portsmouth-Physiological and Operative Severity Score for the enUmeration

Table 2. Multivariate logistic regression model for predictors of mortality

	Regression coefficient	Odds ratio	95% confidence interval	P	Score points
American Society of Anesthesiologists score ≥ 3	1.247	3.478	0.81-9.18	0.048	1
Blood urea nitrogen level > 50 mg/dl	2.083	8.032	2.16-15.77	0.001	1
Albumin level < 2.7 mg/dl	1.7	5.48	1.96-14.39	0.0006	1

Table 3. Risk of mortality according to the Numune emergency colorectal resection score

Numune emergency colorectal resection score		Mortality rate (%)
Grade	Score points	
I (70 patients)	0	5 (7.14)
II (30 patients)	1	8 (26.6)
III (38 patients)	≥ 2	24 (63.15)

of Mortality and morbidity (P-POSSUM) and the colorectal-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (cr-POSSUM) were designed based on the POSSUM scoring system.

The most recent of these scoring systems, i.e. cr-POSSUM, consists of 10 parameters (six for the physiological severity score and four for the operative severity score), and the final score is calculated by means of a logarithmic equation.[10] Although some medical electronic software for calculating this score exists, this scoring system is impractical, given that it necessitates greater effort and more data. Moreover, it has been reported that cr-POSSUM may either overestimate or underestimate mortality.[11,12]

Heriot et al. studied prediction of postoperative morbidity and mortality among elderly patients who underwent colorectal surgery, and they designed the elderly colorectal cancer model.[1] However, this scoring system has not undergone any external validation. In addition, the Association of Coloproctology of Great Britain and Ireland Malignant Large Bowel Obstruction model was generated to evaluate in-hospital mortality. This consists of four parameters.[14] It may be practical to use but, like the elderly colorectal cancer model, it has not been externally validated.

Furthermore, Sluis et al. published the Identification of Risk in Colorectal Surgery score. They stated that their scoring system presented greater discriminatory capacity than that of the cr-POSSUM scoring system and that of the American Society of Anesthesiologists score classification for predicting postoperative mortality.[15] The Identification of Risk in Colorectal Surgery scoring system may be useful generally in colorectal surgery.

Our scoring system consists of three parameters, and the physiological status of the patients is evaluated by means of the American Society of Anesthesiologists score classification. The Numune emergency colorectal resection score is useful in emergency procedures, and is simple to use.

The scoring system of the French Association of Surgery (Association Française de Chirurgie, AFC) uses four simple parameters to predict postoperative mortality, comprising intraoperative fecal contamination, operative time greater than six hours, American Society of Anesthesiologists score > 2 and smoking.[16] These parameters were found to be independent risk factors for mortality after colorectal surgery. However, the Elderly-Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity was found to be better than the AFC scoring system for predicting postoperative mortality after colorectal surgery.[17] We used the American Society of Anesthesiologists score, blood urea nitrogen level and albumin level in the Numune emergency colorectal resection score, and these are helpful for preoperatively predicting the postoperative mortality.

Another scoring system that has been used to predict postoperative morbidity and mortality is the American College of Surgeons surgical risk calculator.[18] The colon-specific model of this scoring system uses multiple factors affecting postoperative morbidity and mortality. This surgical risk calculator may help surgeons to estimate patient-specific postoperative risks but, again, it requires too many parameters, in comparison with the Numune emergency colorectal resection score.

Some medical calculators or scoring systems are available electronically. These software programs may help in using the scoring systems correctly, but are more useful in elective surgical procedures. For emergency surgery, systems that are more practical and easier to use, like the Numune emergency colorectal resection score are more useful.

However, one shortcoming of our scoring system is that it contains the American Society of Anesthesiologists score, which is subjective and can give rise to inter-observer variability.[19] Our scoring system may help clinicians to select high-risk patients for transfer to an advanced center.

There are some limitations to our study. We did not have any control group, and so the positive predictive value of the study was low. The analyses were not assessed regarding the underlying indications or type of surgery. All of these are shortcomings of the study. The patients' ages were found to be significant only in the univariate analyses. This may have been related to the distribution of the ages of the patients included in our study. Future studies may reveal that age is an important parameter and, if so, our scoring system may need to be updated.

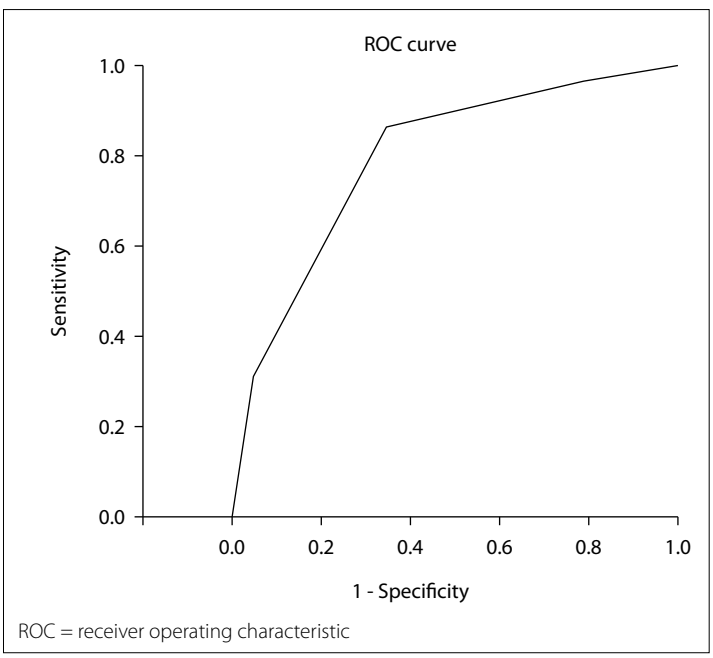

Figure 1. The area under the receiver operating characteristic curve (AUROC) was 0.794 (95% confidence interval, CI: 0.704-0.885) for the Numune emergency colorectal resection score.

CONCLUSION

Surgeons need scoring systems or some parameters in order to predict postoperative morbidity and, especially, mortality. Therefore, researchers need to make efforts towards devising optimal scoring systems for use both in elective and in emergency surgery. The Numune emergency colorectal resection score for use in relation to emergency surgical procedures seems to be an option for predicting postoperative mortality among patients undergoing emergency colorectal surgery.

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Depression and anxiety among patients undergoing dialysis and kidney transplantation: a cross-sectional study

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KEY WORDS:
Depression.
Anxiety.
Quality of life.
Kidney failure, chronic.
Renal replacement therapy.

ABSTRACT

BACKGROUND: Depression and anxiety are the most prevalent psychological disorders among end-stage renal disease patients and are associated with various conditions that result in poorer health outcomes, e.g. reduced quality of life and survival. We aimed to investigate the prevalences of depression and anxiety among patients undergoing renal replacement therapy.

DESIGN AND SETTING: Cross-sectional study in Belo Horizonte, Brazil.

METHODS: Patients' depression and anxiety levels were assessed using the Beck Inventory. The independent variables were the 36-Item Short-Form Health Survey (SF-36), Charlson Comorbidity Index and Global Subjective Assessment, along with sociodemographic and clinical characteristics.

RESULTS: 205 patients were included. Depression and anxiety symptoms were detected in 41.7% and 32.3% of dialysis patients and 13.3% and 20.3% of transplantation patients, respectively. Lower SF-36 mental summary scores were associated with depression among transplantation patients (odds ratio, OR: 0.923; 95% confidence interval, CI: 0.85-0.99; P = 0.03) and dialysis patients (OR: 0.882; 95% CI: 0.83-0.93; P ≤ 0.001). Physical component summary was associated with depression among dialysis patients (OR: 0.906; 95% CI: 0.85-0.96; P = 0.001). Loss of vascular access (OR: 3.672; 95% CI: 1.05-12.78; P = 0.04), comorbidities (OR: 1.578; 95% CI: 1.09-2.27; P = 0.01) and poorer SF-36 mental (OR: 0.928; 95% CI: 0.88-0.97; P = 0.002) and physical (OR: 0.943; 95% CI: 0.89-0.99; P = 0.03) summary scores were associated with anxiety among dialysis patients.

CONCLUSIONS: Depression and anxiety symptoms occurred more frequently among patients undergoing dialysis. Quality of life, comorbidities and loss of vascular access were associated factors.

INTRODUCTION

Despite advancements in renal replacement therapies and increased survival, patients still face several physical, psychological and social limitations as consequences of chronic kidney disease and treatment complexity.[1,2] The daily struggle with end-stage renal disease symptoms and related comorbidities, along with the need to cope with psychosocial stressors, directly impacts patients' quality of life and mental health.[3,4]

Depression and anxiety are considered to be the most common end-stage renal disease-related psychological disorders, with higher prevalence and incidence rates in this population than those in the general population.[5-10] According to the World Health Organization, the estimated global prevalence rates of depression and anxiety in 2015 were 4.4% and 3.6%, respectively, with an increase in reported cases of 18% between 2005 and 2015.[11] The anxiety and depression rates that have been estimated among end-stage renal disease patients are not accurate: they range from 0 to 100%, depending on the diagnostic criteria, assessment tool and population characteristics.[12] A systematic review of 55 studies revealed prevalence rates of 38% and 27% for anxiety and depression, respectively, among end-stage renal disease patients.[13]

The high frequency and impact of affective symptoms in nephrology practice have led the research community to devote increasing attention to depression and anxiety over the last few years.[7] In end-stage renal disease, these mental disorders are associated with various conditions that lead to poorer health outcomes, with direct impacts on patients' quality of life and survival.[14-23] Anxiety and depression are also associated with unhealthy forms of behavior, such as alcohol and tobacco use, poor eating habits, sedentary lifestyle and non-compliance with treatment.[24] These factors translate into increased risks of clinical events and the need for emergency services, thus resulting in higher healthcare costs.[25-26]

Given the need for better understanding of affective disorders and associated factors in end-stage renal disease, the present study set out to 1) investigate the prevalence of depression and anxiety among patients undergoing different types of renal replacement therapy and 2) investigate the factors associated with the presence and severity of depression and anxiety symptoms. Kidney transplantation is believed to favor a better clinical condition and a daily routine that is more active and less dependent on the restrictions imposed by dialysis. Our hypothesis was that dialysis patients would present higher prevalence of depression and anxiety symptoms than a group of transplantation patients.

METHODS

Study design

This investigation consisted of a cross-sectional follow-up study on participants in a cohort that had been established in 2006. The cohort included patients who were undergoing renal replacement therapy at 10 public dialysis services funded by the Brazilian public healthcare system in Belo Horizonte, Minas Gerais, Brazil[27] (**Figure 1**).

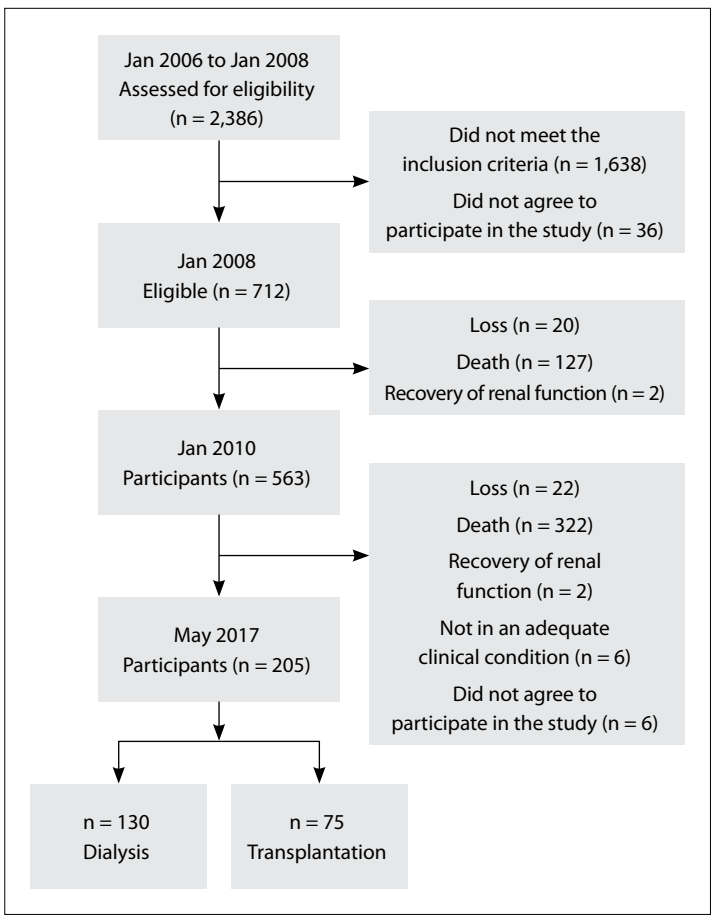

Figure 1. Flowchart of the study design.

Participants

The initial cohort included all patients aged 18 years or over who started to undergo dialysis between January 1, 2006, and January 1, 2008, with a minimum of three months of treatment and no previous history of kidney transplantation. A total of 748 out of 2,386 patients met the selection criteria, and 36 of these patients refused to participate. Therefore, 712 patients formed the initial sample and were followed up over a non-concurrent or retrospective period (January 2006 to January 2008) and a concurrent or prospective period (January 2006 to May 2017).

The participants in the present cross-sectional study were patients who were undergoing dialysis or were surviving transplantation between February and May 2017, and whose physical condition and cognitive ability were sufficient for them to be able to complete the questionnaires. Patients who refused to participate, those who recovered their renal function and those who were referred for treatment elsewhere were excluded.

Ethical considerations

The Institutional Review Board (IRB) at the Federal University of Minas Gerais (UFMG) approved this study (under procedural no. 1.747.336), and all participants signed an informed consent form.

Measurements

Sociodemographic and clinical data were collected during structured interviews or were extracted from the medical records maintained by the participating units. Comorbidities were measured using the Charlson Comorbidity Index (CCI): this is a scoring system comprising 19 comorbidity items with assigned weights ranging from one to six, such that higher summed scores correspond to clinical conditions of greater severity.[28] Nutritional status was determined using the Subjective Global Assessment (SGA), which is a method that categorizes patients as well-nourished, suspected of being malnourished or severely malnourished, based on features of their physical examinations and clinical histories.[29]

Additional groups of covariates were selected as follows:

- **sociodemographic:** sex, age, ethnic group, marital status, religion, level of education, occupation and income.
- **clinical:** length of time undergoing renal replacement therapies; whether listed in transplantation waiting lists; occurrence of graft loss after renal transplantation; current vascular access; number of visits and admissions; and different types of medications used.
- **life habits:** social activities (participation in unions, associations, organizations and diverse groups, such as seniors', men's/women's, religious or political groups); recreational activities (attendance of parties, clubs, soccer stadiums and

gatherings with family/friends); and tobacco and alcohol use. We defined alcohol use as consumption of five or more drinks (for males) or four or more drinks (for females) on a single occasion within the last 30 days.

- **healthcare service** (type of renal replacement therapy facility and travel time): for classification purposes, the facilities were grouped according to indicators of capacity to handle cases of increasing levels of complexity (graded from one to three), through a calculation using principal component analysis (PCA). The characteristics associated with the level of complexity with minimal variability between facilities included the type of service (outpatient or inpatient), teaching activities (yes or no) and kidney transplantation service availability (yes or no).

Depression and anxiety symptoms were assessed using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), validated for the Brazilian population.[30] The BDI and BAI are questionnaires consisting of 21 depression-related and 21 anxiety-related items to evaluate the presence and severity of symptoms over the course of the last week. Items are scored from 0 to 3, with a total summed score ranging from 0 to 63 points. The scores indicating depression and anxiety are those greater than the cutoff of 11 and 10 points, respectively. Higher scores correspond to more severe symptoms, and the levels of depression and anxiety are graded as minimal or absent, mild, moderate or severe. The BAI and BDI tests were applied in accordance with Resolution 9 of the Brazilian Federal Psychology Council.[31]

The quality-of-life assessment was based on the Portuguese version of the 36-item Short-Form Health Survey (SF-36).[32] This instrument comprises eight domains (physical functioning, role-physical, bodily pain, general health status, vitality, social functioning, role-emotional and mental health) and two summary measurements (physical and mental component summaries). Its scores can range from 0 to 100, and scores closer to 100 indicate better quality of life.

The patients were interviewed by trained health-related undergraduate students who were participating in the research project. The interviews were conducted over the course of dialysis sessions (hemodialysis patients) or during follow-up visits (peritoneal dialysis and kidney transplantation patients).

Statistical analysis

Descriptive statistics were produced, based on frequencies for categorical variables, or on means ± standard deviations (SDs) for quantitative variables with normal distribution or medians for those with non-normal distribution. The non-paired Student t test and the Mann-Whitney test were used to compare normally and non-normally distributed quantitative variables, respectively. Pearson's chi-square test and Fisher's exact test were used to compare categorical variables. Risk factors for depression and anxiety and symptom severity were analyzed using age- and sex-adjusted multivariate logistic regression models. For the logistic regression analysis, all variables that showed a significance level of 0.20 or lower were tested and only those with a significance level of 0.05 or lower were presented in the final model. Statistical analyses were performed using SPSS version 16.0.

RESULTS

Patient characteristics

This cross-sectional analysis included 205 patients: 130 of them were on dialysis and 75 of them had undergone transplantation. A majority of the patients were male (52.7%), and many were married or in a *de facto* relationship (56.1%). The mean age was 54.5 years (SD = 12.7). In addition, many of the patients had not completed elementary education (58.2%), most did not have a job (78.5%) and most were living on some form of government-provided benefit (79.8%) (**Tables 1** and **2**).

The dialysis and transplantation patients differed in relation to the following: capacity to perform recreational activities within daily living (62.3% and 80.0%, respectively); capacity to work (13.8% and 34.7%, respectively); benefits as the major source of income (88.2% and 64.1%, respectively); and good nutritional status (89.1% and 97.3%, respectively). Overall, symptoms of both depression and anxiety were observed in 31.2% and 27.9%, respectively, of the sample studied. Moreover, depression affected 41.7% and 13.3% of the dialysis and transplantation patients, respectively, whereas anxiety affected 32.3% and 20.3% of the dialysis and transplantation patients, respectively (**Tables 1** and **2**).

Characteristics of the patients with depressive symptoms

Univariate analysis revealed that most of the transplantation patients with depressive symptoms were women (P = 0.001), most were not married or in a *de facto* relationship (P = 0.02) and many had lower scores in the SF-36 domains of bodily pain (P = 0.001), social functioning (P = 0.02), role-emotional (P = 0.001) and mental health (P ≤ 0.001), and in the mental component summary (P ≤ 0.001) (**Table 1**). Compared with non-depressive dialysis patients, depressed dialysis patients mostly had brown/black skin color (P = 0.01), presented more comorbidities, as shown by a higher CCI (P = 0.01), had had higher numbers of visits (P = 0.01) over the last 12 months, had shorter travel times to the healthcare service (P = 0.02) and had lower SF-36 scores (**Table 1**).

Logistic regression revealed associations between the mental component summary of the SF-36 and depression among transplantation patients (OR = 0.923; P = 0.03) and dialysis patients (OR = 0.882; P ≤ 0.001). On the other hand, associations between the

Table 1. Sociodemographic and clinical characteristics of transplantation and dialysis patients according to symptoms of depression

	Total (n = 205)	Transplantation (n = 75)		P-value	Dialysis (n = 130)		P-value
		BDI ≤ 11 (n = 65)	BDI ≥ 12 (n = 10)		BDI ≤ 11 (n = 53)	BDI ≥ 12 (n = 77)	
	M ± SD/n (%)	M ± SD/n (%)	M ± SD/n (%)		M ± SD/n (%)	M ± SD/n (%)	
Sociodemographic variables							
Age	54.5 ± 12.7	51.9 ± 11.3	50.7 ± 9.1	0.75	56.5 ± 13.2	55.6 ± 13.1	0.70
Sex (female)	97 (47.3)	24 (36.9)	9 (90.0)	**0.001**	41 (55.4)	21 (39.6)	0.07
Skin color (brown/black)	148 (75.5)	44 (72.1)	6 (60.0)	0.46	51 (70.8)	45 (90.0)	0.01
Religion (yes)	191 (93.6)	58 (90.6)	9 (90.0)	1	72 (97.3)	49 (92.5)	0.23
Married/*de facto* relationship	115 (56.1)	46 (70.8)	3 (30.0)	**0.02**	41 (55.4)	25 (47.2)	0.36
Schooling							
Up to 9 years	114 (58.2)	32 (50.0)	5 (50.0)		42 (60.9)	34 (66.7)	
10 to 12 years	58 (29.6)	21 (32.8)	4 (40.0)	0.64	18 (26.1)	14 (27.5)	0.43
Over 12 years	24 (12.2)	11 (17.2)	1 (10.0)		9 (13.0)	3 (5.9)	
Job (yes)	44 (21.5)	24 (36.9)	2 (20.0)	0.47	11 (14.9)	7 (13.2)	0.79
Source of income							
Work	37 (20.2)	21 (37.5)	2 (25.0)	0.70	10 (14.9)	4 (8.2)	0.26
Benefits	146 (79.8)	35 (62.5)	6 (75.0)		57 (85.1)	45 (91.8)	
Clinical variables							
Time on dialysis (months)	120.1 ± 8.1	44.5 ± 39.6	47.88 ± 33.9	0.82	120.65 ± 8.30	119.38 ± 8.10	0.40
Time since Tx (months)	77.6 ± 38.0	77.0 ± 38.4	81.6 ± 36.9	0.72	- -	- -	- -
Waiting list for Tx (yes)	89 (43.4)	- -	- -	- -	51 (68.9)	37 (69.8)	0.9
Graft loss after renal Tx	17 (8.2)	- -	- -	- -	9 (12.2)	8 (15.1)	0.63
Vascular access (fistula)	106 (51.7)	- -	- -	- -	57 (77.0)	46 (86.8)	0.34
Loss of vascular access	26 (20.2)	- -	- -	- -	13 (17.8)	13 (24.5)	0.35
CCI	2.00	2.00	1.00	0.67	1.00	2.00	**0.01**
Visits	122 (59.5)	33 (50.8)	7 (70.0)	0.32	40 (54.1)	40 (75.5)	**0.01**
Hospital admissions	84 (41.0)	26 (40.0)	5 (50.0)	0.73	25 (33.8)	27 (50.9)	0.05
Number of medications	6.0	6.0	6.0	0.44	5.0	6.0	0.89
SGA (well-nourished)	187 (92.1)	63 (96.9)	10 (100)	1	68 (91.9)	45 (84.9)	0.21
Service unit							
RRT unit							
Group 1	35 (17.2)	0	0		19 (26.0)	16 (30.2)	
Group 2	81 (39.9)	25 (38.5)	3 (33.3)	1	29 (39.7)	22 (41.5)	0.74
Group 3	87 (42.9)	40 (61.5)	6 (66.7)		25 (34.2)	15 (28.3)	
Distance to unit (min)	50.0	63.1 ± 39.4	54.4 ± 50.00	0.28	50.0	40.0	**0.02**
Habits							
Smoking	16 (7.8)	3 (4.7)	1 (10.0)	0.44	8 (10.8)	4 (7.5)	0.53
Alcoholic drinks	26 (12.7)	10 (15.4)	0	0.34	10 (13.5)	6 (11.3)	0.71
Recreational activities (yes)	141 (68.8)	52 (80.0)	8 (80.0)	1	44 (59.5)	36 (67.9)	0.33
Social activities (yes)	85 (41.5)	36 (55.4)	5 (50.0)	1	26 (35.1)	18 (34.0)	0.89
SF-36 scores							
Physical functioning	59.6 ± 28.2	74.0 ± 24.8	68.0 ± 21.6	0.46	57.2 ± 25.4	43.1 ± 28.0	**0.005**
Role-physical	50.1 ± 43.4	71.9 ± 39.6	42.5 ± 45.7	0.08	49.3 ± 41.7	25.4 ± 34.4	**0.001**
Bodily pain	57.4 ± 28.1	69.1 ± 23.5	47.5 ± 17.9	**0.001**	62.1 ± 28.3	38.0 ± 24.2	**< 0.001**
General health status	57.0 ± 24.4	70.4 ± 20.9	58.2 ± 26.2	0.1	61.1 ± 17.8	34.2 ± 20.9	**< 0.001**
Vitality	57.2 ± 22.1	66.6 ± 19.2	47.0 ± 27.8	0.05	61.8 ± 16.7	40.6 ± 21.7	**< 0.001**
Social functioning	76.1 ± 27.0	87.6 ± 17.8	70.0 ± 40.4	**0.02**	81.4 ± 19.5	55.5 ± 31.4	**< 0.001**
Role-emotional	66.4 ± 43.1	88.7 ± 26.5	53.4 ± 47.6	**0.001**	69.8 ± 42.8	36.5 ± 42.4	**< 0.001**
Mental health	70.7 ± 19.7	76.2 ± 19.4	51.2 ± 10.7	**0.000**	77.7 ± 13.4	57.5 ± 20.4	**< 0.001**
Physical component summary	39.1 ± 11.0	45.4 ± 9.4	41.7 ± 10.2	0.25	38.7 ± 9.7	31.3 ± 9.9	**< 0.001**
Mental component summary	50.1 ± 11.1	54.1 ± 8.6	41.0 ± 13.8	0.000	53.6 ± 7.8	41.8 ± 12.0	**< 0.001**

BDI = Beck Depression Inventory; CCI = Charlson Comorbidity Index; SGA = Subjective Global Assessment; SF-36 = 36-item Short-Form Health Survey; M = mean; SD = standard deviation; RRT = renal replacement therapy; Tx = transplantation. BDI > 11 = symptoms of depression. Loss of vascular access: number of losses of vascular access in the last 12 months. Visits and hospital admissions: number of patients with at least one visit/admission in the last 12 months. Continuous variables with normal distribution (Shapiro-Wilk normality test) were summarized using the mean ± standard deviation (SD) and were compared using the t test. For other quantitative variables, the median was used as a summary measurement, and the Mann-Whitney test was used for comparisons within the group.

Table 2. Sociodemographic and clinical characteristics of transplantation and dialysis patients according to symptoms of anxiety

	Total (n = 205)	Transplantation (n = 75)		P-value	Dialysis (n = 130)		P-value
		BAI ≤ 10 (n = 60)	BAI ≥ 11 (n = 15)		BAI ≤ 10 (n = 89)	BAI ≥ 11 (n = 41)	
	M ± SD/n (%)	M ± SD/n (%)	M ± SD/n (%)		M ± SD/n (%)	M ± SD/n (%)	
Sociodemographic variables							
Age	54.5 ± 12.7	51.9 ± 11.1	51.3 ± 11.6	0.86	56.7 ± 13.7	54.4 ± 11.3	0.36
Sex (female)	97 (47.3)	22 (37.3)	11 (73.3)	**0.01**	38 (44.2)	23 (56.1)	0.20
Skin color (brown/black)	148 (75.5)	39 (70.9)	11 (73.3)	1	61 (73.5)	36 (92.3)	**0.01**
Religion (yes)	191 (93.6)	52 (89.7)	14 (93.3)	1	82 (95.3)	39 (95.1)	1
Married/*de facto* relationship	115 (56.1)	40 (67.8)	8 (53.3)	0.29	43 (50.0)	23 (56.1)	0.52
Schooling							
Up to 9 years	114 (58.2)	27 (46.6)	9 (60.0)	0.64	50 (61.7)	25 (65.8)	0.84
10 to 12 years	58 (29.6)	21 (36.2)	4 (26.7)		22 (27.2)	10 (26.3)	
Over 12 years	24 (12.2)	10 (17.2)	2 (13.3)		9 (11.1)	3 (7.9)	
Job (yes)	44 (21.5)	21 (35.6)	5 (33.3)	0.87	13 (15.1)	5 (12.2)	0.65
Source of income							
Work	37 (20.2)	19 (37.3)	4 (33.3)	1	9 (11.5)	5 (13.2)	0.77
Benefits	146 (79.8)	32 (62.7)	8 (66.7)		69 (88.5)	33 (86.8)	
Clinical variables							
Time on dialysis (months)	120.1 ± 8.1	42.3 ± 39.8	51.3 ± 33.1	0.45	119.6 ± 8.1	121.1 ± 8.3	0.34
Time since Tx (months)	77.6 ± 38.0	80.0 ± 38.8	72.0 ± 33.4	0.46	- -	- -	- -
Waiting list for Tx (yes)	89 (43.4)	- -	- -	- -	62 (72.1)	26 (63.4)	0.32
Graft loss after renal Tx	17 (8.2)	- -	- -	- -	14 (16.3)	3 (7.3)	0.21
Vascular access (fistula)	106 (51.7)	- -	- -	- -	69 (80.2)	35 (85.4)	0.76
Loss of vascular access	26 (20.2)	- -	- -	- -	12 (14.1)	14 (34.1)	**0.009**
CCI	2.00	2.00	2.00	**0.01**	1.00	2.00	**0.001**
Visits	122 (59.5)	29 (49.2)	11 (73.3)	0.14	51 (59.3)	29 (70.7)	0.21
Hospital admissions	84 (41.0)	25 (42.4)	5 (33.3)	0.52	29 (33.7)	24 (58.5)	**0.008**
Number of medications	6.0	7.0	6.0	0.32	6.0	5.5	0.50
SGA (well-nourished)	187 (92.1)	57 (96.6)	15 (100)	1	80 (93.0)	33 (80.5)	0.06
Service unit							
RRT unit							
Group 1	35 (17.2)	0	0	0.13	24 (28.2)	11 (26.8)	0.27
Group 2	81 (39.9)	25 (43.1)	3 (20.0)		30 (35.3)	20 (48.8)	
Group 3	87 (42.9)	33 (56.9)	12 (80.0)		31 (36.5)	10 (24.4)	
Distance to unit (min)	50.0	60.2 ± 37.1	60.7 ± 56.2	0.9	47.5	40.0	0.09
Habits							
Smoking	16 (7.8)	3 (5.2)	1 (6.7)	1	8 (9.3)	4 (9.8)	1
Alcoholic drinks	26 (12.7)	10 (16.9)	0	0.21	12 (14.0)	4 (9.8)	0.50
Recreational activities (yes)	141 (68.8)	46 (78.0)	13 (86.7)	0.72	54 (62.8)	27 (65.9)	0.73
Social activities (yes)	85 (41.5)	32 (54.2)	8 (53.3)	0.95	27 (31.4)	17 (41.5)	0.26
SF-36 scores							
Physical functioning	59.6 ± 28.2	75.1 ± 23.3	67.0 ± 19.8	0.25	54.2 ± 27.0	45.6 ± 27.4	0.09
Role-physical	50.1 ± 43.4	75.0 ± 38.2	41.6 ± 44.9	**0.01**	45.0 ± 41.5	28.0 ± 36.3	**0.02**
Bodily pain	57.4 ± 28.1	70.5 ± 24.3	52.0 ± 11.8	**0.006**	61.2 ± 27.2	33.4 ± 24.0	**< 0.001**
General health status	57.0 ± 24.4	70.4 ± 21.5	62.4 ± 23.8	0.21	55.3 ± 21.6	38.8 ± 22.7	**< 0.001**
Vitality	57.2 ± 22.1	66.6 ± 20.0	54.6 ± 25.0	0.10	57.1 ± 20.3	44.8 ± 22.0	**0.004**
Social functioning	76.1 ± 27.0	87.5 ± 18.2	76.6 ± 34.9	0.1	79.1 ± 23.4	53.3 ± 29.3	**< 0.001**
Role-emotional	66.4 ± 43.1	89.2 ± 26.5	66.7 ± 43.6	**0.01**	64.7 ± 43.4	38.1 ± 45.0	**0.002**
Mental health	70.7 ± 19.7	77.4 ± 19.4	56.2 ± 15.1	**0.000**	74.4 ± 17.2	58.8 ± 19.5	**< 0.001**
Physical component summary	39.1 ± 11.0	46.0 ± 9.9	41.3 ± 7.5	0.09	37.5 ± 10.0	31.8 ± 10.3	**0.004**
Mental component summary	50.1 ± 11.1	54.2 ± 8.9	45.7 ± 13.2	**0.004**	51.8 ± 9.9	42.4 ± 11.7	**< 0.001**

BAI = Beck Anxiety Inventory; CCI = Charlson Comorbidity Index; SGA = Subjective Global Assessment; SF-36 = 36-Item Short-Form Health Survey; M = mean; SD = standard deviation; RRT = renal replacement therapy; Tx = transplantation.

BAI > 11 = symptoms of anxiety. Loss of vascular access: number of losses of vascular access in the last 12 months. Visits and hospital admissions: number of patients with at least one visit/admission in the last 12 months. Continuous variables with normal distribution (Shapiro-Wilk normality test) were summarized using the mean ± standard deviation (SD) and were compared using the t test. For other quantitative variables, the median was used as a summary measurement, and the Mann-Whitney test was used for comparisons within the group.

physical component summary of the SF-36 and depression were only seen among the dialysis patients (OR = 0.906; P = 0.001) (**Table 3**).

Characteristics of the patients with anxiety symptoms

Univariate analysis revealed that most of the transplantation patients with anxiety symptoms were women (P = 0.01) with higher CCI (P = 0.01) and lower scores in the SF-36 domains of bodily pain (P = 0.006), role physical (P = 0.01), role emotional (P = 0.01) and mental health (P ≤ 0.001), and in the mental component summary (P = 0.004) (**Table 2**). Compared with dialysis patients who did not show symptoms of anxiety, those who showed such symptoms tended to have brown or black skin color (P = 0.01), higher CCI (P = 0.001), higher numbers of hospital admissions (P = 0.008), histories of loss of vascular access over the last 12 months (P = 0.009) and lower scores in the SF-36 domains of role-physical (P = 0.02), bodily pain (P < 0.001), general health status (P ≤ 0.001), vitality (P = 0.004), social functioning (P ≤ 0.001), role-emotional (P = 0.002) and mental health (P ≤ 0.001), and in the physical component summary (P = 0.004) and mental component summary (P ≤ 0.001) (**Table 2**).

Logistic regression analysis showed that loss of vascular access over the last 12 months (OR = 3.672; P = 0.04), CCI (OR = 1.578; P = 0.01) and the physical component summary (OR = 0.943; P = 0.03) and mental component summary (OR = 0.928; P = 0.002) of the SF-36 were associated factors among dialysis patients (**Table 4**).

Severity of depression and anxiety symptoms

Patients scoring higher than 20 points in the BDI and BAI were diagnosed as presenting moderate to severe depression or anxiety. Logistic regression analysis revealed that poorer nutritional status (OR = 16.264; P = 0.02) and poorer general health status (OR = 0.961; P = 0.02) were associated with worsening of depression, whereas the presence of bodily pain (OR = 0.935; P = 0.004) and social functioning, as participation in some social activity at least once a month (OR = 0.081; P = 0.01), were associated with anxiety symptoms of greater severity (**Table 5**).

Table 3. Results from the logistic regression analysis* (only factors associated with depression; P < 0.05)

Variables	Transplantation				Dialysis			
	ß	OR	95% CI	P-value	ß	OR	95% CI	P-value
Mental component summary	-0.080	0.923	0.85-0.99	**0.03**	-0.125	0.882	0.83-0.93	**< 0.001**
Physical component summary	--	--	--	--	-0.099	0.906	0.85-0.96	**0.001**

*Logistic regression model adjusted for age and sex.
OR = odds ratio; CI = confidence interval.

Table 4. Results from the logistic regression analysis* (only factors associated with anxiety; P < 0.05)

Variables	Transplantation				Dialysis			
	ß	OR	95% CI	P-value	ß	OR	95% CI	P-value
Loss of vascular access	--	--	--	--	1.301	3.672	1.05-12.78	**0.04**
CCI	--	--	--	--	0.456	1.578	1.09-2.27	**0.01**
Mental component summary	--	--	--	--	-0.074	0.928	0.88-0.97	**0.002**
Physical component summary	--	--	--	--	-0.059	0.943	0.89-0.99	**0.03**

*Logistic regression model adjusted for age and sex.
OR = odds ratio; CI = confidence interval; CCI = Charlson Comorbidity Index; loss of vascular access in the last 12 months.

Table 5. Results from the logistic regression analysis* considering all patients (only factors associated with the severity of the symptoms of depression and anxiety; P < 0.05)

Variables	Depression (BDI score ≥ 20)				Anxiety (BAI score ≥ 20)			
	ß	OR	95% CI	P-value	ß	OR	95% CI	P-value
Bodily pain	--	--	--	--	-0.067	0.935	0.89-0.97	**0.004**
Social functioning	--	--	--	--	-2.516	0.081	0.01-0-13	**0.01**
SGA	2.789	16.264	1.34-196.26	**0.02**	--	--	--	--
General health status	-0.040	0.961	0.928-0.995	**0.02**	--	--	--	--

BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; OR = odds ratio; CI = confidence interval.
Social functioning = participation in some social activity at least once a month; suspected of being malnourished or severely malnourished according to the Subjective Global Assessment (SGA). *Logistic regression model adjusted for age and sex; combined analysis for dialysis and transplantation patients.

DISCUSSION

In this study, the prevalence rates of symptoms of depression and anxiety were 31.2% and 27.9%, respectively, among the overall sample studied. Furthermore, depression affected approximately three times more dialysis patients than transplantation patients, whereas anxiety affected 1.5-times more dialysis patients. Depression was associated with the mental component summary of the SF-36 among both transplantation and dialysis patients. However, the physical component summary of the SF-36 only showed an association with dialysis. Anxiety was associated with loss of vascular access over the last 12 months and with the physical and mental component summaries of the SF-36 among dialysis patients. In the overall population studied, poorer nutritional status and poorer general health status were associated with worsening of depression, whereas low levels of recreational activities in daily living and presence of bodily pain were associated with anxiety symptoms of greater severity.

Symptoms of depression and anxiety are very common in cases of chronic health conditions, with higher prevalence among affected individuals than among the general population.[7,9] The development of mental disorders can be influenced by patients' social situation, such that the clinical condition of chronicity implies limitation or even loss of work capacity, financial deterioration and increased isolation in interpersonal relations.[33]

Research on end-stage renal disease has revealed anxiety and depression rates ranging from 12 to 60% and 10 to 70%, respectively.[7-10,12-15] These percentages are subject to variations according to the features of specific studies, such as the diagnostic criteria, assessment tools and population characteristics.

The type of renal replacement therapy has been shown to be an important factor associated with mental health. In previous studies, transplantation patients were found to score lower than dialysis patients for both anxiety and depression.[34-36] The mental health of hemodialysis and peritoneal dialysis patients is thought to be impacted to a greater extent than that of transplantation patients because of the strict routine of dialysis sessions, along with the countless restrictions that limit these individuals' full participation in social, familial and productive activities. In contrast, kidney transplantation promotes greater wellbeing and freedom from dialysis and related restrictions and has a positive impact on self-perceived health.[1,34-40]

This phenomenon is particularly true for physical functioning, as shown by improved clinical parameters and nutritional status.[33,38] Good physical functioning translates into positive changes in the lives of transplantation patients overall, including vitality and resumption of activities of daily living and interpersonal relationships, with resulting improvements in these individuals' general emotional state. In a study on 80 renal transplantation patients, 75% reported having considerable improvement in their physical condition one and four years after the surgical procedure, which directly impacted their work and social activities.[37]

In this study, poorer quality of life was associated with depressive symptoms among transplantation and dialysis patients alike, whereas anxiety was associated with low quality of life in dialysis patients only. The relationship between mental disorders and quality of life is complex and needs to be discussed in a comprehensive manner. Despite advancements in renal replacement therapies, improved control over chronic kidney disease symptoms cannot prevent deterioration of quality of life. This has a significant impact on patient vitality and physical and mental capacity.[33] Depression and anxiety not only interfere with the routine and habits of the individuals affected, but also impact self-perceived health and the ability to manage the many positive and negative aspects of life. Self-care skills of this nature are vital for improved clinical outcomes.[14-19] Thus, the quality of life of end-stage renal disease patients is reduced in the presence of affective symptoms, which leads to poor clinical outcomes and decreased ability to face the demands of the disease and its treatment.

Negative correlations between emotional disorders and quality of life domains have been widely reported.[14-15,18-22] Perales Montilla et al.[41] compared the capacity of self-reported somatic symptoms and depression and anxiety for predicting quality of life among patients with chronic renal disease. Their results indicated that mood was a predictor of reductions in the physical and mental components of the SF-36, compared with the number and severity of physical symptoms.[41] A cross-sectional study on 1,332 hemodialysis patients revealed that physical, psychological and social quality-of-life domains were negatively impacted by symptoms of depression and anxiety.[21] In another study, depression was negatively correlated with all SF-36 scores among 105 patients undergoing peritoneal dialysis.[18]

The relationship between renal replacement therapy type and affective symptoms or quality of life differed between dialysis and transplantation patients in the present study. For dialysis patients, lower physical and mental component scores were associated with both conditions (depression and anxiety), while for transplantation patients, a relationship between mental component scores and depression was the only association found. Transplantation is the best alternative for replacement therapy, but the quality of life of transplantation patients is not comparable with that of the general population.[39,42] Some studies have shown that, unlike physical quality-of-life domains, mental domains are not significantly affected by kidney transplantation.[43]

In a comparative evaluation of patients on hemodialysis and peritoneal dialysis and those who underwent renal transplantation, Fructuoso et al.[44] showed that renal transplantation patients had higher values only in the physical domains. On the other hand, no significant differences were found in the mental domains between these groups of patients.[44] Similar results were found in a study conducted by Czyżewski et al.,[33] in which 47 transplanted patients

had better outcomes in the physical domains of the SF-36, compared with 40 patients on dialysis, and no difference in the values was reported for the mental domains.[33]

Notably, transplantation patients do not fully regain pre-chronic kidney disease levels of function and remain chronic patients requiring complex ongoing treatment. Post-transplantation challenges arise, and these interfere with the reestablishment of quality of life (and therefore mental health), such as living with feelings of uncertainty regarding graft survival, potential graft rejection and hospitalization; adherence to strict drug regimens; dealing with the side effects of immunosuppressant medication and bodily image changes; and the need for constant surveillance and self-care.[37-39,42]

Among the dialysis patients of the present study, anxiety was associated with clinical status, as shown by the poorer scores for the physical and mental quality-of-life components, along with higher rates of comorbidities and loss of vascular access. The lack of additional factors associated with anxiety in the transplantation patient group can be explained by the fact that kidney transplantation promotes better health outcomes and greater freedom from treatment, compared with dialysis.[36,37] Similar findings were described by Feroze et al.,[43] who demonstrated that anxiety symptoms were connected with specific characteristics of dialytic treatment and comorbidities.[43]

Patients on hemodialysis or peritoneal dialysis are subjected to more onerous dialysis-related restrictions, have poorer physical parameters and experience more comorbidities and greater symptom burden. They therefore have a heavier burden of concerns and challenges, which arise from their various healthcare demands and needs. A cross-sectional study on 187 end-stage renal disease patients evaluated the symptom burden due to chronic kidney disease and the corresponding relationship with negative emotional states. It was concluded that psychological disturbances were associated with higher symptom burden and greater severity.[45]

Vascular access is one such challenge, particularly when an arteriovenous fistula (the most common and safest form of access for hemodialysis patients) is involved. The association between anxiety and loss of vascular access may be understood through considering the importance of this access for patient survival given that this forms the route through which effective dialysis can be performed. Alongside clinical complications, loss of vascular access gives rise to negative emotions such as anguish and discomfort. Chronic pain and limitations regarding several aspects of life often also form part of this picture, thereby contributing towards development and persistence of anxiety disorders.[43]

Several factors are known to affect the prognosis and severity of anxiety and depression, such as individual characteristics, genetic load, stressful life events, concurrent mental disorders and health status.[46] In the present study, greater severity of depressive symptoms was associated with worse general health status and poorer nutritional status.

The relationship between nutritional status and the severity of depressive symptoms needs to be appreciated from different perspectives. One potential explanation for this relationship is the negative impact of affective disorders on eating behavior. However, these disorders may be concurrent with ongoing nutritional deficits and underlying disease progression.[47]

The role of mental health in healthy behaviors also needs to be emphasized. This includes adequate food intake, since depression is known to interfere with eating habits and may lead to either increased or decreased appetite.[44] Additionally, depression has been positively correlated with undernourishment and poorer levels of hemoglobin, ferritin and albumin, in some end-stage renal disease studies.[47,48]

The presence of bodily pain and less frequent participation in recreational activities were associated with greater severity of anxiety symptoms in the present study. Anxiety has been correlated with complaints of pain. Some studies have shown that patients with chronic pain had elevated levels of concern, tension and nervousness with regard to their illness and their general clinical condition, which influenced their perception of the painful experience.[49] On the other hand, states of pain, whether acute or chronic, favor psychological manifestations and become a factor in increasing the incidence of mood and anxiety disorders among these patients, compared with the general population.[49,50]

Considering that chronic kidney disease increases the risk of having pathological conditions such as diabetes mellitus, neurological conditions, bone diseases and vascular diseases, patients undergoing renal replacement therapy are more likely to experience different types of pain of variable intensity and in a variety of locations. These patients' types of pain are associated not only with their pathological condition but also with the intercurrences and specificities of the renal treatment itself.[50]

A cross-sectional study on 205 patients on dialysis showed that there was higher prevalence of mental disorders among patients with moderate or severe chronic pain than among those with mild or no pain. Severe irritability and anxiousness, and inability to cope with stress, were also more common among patients with pain than among those without pain.[51] Overall, chronic kidney disease patients participate less in recreational activities after they have started to undergo renal replacement therapies.[52] Although their reduced engagement in social activities may be partly due to their clinical status, the type of renal replacement therapy also needs to be considered, as shown by the lower scores among patients undergoing dialysis.[35]

A systematic review of the literature that examined studies comparing the level of engagement in activities of daily living among adult chronic kidney disease patients who underwent different types of therapy concluded that transplantation patients experienced greater levels of social inclusion, while hemodialysis and peritoneal dialysis patients did not differ significantly in this regard.[52] The benefits of recreational activities for emotional wellbeing and quality of life include feelings of satisfaction, perceived freedom of choice and engagement in and expansion of social networks.

Although the data in our study were derived from a cross-sectional follow-up study on participants from another cohort that had been established in 2006, this work has made a contribution to the scarce scientific literature. Nonetheless, at the end of the follow-up, 507 patients were censored, and there were 449 deaths, representing 40.06% of the initial sample. A high mortality rate is expected among end-stage renal patients, especially in the first years of dialysis, because of several factors such as advanced age, diabetes mellitus, the underlying cause of chronic kidney disease and residence in cities with worse developmental rates.[52-55] Accordingly, the patients participating in our study were the ones who survived and therefore were in a better clinical and emotional condition.

Some limitations of the present study need to be considered. Firstly, simultaneous occurrence of end-stage renal disease and affective disorder symptoms needs to be considered. Coexistence of symptoms associated with both the uremic state and depressive mood, such as fatigue, reduced appetite, memory impairment and irritability, may occur.

Secondly, despite broad application and validation for end-stage renal disease patient populations, Beck's inventories have limitations that may interfere with making diagnoses of depression and anxiety, such as use of self-report questionnaires and inclusion of somatic symptoms that are not exclusive to emotional disorders. Additionally, given that uremic parameters and graft function were not considered in the present study, associations between affective symptoms and actual renal function status could not be established. Transplantation patients with impaired graft function usually have higher levels of depression or anxiety because they face the fear of having to start to undergo dialysis again.

Thirdly, the results of the present study were derived from a sub-cohort with a 10-year follow-up. Therefore, survival biases may not have been eliminated, given that the participants potentially reflected those with better health status. Among dialysis patients, long-term survivors may exhibit less evidence of depression or anxiety or may experience severely affected mental health when they have no options for transplantation.

Fourthly, the low number of patients in the renal transplantation group may have hindered possible detection of an association between anxiety and quality of life. This evaluation could not be made in the present study.

Lastly, given the cross-sectional study design, no causal links could be established, and the progression of depression and anxiety symptoms over time could not be measured. For these factors to be measured, longitudinal approaches are required.

CONCLUSION

This study revealed that depression and anxiety are common conditions among chronic kidney disease patients and that they occur more frequently among those undergoing dialysis than among those undergoing transplantation. Lower quality-of-life scores were associated with symptoms of depression in both types of renal replacement therapy. Presence of comorbidities, loss of vascular access and worse quality of life were associated with anxiety symptoms among dialysis patients, whereas none of these factors was associated with anxiety symptoms among transplantation patients. Treatment of affective disorders needs to be effectively included within the routine care provided for chronic kidney disease patients and should be maintained across the continuum of care. Further investigations are warranted to identify major risk factors and design better interventions for management, control and prevention.

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Translation, cross-cultural adaptation and validation of the Norwich Patellar Instability score for use in Brazilian Portuguese

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ABSTRACT

BACKGROUND: The Norwich Patellar Instability (NPI) score is a tool for evaluating the impact of patellofemoral instability on joint function. It has not been translated or culturally adapted for the Brazilian population before.

OBJECTIVE: This study had the aims of translating and culturally adapting the NPI score for use in Brazilian Portuguese and subsequently assessing its validity for this population.

DESIGN AND SETTING: Translation, cross-cultural adaptation and validation study conducted at the State Public Servants' Institute of São Paulo, Brazil.

METHODS: Sixty patients of both sexes (aged 16-40 years) with diagnoses of patellar dislocation were recruited. The translation and cultural adaptation were undertaken through translation into Brazilian Portuguese and back-translation to English by an independent translator. Face validity was assessed by a committee of experts and by 20 patients. Concurrent validity was assessed through comparing the Brazilian Portuguese NPI score with the Brazilian Portuguese versions of the Lysholm knee score and the Kujala patellofemoral disorder score among the other 40 patients. Correlation analysis between the three scores was performed using Pearson correlation coefficients with significance levels of $P < 0.05$.

RESULTS: The Brazilian Portuguese version of the NPI score showed moderate correlation with the Brazilian Portuguese versions of the Lysholm score (r = -0.56; 95% confidence interval, CI: -0.74 to -0.30; $P < 0.01$) and Kujala score (r = -0.57; 95% CI: -0.75 to -0.31; $P < 0.01$).

CONCLUSION: The Brazilian Portuguese version of the NPI score is a validated tool for assessing patient-reported patellar instability for the Brazilian population.

INTRODUCTION

Patellofemoral instability is characterized by episodes of subluxation and dislocation of the patellofemoral joint. It mainly affects young individuals of both sexes, with predominance in females. It accounts for approximately 3% of all injuries involving the knee joint.[1] The risk factors that have been identified include: trochlear dysplasia, lateral patellar tilt > 20º, patellar height ratio > 1.2 according to the Caton–Deschamps index, tibial tuberosity to trochlear groove (TT-TG) distance > 16 mm, skeletal immaturity at the first episode of dislocation and history of contralateral patellar dislocation.[2,3]

Treatment for patellofemoral instability may be surgical or conservative, depending on the number of episodes of dislocation and anatomical risk factors. No consensus has been reached regarding which method is better, in terms of function, quality of life and number of recurrences.[4-6]

Outcome measurements can be used to determine functional performance and to aid in decision-making on treatment options. Currently, the outcome measurements that are used for assessing people with knee disorders include the Fulkerson patellofemoral score,[7] the International Knee Documentation Committee form,[8,9] the Lysholm knee score,[10,11] the Kujala patellofemoral disorder score[12,13] and the Norwich Patellar Instability (NPI) score.[14] Of these, only the NPI score was designed specifically for people with patellofemoral instability. Nevertheless, all of these measurements *except* the NPI score have been translated and culturally adapted for the Brazilian population. The NPI score shows moderate inverse correlation with the Kujala patellofemoral disorder score and the Lysholm knee score (rho = -0.66 to -0.54; $P < 0.05$) and has high internal consistency (Cronbach's alpha = 0.93).[14]

Since the NPI score has not been translated or culturally adapted for the Brazilian population, and since this is the only score specifically designed for individuals with patellofemoral instability, the aims of the present study were firstly to translate and culturally adapt the NPI score for

use in Brazilian Portuguese and secondly to assess its validity for the Brazilian population.

METHODS

Ethical considerations

This study was approved by the research ethics committee of the State Public Servants' Institute of São Paulo on August 16, 2018 (approval number: 2.825.402). All participants signed an informed consent form or an assent form, depending on their age.

Procedures

Translation and cultural adaptation

The translation and cultural adaptation of the NPI score followed the procedure proposed by Price et al.[15] The original English version of the NPI score was translated into Brazilian Portuguese by a bilingual expert certified translator who had no prior knowledge of the score. The Brazilian Portuguese version was then sent to another bilingual expert certified translator who independently back-translated the score into English without access to the original score. A multidisciplinary committee composed of two orthopedic knee surgeons and one physical therapist was responsible for comparing the Brazilian Portuguese translation of the original version with the back translation, to verify the semantics and idiomatic and cultural equivalence.

The NPI score consists of 19 questions relating to the perception of instability among subjects with histories of patellofemoral instability in sports and activities of daily life. It is scored from 0 (slightest sensation of instability) to 250 (greatest sensation of instability). The Brazilian Portuguese version consists of two parts: the first is the patient-completed questionnaire (**Figure 1**), and the second is a scoring sheet, which is used by a researcher to assign scores for each response, to determine the final score (**Figure 2**).

Validity

Participants

Sixty participants (16 males; 44 females; mean age 20.85 years) were recruited from an orthopedic specialty outpatient clinic at the State Public Servants' Institute of São Paulo. All consecutive patients admitted were invited until we had 60 participants, and they had the same cultural/social background. Eligible participants were required to have a documented episode of unilateral or bilateral patellar dislocation. All participants were required to present with two of the following clinical signs of patellofemoral instability: positive apprehension test, tenderness of the medial retinaculum on palpation or reported patellar instability on rotation or knee extension activities. Participants were excluded if they had previously experienced meniscal, cruciate or collateral ligament injury of the knee, history of hip, knee or ankle osteoarthritis, and if they reported a previous lower limb fracture or had undergone spinal or lower limb surgery irrespective of the surgical indication.

The pre-final version of the Brazilian Portuguese NPI score was piloted with 20 individuals of the 60 participants who had been diagnosed with patellar dislocation. This was used to evaluate their understanding of each item of the score. Once the Brazilian Portuguese NPI score version had been developed, the other 40 participants with patellar dislocation were invited to the next phase of the study, to assess the concurrent validity of the score. The participants filled out the questionnaire in person and without any assistance.

Concurrent validity was assessed by comparing the NPI score with the Brazilian Portuguese versions of the Lysholm knee score[11] and the Kujala patellofemoral disorder score.[13] The Lysholm knee score[10] was created with the purpose of assessing symptoms of ligament injury and knee-related instability. It consists of eight closed questions with scores for each one. Its final score ranges from zero to 100, such that higher scores indicate that the patient is in better condition.[16] The Kujala patellofemoral disorder score[12] consists of 13 closed questions relating to the function of the knee joint, and it is directed towards patients with a history of patellofemoral joint involvement (pain and dysfunction). Its final score also ranges from zero to 100, such that higher scores indicate that the patient is in better function.

Statistical analysis

The descriptive data were represented by the mean (with standard deviation). The assumption of normality was evaluated through visual inspection of the histogram and using the Shapiro-Wilk test. This showed that symmetrical distribution was present for all the data analyzed. The Pearson correlation coefficient was used to analyze the correlation between the NPI score, Lysholm knee score[11] and Kujala patellofemoral disorder score,[13] with an alpha error of $P < 0.05$. All data were presented with their 95% confidence intervals (CI). The statistical analysis was performed using the R software, version 3.4.4 for Windows (R Foundation, Vienna, Austria).

RESULTS

The 40 participants with atraumatic patellar dislocation who participated in the validation process answered all the items of the questionnaires. Their demographic characteristics and score results are presented in **Table 1**.

Table 2 shows the questions of the original NPI score and of the translation into Brazilian Portuguese. **Figures 1** and **2** show the translated and validated Brazilian Portuguese version of the NPI score and the score sheet.

QUESTIONÁRIO NORWICH PARA INSTABILIDADE PATELOFEMORAL

Nome do paciente

Lateralidade direito-esquerdo_____ Data _____

Abaixo está apresentada uma lista de atividades que podem causar uma sensação em seu joelho como "sair do lugar" ou senti-lo instável

Por favor leia atentamente cada parágrafo marcando o quadro que melhor descreve a frequência com que seu joelho "sai do lugar" ou parece instável quando você realiza cada uma dessas atividades ***(por favor, marque um quadro para cada questão)***

1. Movimento de rotação/mudança de direção durante esportes/jogos

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

2. Mudança de direção em corridas

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

3. Corrida em linha reta em superfícies irregulares

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

4. Andar em superfícies escorregadias, molhadas ou cobertas por gelo

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

5. Correr lateralmente

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

6. Pular em um pé só

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

7. Pular

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

8. Correr em linha reta em superfícies planas

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

9. Descer escadas

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

10. Agachar-se

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

11. Ajoelhar-se

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

12. Andar em linha reta em superfícies irregulares

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

13. Subir escadas

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

14. Pisar em degrau mais alto

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

15. Cruzar as pernas quando sentado

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

16. Andar em linha reta em superfícies planas

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

17. Entrar ou sair do carro

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

18. Guiar um carrinho de supermercado muito difícil de virar ou muito pesado

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

19. Virar-se para olhar para trás por sobre o ombro

Sempre ☐ Frequentemente ☐ Ocasionalmente ☐ Raramente ☐ Nunca ☐ Não faço ☐

Figure 1. Translated and validated Brazilian Portuguese version of the Norwich Patellar Instability score.

QUESTIONÁRIO NORWICH PARA INSTABILIDADE PATELOFEMORAL – FOLHA DE PONTUAÇÃO

A pontuação vai de 0 a 250
A pontuação total é então convertida em porcentagem baseada no número de respostas obtidas.
Uma maior porcentagem indica maior gravidade da instabilidade patelar

	Sempre ☐	Frequentemente ☐	Ocasionalmente ☐	Raramente ☐	Nunca ☐	Não faço ☐
1. Movimento de rotação/mudança de direção durante esportes/jogos	**5**	**4**	**3**	**2**	**0**	
2. Mudança de direção em corridas	**7**	**5**	**3**	**2**	**0**	
3. Corrida em linha reta em superfícies irregulares	**7**	**5**	**3**	**2**	**0**	
4. Andar em superfícies escorregadias, molhadas ou cobertas por gelo	**7**	**5**	**3**	**2**	**0**	
5. Correr lateralmente	**10**	**7**	**5**	**3**	**0**	
6. Pular em um pé só	**10**	**7**	**5**	**3**	**0**	
7. Pular	**10**	**7**	**5**	**3**	**0**	
8. Correr em linha reta em superfícies planas	**10**	**7**	**5**	**3**	**0**	
9. Descer escadas	**10**	**7**	**5**	**3**	**0**	
10. Agachar-se	**10**	**7**	**5**	**3**	**0**	
11. Ajoelhar-se	**10**	**7**	**5**	**3**	**0**	
12. Andar em linha reta em superfícies irregulares	**15**	**10**	**7**	**5**	**0**	
13. Subir escadas	**15**	**10**	**7**	**5**	**0**	
14. Pisar em degrau mais alto	**15**	**10**	**7**	**5**	**0**	
15. Cruzar as pernas quando sentado	**15**	**10**	**7**	**5**	**0**	
16. Andar em linha reta em superfícies planas	**22**	**15**	**10**	**7**	**0**	
17. Entrar ou sair do carro	**22**	**15**	**10**	**7**	**0**	
18. Guiar um carrinho de supermercado muito difícil de virar ou muito pesado	**25**	**22**	**15**	**10**	**0**	
19. Virar-se para olhar para trás por sobre o ombro	**25**	**22**	**15**	**10**	**0**	

PONTUAÇÃO FINAL _____

PORCENTAGEM _____

Figure 2. Score sheet of the Norwich Patellar Instability score translated into Brazilian Portuguese.

The Brazilian version of the NPI score showed moderate correlation with the Brazilian Portuguese versions of the Lysholm knee score[11] (r = -0.56; 95% CI: -0.74 to -0.30; P < 0.01) and the Kujala patellofemoral disorder score[13] (r = -0.57; 95% CI: -0.75 to -0.31; P < 0.01). These results are summarized in **Table 3**.

DISCUSSION

This study demonstrated the translation, cultural adaptation and validation of the NPI score for use in the Brazilian population and its correlation with the Brazilian versions of the Lysholm knee score and the Kujala patellofemoral disorder score.

The translation and cultural adaptation of the NPI score followed the procedure proposed by Price et al.[15] This procedure was adapted from Guillemin et al.,[18] Bullinger et al.[19] and Beaton et al.[20] This procedure was used because: (1) patellofemoral instability comprises only 2%-3% of all knee injuries[1] and, therefore, the affected individuals constituted a rare population; and (2) several authors have successfully used this procedure in other translation, validation and cultural adaptation processes.[21-23]

The Kujala patellofemoral disorder score[12] and the Lysholm knee score[10] are among the scores most used for evaluation of patellofemoral dysfunction in studies aiming to evaluate the efficacy of treatments for this condition.[24-26] Both of these scores contain only a single item on knee instability, and only the first of them has an item on patellofemoral instability. However, this latter item only presents low correlation with the NPI score.[14] This situation makes it difficult to accurately quantify the effect of these treatments on patients with patellofemoral instability and to adequately follow up the population.

Development of the NPI[14] score has been found to be extremely important for adequate assessment of therapies for individuals with patellofemoral instability. It is currently the only tool available for this purpose. The NPI[14] score consists of 19 questions that were based on a previous study that had aimed to assess which activities cause greater sensation of instability in these patients.[17] Translation and validation of this score for Brazilian populations are important for development of studies in this country, including multicenter studies, and for extrapolation of the results thus obtained for use in clinical practice.

The results obtained from the present study regarding validation were similar to the findings previously reported[14] from the development of the NPI score. That study also reported that there was a moderate correlation between the NPI score and the Lysholm knee score and the Kujala patellofemoral disorder score.[14] As in the earlier study, the findings from the present study can be explained through the relationship between the NPI score and patellofemoral joint disorders and between this score and general knee instability. However, we hypothesize that a strong correlation between these instruments could not be observed in both studies because only the NPI score was developed specifically to assess cohorts with patellar instability.

Table 1. Characteristics of the participants

Variable	Mean (standard deviation)
Age (years)	20.22 (6.55)
Height (m)	1.67 (0.09)
Weight (kg)	64.72 (14.72)
Body mass index (kg/m^2)	23.04 (4.39)
Number of episodes of dislocation	3.02 (2.27)
Age at the first episode of dislocation (years)	14.52 (4.41)
Lysholm knee score	59.65 (19.18)
Kujala patellofemoral disorder score	66.00 (14.83)
Norwich Patellar Instability score	96.02 (51.33)

m: meter; kg: kilograms; kg/m^2: kilograms/square meter.

Table 2. Original and translated versions of the Norwich Patellar Instability score

Original version	Translated version
1. Twisting/changing direction during sports/games	1. Movimento de rotação /mudança de direção durante esportes / jogos
2. Changing direction when running	2. Mudança de direção em corridas
3. Running in a straight line on *uneven* surfaces	3. Corrida em linha reta em superfícies irregulares
4. Walking on slippery, wet, or icy surfaces	4. Andar em superfícies escorregadias, molhadas ou cobertas por gelo
5. Running sideways	5. Correr lateralmente
6. Hopping	6. Pular em um pé só
7. Jumping	7. Pular
8. Running in a straight line on *even* surfaces	8. Correr em linha reta em superfícies planas
9. Going downstairs	9. Descer escadas
10. Squatting	10. Agachar-se
11. Kneeling	11. Ajoelhar-se
12. Walking in a straight line on *uneven* surfaces	12. Andar em linha reta em superfícies irregulares
13. Climbing stairs	13. Subir escadas
14. Stepping onto or over a high step	14. Pisar em degrau mais alto
15. Crossing your legs when sitting	15. Cruzar as pernas quando sentado
16. Walking in a straight line on *even* surfaces	16. Andar em linha reta em superfícies planas
17. Getting into or out of a car	17. Entrar e sair do carro
18. Turning a heavy trolley round a supermarket aisle	18. Guiar um carrinho de supermercado muito difícil de virar ou muito pesado
19. Turning to look over your shoulder	19. Virar-se para olhar para trás por sobre o ombro
Always	Sempre
Often	Frequentemente
Sometimes	Ocasionalmente
Rarely	Raramente
Never	Nunca
Do not do	Não faço

Table 3. Correlation between the Norwich Patellar Instability score and alternative and similar instruments

Score	Pearson correlation coefficient	95% confidence interval	P-value
Lysholm knee score	-0.56	-0.74 to -0.30	< 0.01
Kujala patellofemoral disorder score	-0.57	-0.75 to -0.31	< 0.01

Although the cohorts used in the two studies were different (such that in the earlier study, only individuals who were surgically managed were recruited), the results regarding validity were very similar. This suggests that the NPI score can be used for both conservatively and surgically managed patellar instability patients.

The most notable limitation of this study was that the responsiveness of the NPI score, i.e. the capability of the instrument to detect changes in the progression of a disease,[27] was not assessed. Further studies are warranted, to assess the reliability, responsiveness and floor and ceiling effects of the Brazilian Portuguese version of the NPI score, and to establish its minimal clinically important difference (MCID). Establishment of the MCID would be particularly helpful for evaluating patient-reported outcomes, for guiding clinical practice and, ultimately, for enabling more optimally directed patient care.

Based on the findings from the present study, the Brazilian Portuguese version of the NPI score was satisfactorily translated. It proved to be a valid tool for use in research and clinical practice, in following up patients with patellofemoral instability.

CONCLUSION

The NPI score has now been translated and culturally adapted and has been demonstrated to have validity for use in Brazilian Portuguese. Following this, the NPI score may now be considered for use within clinical and research practice, to aid in assessment and decision-making for individuals with patellofemoral instability.

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Analysis on the risk factors for organ damage in patients with systemic lupus erythematosus: a cross-sectional single-center experience

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KEY WORDS:
Lupus erythematosus, systemic.
Risk factors.
Quality of life.

ABSTRACT

BACKGROUND: Organ damage in patients with systemic lupus erythematosus (SLE) occurs as a consequence of the disease itself, the therapy applied and the accompanying conditions and complications. Organ damage predicts further organ damage and is associated with an increased risk of death.

OBJECTIVE: This study aimed to assess the degree of irreversible organ changes in SLE patients, using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index (SDI); to establish correlations between organ damage and disease activity, quality of life, intensity of fatigue and serological factors; and to ascertain the risk factors for organ damage.

DESIGN AND SETTING: Cross-sectional single-center study conducted at the Institute for Treatment and Rehabilitation "Niška Banja", Niš, Serbia.

METHODS: 83 patients with SLE were enrolled: 58 patients formed the group with organ damage (SDI ≥ 1), and 25 patients without organ damage served as controls (SDI = 0).

RESULTS: Organ damage correlated with age (P = 0.002), disease duration (P = 0.015), disease activity (grade 1, P = 0.014; and grade 2, P = 0.007), poor quality of life, severe fatigue (P = 0.047) and treatment with azathioprine (P = 0.037). The following factors were protective: use of hydroxychloroquine (P = 0.048) and higher scores obtained for the physical (P = 0.011), mental (P = 0.022) and general health (P = 0.008) domains.

CONCLUSION: It is very important to evaluate risk factors for organ damage in the body, including physicians' overall assessment, to try to positively influence better treatment outcomes.

INTRODUCTION

The multisystemic nature of systemic lupus erythematosus (SLE), its involvement of vital organs and its unpredictable disease course with exacerbations and remissions give rise to the possibility of development of irreversible changes in individual organs even at early phases of the disease, and particularly after several years.[1] Tissue and organ damage occurs as a consequence of the disease itself, the therapy applied (primarily corticosteroid and cytostatic), and the accompanying conditions and complications. Tissue and organ damage are associated with an increased risk of death.[2,3]

Adequate evaluation of disease activity, assessment of organ damage using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index for SLE (SDI)[4] and quality of life assessment among SLE patients contribute towards better surveillance and treatment, and improved prognosis for the disease.[5,6]

OBJECTIVE

Our aims in this paper were to examine the degree of irreversible organ changes in SLE patients using the SDI; to establish correlations between organ damage and disease activity, biological disease markers, quality of life and severity of fatigue; and to ascertain the risk factors for organ damage in SLE patients.

METHODS

Before enrollment in the study, all the examinees were informed about the study objectives and their informed written consent was obtained. The study was approved by our institution's ethics committee (date: November 28, 2013; number: 03-14421/1).

All patients with SLE who were hospitalised in the Rheumatology Clinic, Institute "Niška Banja" during 2012/13, with the duration of the disease longer than six months, were eligible for this study. The patients' diagnosis of SLE was made on the basis of the revised ACR criteria of 1997.[7] This cross-sectional study involved 83 patients with SLE (77 women and 6 men), with mean age of 45.8 ± 9.2 years and average disease duration of 10.6 ± 7.9 years.

Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the physician's global assessment.[8] SLEDAI assesses activity in nine organ systems based on the presence or absence of 24 variables at the time of the examination and up to 10 days after the examination. The values range from 0 to 105. Physician's global assessment grade was assigned by the researchers on the basis of anamnesis, physical examination and supplementary investigations. The grade ranged from 0 to 3 (0 – no activity; 1 – mild activity; 2 – moderate activity; 3 – severe disease).

The degree of organ damage was evaluated using the standardized damage index (SDI).[4] The SDI assesses damage in nine organ systems and three disease complications. It measures the presence of irreversible changes in the eyes, skin and neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal and musculoskeletal systems, along with the presence of gonadal insufficiency, diabetes mellitus and malignancy. Each of the characteristics adds an appropriate number of points to the overall score and is precisely defined in the SDI glossary. The total possible score for the damage index is 47.

Based on the damage index value, the SLE patients were divided into two groups: a study group comprising 58 patients (69.9%) with organ damage (SDI ≥ 1); and a control group comprising 25 patients (30.1%) without organ damage (SDI = 0). At the disease onset, the two groups were homogenous regarding the factors of gender and age. Quality of life was assessed on the basis of the standardized Medical Outcome Survey Short Form 36 (SF-36).[5] In this study, the values of three summary domains were primarily considered: physical (SF-36P), mental (SF-36M) and general health (SF-36G). The SF-36 questionnaire contains 36 questions in total, grouped into eight domains, along with a question relating to status change. The responses are scored from 0 to 100, in accordance with the key that is made available, such that higher scores indicate better quality of life.

The severity of fatigue was assessed using the Fatigue Severity Scale (FSS).[9] The FSS consists of nine statements for which possible answers graded from 1 to 7 are presented. The questions in the FSS relate to the preceding 14 days. Fatigue is graded as serious if the average value on the Fatigue Severity Scale exceeds the grade of 4.

The following demographic factors were observed: gender, age, disease duration, age at disease onset, time elapsed until diagnosis and education level (0-12 years or over 12 years). The following clinical factors were observed: number of diagnostic criteria, SLEDAI, physician's global assessment, hypertension, proteinuria, antiphospholipid syndrome, osteopenia, osteoporosis, cardiovascular diseases, involvement of the kidneys and central nervous system (CNS), severity of fatigue and quality of life expressed in terms of the physical, mental and general health domains. The following serological factors were determined: presence of anti-double-stranded deoxyribonucleic acid (anti-dsDNA), antinucleosome and anti-C1q antibodies; and the levels of monocyte chemoattractant protein-1 (MCP-1) in the serum (sMCP-1) and urine (uMCP-1). The presence of antibodies was determined using the enzyme-linked immunosorbent assay (ELISA) test in an Alegria automated ELISA reader, manufactured by Orgentec (Germany). The levels of sMCP-1 and uMCP-1 were measured using the sandwich enzyme immunosorbent assay method, in accordance with the manufacturer's instructions (R&D Systems, Inc., Minneapolis, USA). The therapeutic factors used included prednisone, hydroxychloroquine, azathioprine, mycophenolate mofetil and pulse doses of cyclophosphamide.

Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) software, version 20. The descriptive statistical analysis involved the following statistical parameters: arithmetic mean, standard deviation, range (minimum-maximum), absolute frequency (n) and structure index (%). Using the analytical statistical methodology, the statistical significance of the differences in frequency of appearance of certain characteristics in all examinees and according to group was measured.

The statistical testing was done using the chi-square test, or Fisher's test for frequencies below five units. Comparisons of the mean values of characteristics between the groups were made using the t test for independent samples. Pearson's correlation for parametric samples was used to measure the associations of particular characteristics, through correlation analysis. The predictive impact of individual variables on the dependent outcome variable was assessed using univariate and multivariate regression analyses. All the factors that were significant in the univariate model were included in a logistic multivariate analysis ("enter" method). An evaluation error level of below 5% ($P < 0.05$) was used at the threshold of statistical significance.

RESULTS

The parametric characteristics of the examinees in the study and control group are shown in **Table 1**. The patients in the study group with organ damage and SDI ≥ 1 were statistically significantly older than those in the control group (47.9 ± 8.7 versus 40.8 ± 8.5 years; $t = 3.464$; $P = 0.001$) and presented longer disease duration (12.1 ± 8.6 versus 7.3 ± 4.8 years; $t = 2.617$; $P = 0.011$). We did not find any statistically significant difference in the age at disease onset between the groups studied ($t = 1.056$; $P = 0.294$),

or any significant difference in time elapsed from the onset of symptoms to diagnosis (t = 0.725; P = 0.471).

The mean values of the activity index, SF-36 survey scores and fatigue scale are also presented in **Table 1**. There was no significant difference between the groups studied regarding disease activity and severity of fatigue, but the group with organ damage had significantly lower quality of life than the controls.

The mean value of the damage index for all the SLE patients was 1.8 ± 2.0 (median 1, minimum 0 and maximum 9); 25 patients (30.1%) did not have any organ damage (SDI = 0), 21 patients (25.3%) presented SDI = 1; 20 patients (24.1%) had SDI = 2 or 3; and 17 patients (20.5%) had SDI ≥ 4. Regarding specific organ damage, neuropsychiatric and musculoskeletal changes were most common, found in 23 patients (27.7%). In 21 patients (25.3%), cardiovascular changes were seen, while eye lesions were found in 14 patients (16.9%). Renal and pulmonary changes were seen in 13 patients (15.7%), skin lesions in three cases (3.6%) and gastrointestinal changes were observed in two patients (2.4%). Malignancies were encountered in five patients (6.0%), and diabetes mellitus in two cases (2.4%).

There were statistically significant positive correlations between SDI and age (r = 0.348; P = 0.001), disease duration (r = 0.412; P < 0.001), SLEDAI (r = 0.359; P = 0.001), physician's global assessment (r = 0.357; P = 0.001) and fatigue (r = 0.296; P = 0.007). Negative correlations with quality of life were established in relation to SF-36P (r = -0.389; P < 0.001), SF-36M (r = -0.314; P = 0.004) and SF-36G (r = -0.386; P < 0.001), meaning that more extensive organ damage was associated with poorer quality of life. SDI did not show correlations with the levels of anti-dsDNA, antinucleosome or anti-C1q antibodies, or with the levels of sMCP-1 and uMCP-1. SLEDAI scores correlated positively with the following study parameters: anti-dsDNA antibodies (r = 0.228; P < 0.05), antinucleosome (r = 0.396; P < 0.001), anti-C1q antibodies (r = 0.260; P < 0.05), sMCP-1 (r = 0.318; P < 0.01) and uMCP-1 (r = 0.431; P < 0.001).

Table 2 shows the results from univariate regression analysis on the independent demographic, serological, clinical and therapeutic parameters in the groups studied with and without organ damage. Among the demographic factors, the statistically significant independent factors favoring organ damage were the age of the examinees viewed as a continuous value (odds ratio, OR = 1.094; P = 0.002) and disease duration expressed as a continuous value (OR = 1.096; P = 0.015). Disease duration of over 10 years was recognized as a statistically significant risk factor, with a risk that was up to three times higher than that of disease duration of less than five years (OR = 3.368; P = 0.045). Among the clinical risk factors, disease activity (expressed as physician's global assessment grade) and severe fatigue were considered significant. Regarding physician's global assessment, grade 1 was a risk factor six times higher than grade 0 (OR = 5.800; P = 0.014) and grade 2 (OR = 10.667; P = 0.007) was a risk factor ten times higher, and these results were considered statistically significant. The patients with scores over 4 on the fatigue scale were exposed to a risk of organ damage that was three times higher than those with values ≤ 4 on this scale (OR = 3.370; P = 0.047). Higher values for the physical (OR = 0.976; P = 0.011), mental (OR = 0.978; P = 0.022) and general health (OR = 0.972; P = 0.008) domain scores were statistically significant protection factors against organ damage. Hydroxychloroquine use was a protection factor against organ damage (OR = 0.378; P = 0.048), while azathioprine treatment was a risk factor (OR = 9.143; P = 0.037). Serological factors, including the levels of anti-dsDNA, antinucleosome and anti-C1q antibodies, along with sMCP-1 and uMCP-1, were not found to be risk factors for organ damage.

Table 3 presents the results from multivariate logistic regression analysis that aimed to assess the impact of multiple factors and to single out those with statistical significance regarding organ damage in SLE patients. The model had nine independent variables, as follows: age, disease duration, physician's global assessment, use of

Table 1. Participants' characteristics

Variables	Group with organ damage		Control group		t	P
	mean	SD	mean	SD		
Age (years)	47.9	8.7	40.8	8.5	3.464	**0.001**
Disease duration (years)	12.1	8.6	7.3	4.8	2.617	**0.011**
Age at disease onset (years)	35.9	9.9	33.5	7.9	1.056	0.294
Time elapsed until diagnosis (months)	14.2	16.5	11.5	12.5	0.725	0.471
Age at diagnosis (years)	37.0	10.1	34.3	8.1	1.155	0.252
SLEDAI	11.8	6.6	9.0	7.8	1.655	0.102
Physician's global assessment	1.5	0.8	1.1	1.0	1.824	0.072
SF-36 physical health score	30.6	24.5	40.8	25.6	2.773	**0.008**
SF-36 mental health score	43.7	25.8	58.5	25.5	2.417	**0.018**
SF-36 global health score	35.0	22.8	51.2	24.5	2.895	**0.005**
Fatigue (FSS)	6.0	1.4	5.4	1.6	1.889	0.062

SD = standard deviation; SLEDAI = systemic lupus erythematosus disease activity index; SF-36 = medical outcome survey short form 36; FSS = fatigue severity scale.

Table 2. Univariate regression analysis on parameters evaluated among systemic lupus erythematosus patients

Factor		SDI = 0	SDI ≥ 1	OR	95% CI	P
		n (%)	n (%)			
Gender	[m]	0 (0.0)	6 (10.3)			
	f	25 (100.0)	52 (89.7)	0.000	0.000	0.999
Age				1.094	1.032-1.160	**0.002**
Age at disease onset				1.028	0.997-1.082	0.292
Disease duration				1.096	1.018-1.180	**0.015**
Time elapsed until diagnosis				1.013	0.978-1.048	0.469
Number of criteria at diagnosis				0.757	0.515-1.114	0.158
SLEDAI				1.065	0.978-1.149	0.106
Anti-dsDNA Ab				0.995	0.989-1.001	0.122
Positive anti-dsDNA Ab		19 (32.8)	39 (67.2)	0.648	0.223-1.888	0.427
Antinucleosome Ab				0.994	0.998-1.000	0.066
Positive antinucleosome Ab		20 (32.3)	42 (27.6)	0.656	0.211-2.045	0.468
Anti-C1q Ab				0.983	0.936-1.004	0.112
Positive anti-C1q Ab		11 (42.3)	15 (57.7)	0.444	0.166-1.188	0.106
Co-positivity for three antibodies		9 (39.1)	14 (60.9)	0.566	0.205-1.560	0.271
sMCP1				1.000	0.999-1.000	0.179
uMCP1				0.996	0.991-1.000	0.074
Prednisone dose				1.023	0.971-1.077	0.399
Hydroxychloroquine		15 (41.7)	21 (58.3)	0.378	0.144-0.991	**0.048**
Azathioprine		1 (5.9)	16 (94.1)	9.143	1.140-73.301	**0.037**
Hydroxychloroquine + Azathioprine		4 (28.6)	10 (71.4)	1.094	0.308-3.886	0.890
Cyclophosphamide pulsed dose		6 (31.6)	13 (77.4)	0.915	0.303-2.765	0.875
Mycophenolate mofetil		4 (33.3)	8 (66.7)	1.190	0.323-4.386	0.793
Physician's global assessment	[0]	8 (66.7)	4 (33.3)			
	1	10 (25.6)	29 (74.4)	5.800	1.432-23.496	**0.014**
	2	3 (15.8)	16 (84.2)	10.667	1.909-59.615	**0.007**
	3	4 (30.8)	9 (69.2)	4.500	0.837-24.183	0.080
Antiphospholipid syndrome		1 (7.7)	12 (92.3)	6.261	0.768-51.068	0.087
Education (years)	[≤ 12]	21 (30.0)	49 (70.0)			
	> 12	4 (30.8)	9 (69.2)	0.964	0.267-3.982	0.956
Hypertension		13 (31.0)	29 (69.0)	0.923	0.361-2.359	0.867
Proteinuria > 0.5 g		8 (28.6)	20 (71.4)	1.118	0.412-3.039	0.826
Osteopenia and osteoporosis	[normal BMD]	7 (33.3)	14 (66.7)			
	osteopenia	17 (32.7)	35 (67.3)	1.029	0.351-3.021	0.958
	osteoporosis	1 (10.0)	9 (90.0)	4.500	0.471-42.970	0.191
Lupus nephritis		2 (28.6)	5 (71.4)	0.882	0.134-5.815	0.896
Lupus CNS		2 (12.5)	14 (87.5)	3.659	0.765-17.501	0.104
Coronary disease, stroke and peripheral atherosclerosis		0 (0.0)	7 (100.0)	0.000	0.000	0.999
Mean value of fatigue scale				1.336	0.980-1.821	0.067
Severe fatigue	[≤ 4]	7 (53.8)	6 (46.2)			
	> 4	18 (25.7)	52 (74.3)	3.370	1.021-11.360	**0.047**
SF-36 physical health score				0.976	0.957-0.994	**0.011**
SF-36 mental health score				0.978	0.959-0.997	**0.022**
SF-36 general health score				0.972	0.952-0.992	**0.008**

[ ] = reference category; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; OR = odds ratio; CI = confidence interval; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; anti-dsDNA Ab = anti-double-stranded deoxyribonucleic acid antibodies; sMCP1 = serum monocyte chemoattractant protein-1; uMCP1 = urinary monocyte chemoattractant protein-1; CNS = central nervous system; SF-36 = Medical Outcome Survey Short Form 36; BMD = bone mineral density.

hydroxychloroquine, use of azathioprine, severe fatigue and SF-36 scores for physical, mental and general health. The whole model was statistically significant ($\chi^2 = 40.250$; $P < 0.001$). The model was able to completely account for 39.9% to 57.0% of damage variance. Only five variables made a statistically significant contribution to the model (physician's global assessment grades 1 and 2, SF-36 physical health, SF-36 mental health and SF-36 general health). Physician's global assessment grade 2 had the highest odds ratio (OR = 31.839; P = 0.010), followed by physician's global assessment grade 1 (OR = 16.927; P = 0.012), SF-36 general health (OR = 0.901; P = 0.034), SF-36 mental health (OR = 0.899; P = 0.034) and SF-36 physical health (OR = 0.856; P = 0.034).

DISCUSSION

Since organ damage is the principal predictor of mortality among SLE patients,[2,3] it is necessary to establish the risk factors for organ damage with permanent sequelae or irreversible loss of function. This formed the aim of the present study. In addition to demographic, clinical and therapeutic factors, the levels of antinucleosome, anti-C1q antibodies and several cytokines like MCP-1, measured in serum and urine, can be estimated as potential risk factors for organ damage in SLE patients. There have been several reports on the significance of these biological markers in relation to SLE,[10-13] but their impact on the appearance of permanent sequelae and irreversible loss of function has not been reported often.

In this study, the patients with organ damage and SDI ≥ 1 were statistically significantly older than those without organ damage[14] and had longer disease duration.[15] In addition, neuropsychiatric and musculoskeletal changes were the most common ones, similar to what was reported from a study conducted in Portugal.[16] The percentage of cardiovascular events in the present study was within the range of values reported from a meta-analysis on the predictors of cardiovascular events among patients with SLE.[17]

The SDI correlated positively with patient age, disease duration, disease activity and severity of fatigue but negatively with the summary domains of the SF-36 survey: physical, mental and general health. The data indicated that SLE patients with higher damage index had worse quality of life and greater severity of fatigue. The results obtained so far have been divergent regarding the correlation between the degree of damage and quality of life.[5,6,18,19,20]

In contrast to the disease activity index, the SDI did not show correlations with anti-dsDNA, antinucleosome or anti-C1q antibodies, or with sMCP-1 and uMCP-1. Although serum and urine MCP-1 are good markers of disease activity, they were not shown here to be indicators of organ damage, and neither were antibody levels.[21,22]

The results from univariate analyses in the present study showed that age, longer disease duration (especially when it was over 10 years), higher physician's global assessment scores, use of azathioprine and greater severity of fatigue were independent risk factors for organ damage, while use of hydroxychloroquine and better quality of life were protective against organ damage. The results from earlier studies have shown that the risk factors for organ damage are numerous and diverse, including not only demographic factors (male gender, advanced age, longer disease duration and African-Caribbean and Indo-Asian origin) but also increased disease activity and renal and CNS involvement.[15]

The time elapsed from the onset of symptoms to diagnosis, lower education levels and presence of a large number of criteria at diagnosis did not show statistical significance in the present study. In a large international study by Bruce et al.,[3] the socioeconomic status factor (represented as education) was not significantly associated with organ damage.

Table 3. Multivariate logistic regression analysis on independent factors among systemic lupus erythematosus patients

Factor		OR	95% CI	P
Age	continuous	1.042	0.944-1.150	0.418
Disease duration	continuous	1.085	0.966-1.218	0.167
Hydroxychloroquine	[no]			
	yes	0.347	0.049-2.446	0.288
Azathioprine	[no]			
	yes	3.256	1.369-5.639	0.921
Physician's global assessment	[0]			
	1	16.927	1.885-151.961	**0.012**
	2	31.839	2.327-435.585	**0.010**
	3	5.405	0.340-86.027	0.232
Severe fatigue	[≤ 4]			
	> 4	0.509	0.050-5.155	0.568
SF-36 physical health score	continuous	0.856	0.752-0.956	**0.034**
SF-36 mental health score	continuous	0.899	0.899-0.963	**0.034**
SF-36 general health score	continuous	0.901	0.874-0.985	**0.034**

OR = odds ratio; CI = confidence interval; SF-36 = medical outcome survey short form 36.

It is very interesting to examine the use of cytostatic agents, corticosteroids and antimalarial agents for treating SLE, since their use can possibly be correlated with organ damage. Over recent years, increasing amounts of data on organ damage caused through use of corticosteroids and their cumulative dose have become available. Thus, it has been recommended that doses of corticosteroids should be as low as possible.[1,3,16,19,22,23] In the present study, use of corticosteroids was not shown to be a risk factor, as also seen in some other studies.[24] The same was seen in relation to mycophenolate mofetil and pulse doses of cyclophosphamide. Use of azathioprine was an independent risk factor, similar to what was reported by Sutton et al.[15] The favorable effects of hydroxychloroquine regarding organ damage prevention in cases of SLE that was obtained in the present study were shown to be similar to those observed in other investigations.[25,26]

Hypertension, coronary disease, stroke, presence of peripheral atherosclerosis, proteinuria, renal involvement, CNS involvement, osteopenia, or osteoporosis, could not be singled out as independent risk factors for cumulative organ damage, according to the results from univariate analysis in the present study.

The presence of antiphospholipid antibodies can predict the development of neuropsychiatric damage.[27] In this light, and based on the situation that 13 out of the 83 SLE cases in the present study presented antiphospholipid syndrome, the reason why no significant association was shown here was probably because of the smaller number of respondents or the therapy applied or the shorter duration of monitoring, in comparison with other investigations.

Quality of life, as a separate category, was analyzed in some studies, bearing in mind that SLE is a chronic disease.[28,29] In the present study, quality of life was assessed using the standardized Medical Outcome Survey Short Form 36. The results from univariate and multivariate analysis showed that better quality of life, especially within the physical and mental domains, was associated with a lower degree of organ damage. The main determinant of organ damage, according to some studies, is overall disease activity.[30,31,32] The multivariate analysis in the present study showed that disease activity evaluated on the basis of physician's global assessment was the most important risk factor for organ damage.

The strength of the present study is the fact that many parameters were taken into consideration as potential risk factors for organ damage in SLE patients: demographic, clinical, therapeutic and serological. Most other studies did not consider such a wide range of parameters. One limitation of our study was the number of participants. Future prospective study with larger numbers of participants, in which demographic, clinical, therapeutic and serological parameters are monitored, should provide stronger evidence of risk factors for organ damage in SLE patients.

CONCLUSION

Although this study was based on a relatively small number of respondents, it showed that the risk factors for organ damage were age, disease duration (especially when this was over 10 years), disease activity, use of azathioprine and severe fatigue. The factors affording protection against organ damage were use of hydroxychloroquine and better quality of life, as expressed through physical, mental and general health scores in a SF-36 survey. Physician's global assessment has a prominent place in the evaluation of disease activity, since it is a simple method and is the most important predictor of organ damage in everyday clinical practice.

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Clinical and epidemiological aspects of scorpionism in the interior of the state of Bahia, Brazil: retrospective epidemiological study

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KEY WORDS:
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ABSTRACT

BACKGROUND: Scorpion accidents have gained great visibility around the world because of the high frequency and severity with which they occur, and have become a global medical-sanitary problem.

OBJECTIVE: The aim of this study was to describe the sociodemographic, clinical and epidemiological profile of scorpionism in the municipality of Jequié, Bahia, Brazil, from 2007 to 2015.

DESIGN AND SETTING: Retrospective epidemiological study in the municipality of Jequié, Bahia, Brazil.

METHODS: This study was based on data collected from the epidemiological investigation notification forms of the injury information system.

RESULTS: There was an increase in the coefficient of incidence of scorpion accidents in Jequié from 23.4/100,000 in 2007 to 413.6/100,000 in 2015. There were 3565 cases: 54.9% were female, 58.8% were aged 20-59 years, 63.5% had brown skin color and 48.6% had incomplete primary education. Most accidents occurred in urban areas (93.1%). Homes were the main place of occurrence (84.5%) and upper limbs were the commonest sting sites (53.0%). Regarding clinical aspects, 66.4% of the cases received hospital assistance within one hour after the bite, 84.1% presented mild severity, 97.1% had local manifestations and 10.2% had systemic symptoms. Serum therapy was administered in 17.3% of the cases, and 99.9% evolved to cure.

CONCLUSION: There was an increase in the incidence of scorpion accidents in the municipality, which demonstrates the need for investment in actions that reduce the morbidity and mortality caused by these accidents, such as educational campaigns and improvements in socioeconomic and health conditions.

INTRODUCTION

Accidents caused by venomous animals have undeniable importance within public health. Among these accidents, those caused by scorpions are gaining great visibility around the world, due to the high frequency and severity with which they occur, and have become a global medical-sanitary problem.[1]

Every year, an estimated 1.5 million cases and an estimated 2,600 deaths due to scorpionism occur worldwide.[2] In Brazil, between 2000 and 2012, there was an increase of 323% in the incidence rate and 475% in mortality due to scorpion accidents, with an average of 19.6 accidents and 0.030 deaths per 100,000 inhabitants.[3]

In Brazil, wide territorial distribution of occurrences has been observed, with emphasis on the northeastern region, which has the highest rates of incidence and mortality. The state of Bahia accounts for more than 30% of the notifications in this region and has the highest average annual mortality rates in this country.[4,5]

Most scorpion species have specific habitat and microhabitat requirements, along with predictable ecological and biogeographic patterns. However, some species have high ecological plasticity and irregular distribution, which favors their occupation of environments that have been disturbed or modified by man. These species find shelter and food near and/or inside human dwellings.[6]

In view of this, and since scorpionism is also a social problem, investigation of this phenomenon at the microregional and local levels becomes important, especially through the use of techniques that can identify areas and social groups of greater risk. A further justification for conducting such investigations is the current lack of studies showing the aspects of scorpion accidents in small urban centers, where these events are quite frequent and access to health services is limited.

OBJECTIVE

In the light of the present situation, the aim of this study was to describe the sociodemographic, clinical and epidemiological profile of scorpionism in the municipality of Jequié, Bahia, Brazil, from 2007 to 2015.

METHODS

This was a retrospective epidemiological study on scorpion accidents reported in the municipality of Jequié, Bahia, Brazil.

The study population was composed of all of the cases of accidents involving scorpion stings that were reported at the Prado Valadares General Hospital (PVGH) between 2007 and 2015. This hospital was chosen as the data-gathering site because it is the only serum dispensing unit in Jequié and is therefore the reference point for hospital care in cases of scorpionism in this municipality.

The data were collected directly from the epidemiological investigation sheets of the notifiable health hazard information system (SINAN, Sistema de Informação de Agravos de Notificação) of the Ministry of Health, which was made available by the Hospital Epidemiology Center of the PVGH. These records relate to investigations on all accidents involving venomous animals. For the present study, only those relating to accidents involving scorpion stings among people living in the municipality of Jequié, Bahia, were selected.

The information in the records formed three blocks of variables that were analyzed: sociodemographic characteristics (sex, age, color/race, schooling, occupation and area of residence); accident characteristics (place of occurrence, area of occurrence, month of occurrence, location of sting and time that elapsed between being stung and receiving hospital care); and clinical factors (local manifestations, systemic manifestations, classification of severity, serum therapy and evolution).

The analysis on the temporal evolution of the notifications was based on coefficients of annual incidence. These were obtained by dividing the absolute number of scorpion accidents reported by the size of the population at risk for each year of the study. The coefficients were expressed as the number per group of 100,000 inhabitants.

The population data that were used to calculate the coefficients were derived from the 2010 demographic census and from inter-census projections (2007 to 2009, 2011 and 2012) and population estimates (2013 to 2015) produced by the Brazilian Institute for Geography and Statistics (IBGE). The website of the Department of Informatics of the National Health System (DATASUS) of the Ministry of Health was also a source of data.

In calculating the coefficients, spreadsheets within Microsoft Excel 2010 were used for data tabulation and the Statistical Package for the Social Sciences (SPSS) software, version 21.0, was used for data analysis.

This study was submitted for assessment to the research ethics committee of the State University of the Southwest of Bahia, Jequié Campus, and was approved under report no. 1,376,751, on December 18, 2015. Because these data were secondary in nature, an exemption from the need to use a free and informed consent form was requested and approved.

RESULTS

Over the period from 2007 to 2015, 3565 cases of scorpionism were reported in the municipality of Jequié (state of Bahia, BA), with the highest number of occurrences in 2014 (n = 722). There was an increase in the incidence of notifications of scorpionism in the municipality (**Figure 1**), from 23.4/100,000 inhabitants in 2007 to 413.6/100,000 inhabitants in 2015, with a peak in 2014 (448.0/100,000 inhabitants). Analysis on the monthly distribution showed that there was no pattern of concentration of accidents between the months. The monthly average number of accidents ranged from 23.1 cases in July to 46.9 in December (**Figure 2**).

The victims (**Table 1**) were predominantly female (54.9%), aged between 20 and 59 years (58.8%), of brown skin color (63.5%), with incomplete primary education (48.6%) and living in the urban area (94.8%). In relation to occupation, 29.0% were minors or only students.

Accidents occurred more frequently in the urban area (93.1%), and the victim's home was the main place of occurrence (84.5%). Regarding the location of the bite, the upper limbs were the body segments most affected, accounting for 53.0% (**Table 2**).

Regarding clinical factors, as described in **Tables 2** and **3**, local manifestations were shown in 97.1% of the injured individuals, with emphasis on pain, paresthesia and edema, respectively, in 92.4%, 20.3% and 18.6% of the cases. Systemic manifestations were observed in 10.2% of the victims, and the most frequent of these were hypertension (4.7%), nausea/vomiting (1.3%) and headache (1.1%).

The time that elapsed between being bitten and receiving hospital care was mostly less than one hour (66.4%). Most of the cases (84.1%) were classified as mild, while 2.0% presented a severe clinical picture. Serum therapy was administered in 17.3% of the cases, and 99.9% evolved to cure.

DISCUSSION

Over the period analyzed, there was an alarming increase in the coefficient of incidence of scorpion accidents in the municipality of Jequié (23.4/100.000 to 413.6/100.000). This was higher than the increase that has been estimated for all of Brazil: between 2001 and 2012, the accident rate went from 10.5/100,000 to 32.3/100,000.[4] The coefficient for Jequié also differs from what has been found in other municipalities in this country, such as in Campina Grande,

state of Paraíba, from 2007 to 2012[7] and in Belo Horizonte, state of Minas Gerais, from 2005 to 2009,[8] where there were declines in the coefficient, from 132.0/100,000 to 108.0/100,000 and from 28.6/100,000 to 24.3/100,000, respectively.

It should be noted that in the present study, the growth shown may reflect not only the increase in the number of cases, but also improvements in the notification process. The coefficient increased in 2009, when the Hospital Epidemiology Center of the PVGH was implemented. Through this, compulsory notifications of diseases and health hazards began to be carried out in a judicious manner. In addition, increased awareness within the population regarding the emergency nature of these accidents may have given rise to greater demand for healthcare services, and thus may have increased the numbers of notifications.

Regarding the monthly distribution, it was observed that the accidents did not present seasonal behavior, and a certain degree

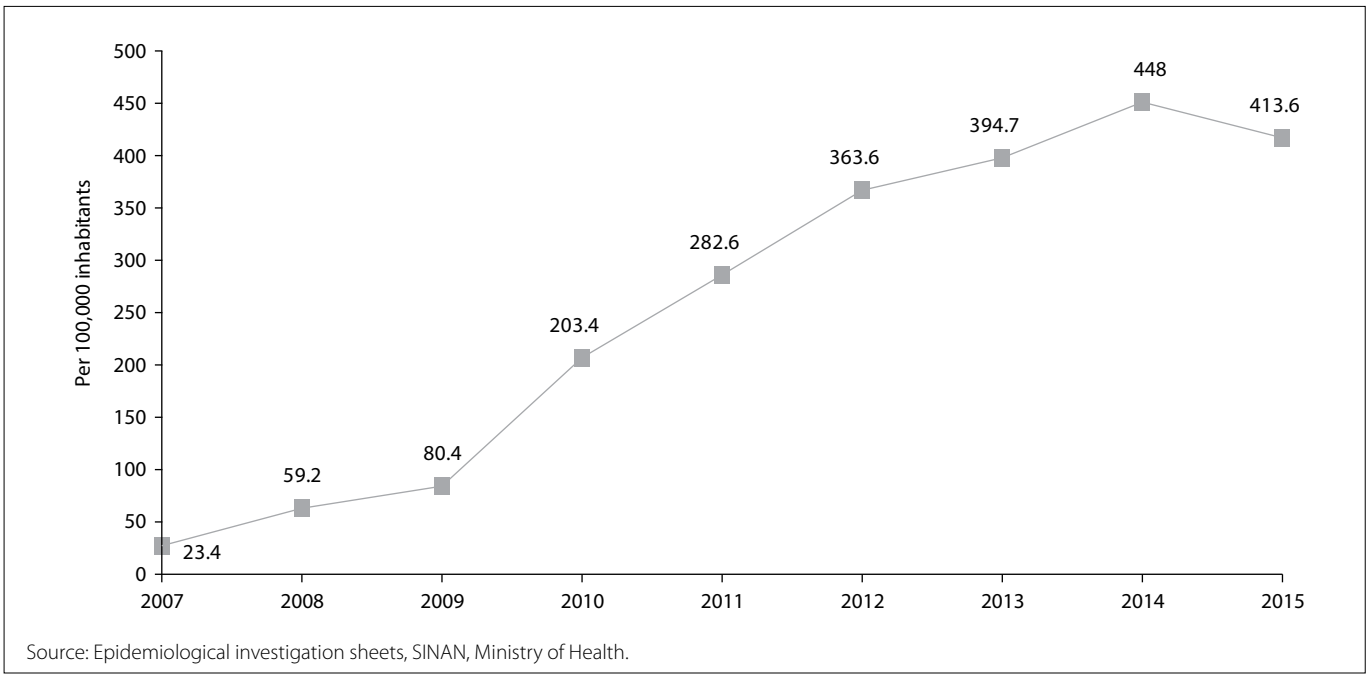

Figure 1. Evolution of the coefficients of incidence of scorpion accidents in the municipality of Jequié, Bahia, Brazil, 2007 to 2015.

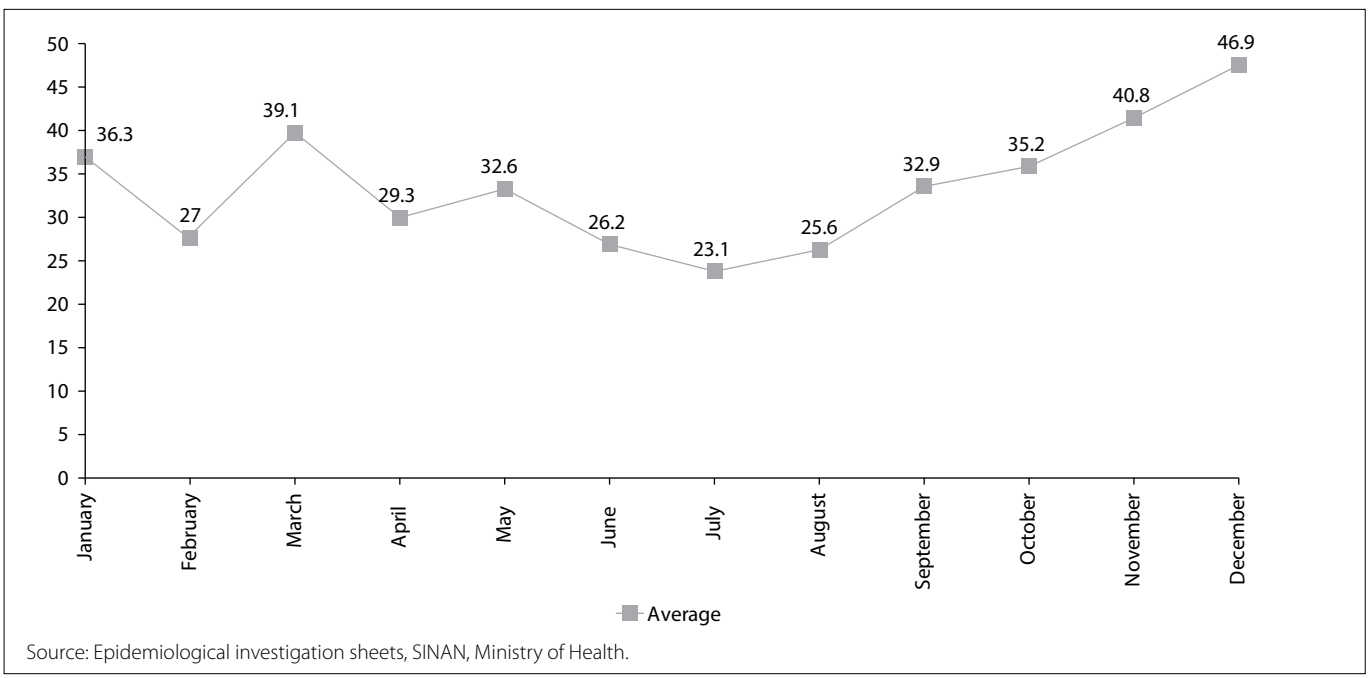

Figure 2. Average monthly number of scorpion accidents reported in the municipality of Jequié, Bahia, Brazil, 2007 to 2015.

of uniformity of occurrence of this health hazard over the months of the year was seen. This finding can be explained by the fact that Jequié presents environmental conditions that are favorable for survival and proliferation of scorpions throughout the year, such as ideal temperatures, humidity and abundant food. This differs from the situations found in the state of Pernambuco[9] and in the city of Belo Horizonte,[8] and in countries such as Iran[10] and Tunisia,[11] where scorpion accidents have been reported to be more frequent in the hotter and rainier periods of the year.

The process of urbanization has been reported to be a factor contributing towards scorpionism. This was also observed in the present study, since 94.8% of the accidents occurred in urban zones, as seen in other studies conducted in different regions of Brazil[7,12] and in Sudan.[13] The urbanization of scorpionism has been explained as being due to disordered urban growth, the inadequacies of infrastructure and the environmental imbalance.[14] Uncontrolled increases in the urban population lead to occupation of irregular areas, with severe infrastructure problems such as lack of basic sanitation and poor housing conditions. These are factors that favor availability of shelter and proliferation of these animals.[15] In addition, the ease of adaptation of scorpions to changes in the environment, in combination with difficulties in implementing preventive programs within the population, boost the risks of occurrence of such accidents.[16]

The higher frequency of accidents suffered by females corroborates other surveys conducted in Brazil[17,12,17] and in other countries.[10,18] The fact that the highest frequency of accidents was at home (85.5%), together with the high proportion of cases

Table 1. Characterization of the cases of scorpionism according to sociodemographic variables. Jequié, Bahia, Brazil, 2007 to 2015

Variables	n	%
Sex (n = 3,563)		
Male	1,608	45.1
Female	1,955	54.9
Age range (years) (n = 3,556)		
0 to 9	365	10.3
10 to 19	616	17.3
20 to 59	2,092	58.8
60 or over	483	13.6
Color/race (n = 2,955)		
White	480	16.2
Black	581	19.7
Brown	1,876	63.5
Asian	14	0.5
Indigenous	4	0.1
Schooling (n = 2,318)		
Completed higher education	52	2.2
Incomplete higher education	55	2.4
Full high school	435	18.8
Incomplete high school	237	10.2
Completed elementary education	73	3.2
Incomplete elementary school	1,127	48.6
Illiterate	339	14.6
Occupation (n = 2,572)		
Minor/student	746	29.0
Domestic	555	21.6
Working in commerce	249	9.7
Rural worker	103	4.0
Mason	140	5.4
Retired	211	8.2
Others	568	22.1
Area of residence (n = 3,555)		
Urban	3,371	94.8
Rural	184	5.2

Source: Epidemiological investigation sheets, SINAN, Ministry of Health.

Table 2. Description of the cases of scorpionism, according to the characteristics of the accident and the clinical characteristics of the victims. Jequié, Bahia, Brazil, 2007 to 2015

Variables	n	%
Occurrence zone (n = 3,530)		
Urban	3,286	93.1
Rural	244	6.9
Place of occurrence (n = 2,826)		
Residence	2,387	84.5
Third-party house	28	1.0
Public highway	68	2.4
Farm	86	3.0
In the workplace	205	7.3
Others	52	1.8
Location of the bite (n = 3,423)		
Upper limbs	1,815	53.0
Lower limbs	1,296	37.9
Others	312	9.1
Local manifestations (n = 3,528)		
No	103	2.9
Yes	3,425	97.1
Systemic manifestations (n = 3,226)		
No	2,897	89.8
Yes	329	10.2
Time elapsed until hospital care (3,243)		
< 1 hour	2,154	66.4
1 to 3 hours	677	20.9
> 3 hours	412	12.7
Severity classification (n = 3,465)		
Mild	2,913	84.1
Moderate	481	13.9
Severe	69	2.0
Serum therapy (n = 3,430)		
No	2,836	82.7
Yes	594	17.3
Evolution (n = 3,214)		
Cure	3,211	99.9
Death due to scorpionism	3	0.1

Source: Epidemiological investigation sheets, SINAN (Sistema de Informação de Agravos de Notificação), Ministry of Health.

in which the victim's occupation related to domestic activities, provides emphasis in explaining why the proportion of women affected was greater. Females in this setting might have greater exposure related to domestic activities, such as cleaning of places that often serve as shelter for scorpions, such as sinks, bathroom drains, clothing and shoes.[7]

Nevertheless, other studies have pointed out higher occurrence of male scorpionism.[9] Activities performed outside the home, especially those relating to construction and agriculture, have been reported to be related to scorpion accidents.[16]

The high proportion of the scorpion bite victims of the present study that were classified as having the sociodemographic characteristic of low schooling corroborates the findings of a previous study on venomous animal poisoning in Brazil.[4] That study showed that there were negative correlations between scorpionism and literacy and the Human Development Index (HDI). These findings contribute towards the hypothesis that socially and economically disadvantaged populations present greater vulnerability to scorpion accidents,[3] considering that schooling contributes towards better socioeconomic conditions.

The location of the bite has been reported to be one of the factors that influence the severity of cases, such that the closer it is to vital organs, the greater the complications and possibilities of side effects will be.[19] In the present study, it was found that the upper limbs were the body segments most affected, similar to what was found in other studies.[9,12,18]

This result shows that scorpion bites usually occur while household chores are being done,[8,12] or when the victims are putting on their clothes or shoes,[12] or while working in environments that are considered to provide suitable shelters for these animals, without using personal protective equipment (PPE) such as gloves and boots.

Another matter that deserves attention is early treatment for injured people. If it is necessary to apply therapeutic serum, this should be administered as soon as possible, so that the venom is immediately neutralized. In the present study, the largest proportion of the victims were hospitalized less than one hour after the sting, similar to what was observed in studies conducted in northeastern Brazil,[7] the state of Ceará[12] and the city of Belo Horizonte.[8] From the point of view of epidemiological surveillance, this finding may mean that there were improvements to access to information concerning the need for urgent medical services in cases of scorpion stings.[8] The findings from the present study indicate that the healthcare service in this region is providing relatively good medical care for the victims of scorpionism.

Furthermore, the fact that attendance was provided quickly may explain why a greater proportion of the cases were classified as mild. This may also explain why most of the accidents did not present systemic manifestations, i.e. they did not present signs and symptoms that would be indicative of greater severity. On the other hand, 97.1% of the cases presented local manifestations, with emphasis on pain, paresthesia and edema. These clinical characteristics are similar to those found in studies conducted in different Brazilian states[12,20] and in regions of Iran[21] and Saudi Arabia.[22]

In general, cases with mild symptoms require simple therapeutic measures such as administration of analgesics and antihistamines. However, in cases with systemic symptoms, use of antivenom and other measures against anaphylactic reactions is recommended.[18] In the present study, the number of cases that received serum therapy did not match the proportion of systemic manifestations. This finding may have been due to other criteria considered in determining that this treatment should be used, or due to possibly unnecessary use of serum.

Regarding case evolution, the clinical profile found may explain the high proportion of cases that were cured, along with the relatively low number of deaths. The description of the deaths corroborates what has been pointed out in the literature. Thus, children have been shown to present greater susceptibility to scorpion toxin, especially those under nine years of age.[11,23] Moreover, a relationship between the time that elapses from receiving the bite to receiving hospital care and the prognosis for the case has been demonstrated.[9]

The use of secondary data can be highlighted as a limitation of this study. The main disadvantages of using secondary data are that variables may be under-registered and cases may be underreported. These situations can be generated both through failure to complete the notification forms and through occurrences of cases with mild symptoms for which healthcare services are

Table 3. Clinical manifestations observed among victims of scorpionism. Jequié, Bahia, Brazil, 2007 to 2015

Manifestations	n	%
Local manifestations		
Pain	3,293	92.4
Paresthesia	723	20.3
Edema	665	18.6
Bruise	24	0.7
Others	223	6.2
Systemic manifestations		
Vomiting/nausea	48	1.3
Headache	39	1.1
Dizziness	27	0.7
Sweating	9	0.3
Arterial hypertension	167	4.7
Arterial hypotension	8	0.2
Tachycardia	5	0.1
Dyspnea	7	0.2
Others	32	0.9

Source: Epidemiological investigation sheets, SINAN (Sistema de Informação de Agravos de Notificação), Ministry of Health.

not sought. Hence, such situations may lead to underestimation of the numbers of accidents and make it difficult to characterize the cases.

However, despite such limitations, the SINAN system of the Brazilian Ministry of Health was seen to be an important tool for conducting epidemiological studies, given that it is the official database for registering diseases and health hazards in Brazil.

CONCLUSION

This study showed that the coefficient of incidence of scorpion accidents in the municipality of Jequié has increased. The clinical and epidemiological profile of the scorpionism cases in this study corroborates what has been found in other surveys in Brazil and in other countries, i.e. predominance of scorpionism in urban areas, among the economically active age group with low schooling levels. The importance of early hospital care for better evolution of cases was also observed.

These findings indicate that multidisciplinary actions involving different healthcare sectors, environmental management and the population itself are essential for reducing morbidity and mortality due to scorpionism. Among such actions, the most important of these are investment in educational campaigns, improvements in socioeconomic and health conditions, and improvements in the hospital care provided for bite victims, so as to ensure immediate care.

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Association between consumption of ultra-processed foods and serum C-reactive protein levels: cross-sectional results from the ELSA-Brasil study

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KEY WORDS:
Diet.
C-reactive protein.
Inflammation.
Obesity.
Cross-sectional studies.

ABSTRACT

BACKGROUND: There may be a direct association between consumption of ultra-processed foods and C-reactive protein (CRP) levels, under the assumption that the high glycemic index of these food products could stimulate the entire chronic inflammation cascade, along with an indirect association mediated by obesity. The types of food consumed, including ultra-processed products, strongly influence obesity, and are also associated with higher serum CRP levels.

OBJECTIVE: Our aim was to investigate whether the caloric contribution of ultra-processed foods to diet is associated with CRP levels, independent of body mass index (BMI).

DESIGN AND SETTING: Cross-sectional analysis on the Longitudinal Study of Adult Health (ELSA-Brasil) baseline cohort (2008-2010).

METHODS: Dietary information, obtained through a food frequency questionnaire, was used to estimate the percentage of energy contribution from ultra-processed food to individuals' total caloric intake. CRP levels were the response variable. Sex-specific associations were estimated using generalized linear models with gamma distribution and log-link function.

RESULTS: Ultra-processed food accounted for 20% of total energy intake. Among men, after adjustments for sociodemographic characteristics, there was no association between ultra-processed food intake and CRP levels. Among women, after adjustment for sociodemographic characteristics, smoking and physical activity, the highest tercile of ultra-processed food intake was associated with mean CRP levels that were 14% higher (95% confidence interval: 1.04-1.24) than those of the lowest tercile. However, after considering BMI, this association lost statistical significance.

CONCLUSION: Our findings suggest that the positive association of ultra-processed food consumption with CRP levels among women seems to be mediated by the presence of adiposity.

INTRODUCTION

Low-grade chronic inflammation is a mechanism common to many chronic non-communicable diseases that can be measured using biomarkers such as C-reactive protein (CRP).[1] Health-related behaviors, including diet, may influence the onset and progression of chronic inflammation.[1] Dietary patterns characterized by high intake of sugars, refined grains, red meat, saturated and trans fats and reduced fiber content have been correlated with higher plasma CRP levels.[2] However, while some studies have suggested that the association between dietary patterns and CRP levels seems to differ according to sex,[3-5] others have not supported this association.[6,7]

Ultra-processed foods are ready-to-eat industrial formulations that are made entirely or predominantly of substances extracted from foods, food constituents or laboratory-synthesized ingredients based on organic materials. These foods present an unbalanced nutritional composition, lack micronutrients and phytochemicals, contain low levels of fiber and protein and are rich in free sugars, total fats, saturated and trans fats and sodium.[8]

Previous studies have identified positive associations between consumption of ultra-processed foods and obesity,[9-13] metabolic syndrome in adolescents,[14] dyslipidemia in children[15] and hypertension in adults.[16] In addition, a recent ecological study that included data from 19 European countries showed a positive association between household availability of ultra-processed foods and the prevalence of obesity among adults.[9]

We did not identify any study investigating the relationship between consumption of ultra-processed foods and inflammatory markers, such as CRP. It is possible that these foods may have a direct association with CRP, under the assumption that the high glycemic index of ultra-processed products could stimulate the entire chronic inflammation cascade,[17] along with an indirect association mediated by obesity. The types of food consumed, including ultra-processed products, strongly influence obesity[9-12] and are also associated with higher serum CRP levels.[18]

OBJECTIVE

The aim of the present study was to investigate whether the consumption of ultra-processed foods is associated with CRP levels, regardless of total energy intake, among men and women who were enrolled at the baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). In addition, its aim was to determine whether this association is independent from body mass index (BMI).

METHODS

Study design, subjects and ethical approval

A cross-sectional analysis was conducted on baseline data (2008-2010) from ELSA-Brasil. This is a multicenter cohort of 15,105 civil servants (aged 35-74 at the time of enrolment) at public universities and research institutions located in six Brazilian states.[19,20] The ELSA-Brasil study was approved by the research ethics committees of the six participating institutions (UFMG: ETIC 186/06; HU/USP: 669/06; UFRGS: 194/061; UFES: 041/06; UFBA: 027/06; FIOCRUZ: 343/06), and all participants signed an informed consent form. Details on the study design and cohort profile can be found in other publications.[19,20]

This analysis excluded subjects with the following characteristics: those with total energy intake (kcal/day) below the 1st and above the 99th percentiles (n = 439); those for whom CRP data was missing (n = 15) and those with CRP values > 99th percentile, which was equivalent to 20.3 mg/l (n = 143); those with a history of bariatric surgery (n = 107); those who had undergone changes to their dietary habits within the six months prior to the interview (n = 4,439); and those with the following conditions: diabetes (n = 1,322), cardiovascular disease (n = 732) and cancer (n = 686). In the end, our sample consisted of 8,468 subjects.

Study variables

The response variable of this study was the CRP level (mg/l), measured in blood after 12 hours of fasting by means of high-sensitivity immunochemistry-nephelometry assay (BN II; Siemens). CRP values lower than the detection limit (0.175 mg/l) were automatically set to half the detection limit (n = 369), i.e. 0.0875 mg/l.

The explanatory variable was the percentage energy contribution towards total energy intake that came from ultra-processed foods. Information on dietary consumption was obtained using a semi-quantitative food frequency questionnaire (FFQ), with 114 food items. This FFQ had previously been shown to present satisfactory reliability for all nutrients.[21]

The energy values of foods in the FFQ were estimated based on the following formula: number of servings consumed per occasion x weight/serving size x daily intake frequency x nutritional composition of the food serving. The nutritional composition of the food items was based on the Nutrition Data System for Research (NDSR) from the University of Minnesota, and on the Brazilian Food Composition Table (TACO, acronym in Portuguese) from the Campinas State University (Universidade Estadual de Campinas, UNICAMP).[22]

Foods were classified according to their level of processing using the NOVA classification,[23] as follows: unprocessed and minimally processed foods; processed food ingredients; processed foods; and ultra-processed foods. The present study considered the percentage of the subjects' total energy intake that came from ultra-processed foods.[24] To calculate this percentage, calories from this food group were divided by total calories, and then multiplied by 100. Lastly, the percentage energy contribution from ultra-processed foods was categorized into terciles.

The following covariates were included:

1) sociodemographic characteristics: age (used as a categorical variable for descriptive and continuous analyses in the regression models), self-declared race/skin color (white, brown/*pardo*, black, Asian descendant or Brazilian indigenous) and educational attainment (university degree, high school, completed elementary school or incomplete elementary school).
2) health-related behaviors: smoking (never smoked, former smoker or current smoker) and physical activity during leisure time (none, light intensity, moderate intensity or high intensity).[25]
3) BMI, calculated as weight/height^2, was used to classify subjects according to their nutritional status (eutrophic: BMI < 25.0 kg/m^2; overweight: BMI ≥ 25.0-29.9 kg/m^2; and obese: BMI ≥ 30 kg/m^2)[26] and was used as a continuous variable in regression models.

Statistical treatment

A descriptive analysis was performed using frequencies or medians (1st and 4th quartiles). The difference in CRP medians based on these variables was evaluated using the Kruskal-Wallis tests, and a trend test was performed for medians, whenever appropriate.

The association between the percentage energy contribution from ultra-processed foods and the CRP levels was estimated using generalized linear models (GLM), with gamma distribution and log-link function. The results were presented as the arithmetic mean ratio (AMR), which expresses the exponential of the regression coefficient (β).

Crude arithmetic mean ratios were firstly estimated (model 0) and then sequential adjustments were made, including the variables of age (model 1), race/skin color and current educational attainment (model 2), smoking and physical activity (model 3) and body mass index (model 4). The models were tested for adequacy. For the linear trend analysis, the terciles of the percentage energy contribution from ultra-processed foods were inserted into the models as a continuous variable. Multiplicative interaction between the percentage energy contribution from ultra-processed foods and sex was investigated by including interaction terms in the adjusted regression models (Model 3 and 4). Evidence of multiplicative interaction between the percentage energy contribution from ultra-processed foods and sex was found (model 4: P-value: tercile 2*female = 0.150; P-value: tercile 3*female = 0.006). Therefore, analyses were presented separately for males and females.

Sensitivity analyses were performed with the following exclusions: 1) subjects with serum CRP > 10 mg/l, which may indicate acute inflammation, although these values can also be seen in cases of chronic inflammation;[22] 2) participants on steroids; and 3) women on contraceptives or hormone replacement therapy. The analyses were done using Stata version 12 (Stata Corporation, College Station, USA).

RESULTS

Among all the participants, most (52.4%) were women; in both sexes, most were aged 45 to 54 years, self-reported their race/skin color as white and had an undergraduate degree. More than half of all the individuals reported that they had never smoked and were not practicing any physical activity or that it was of light intensity. Approximately 16% of the men and 19% of the women presented BMI ≥ 30 kg/m² (**Table 1**). Ultra-processed foods contributed almost 23% of the total energy (kcal) intake.

The median CRP level was 1.20 mg/l (0.64-2.50) for men and 1.47 mg/l (0.72-3.39) for women, and this increased with age only in women (**Table 2**). For both sexes, individuals with incomplete elementary school, light intensity of physical activity, current smokers and obesity presented higher median CRP levels.

Among women, after adjustments for sociodemographic characteristics and behaviors, the arithmetic mean CRP level was 14% higher in the highest tercile of the percentage energy contribution from ultra-processed foods (arithmetic mean ratio: 1.14; 95% confidence interval, CI: 1.04-1.24) than in the lowest tercile of consumption. However, when adjusted for BMI (model 4), this association was no longer significant. The ultra-processed food consumption did not remain associated with CRP levels among men (**Table 3**).

Sensitivity analyses excluding individuals with serum CRP > 10 mg/l and those on steroids did not change the results observed among either men or women; nor did analyses excluding women on contraceptives or hormone replacement. When the same analyses were conducted including those who had changed their eating habits within the last six months, the results did not change.

DISCUSSION

Our results showed that there was a direct association between consumption of ultra-processed foods and CRP levels after adjusting for sociodemographic characteristics and health-related behaviors among women. However, this association

Table 1. Descriptive characteristics of the study population according to sex, ELSA-Brasil (2008-2010)

	Male		Female	
	n (4,029)	%	n (4,439)	%
Age* (years)				
35 to 44	1,007	24.9	1,003	22.5
45 to 54	1,670	41.5	1,817	40.9
55 to 64	1,004	24.9	1,247	28.3
65 to 74	348	8.4	372	8.3
Race/skin color*,**				
White	2,154	53.4	2,353	53
Brown (*pardo*)	1,196	29.7	1,173	26.4
Black	498	12.3	716	16.1
Asian	75	1.8	122	2.7
Indigenous	54	1.4	29	0.6
Educational attainment*				
University degree	2,042	51.0	2,483	55.9
High school	1,340	33.0	1,582	35.7
Completed elementary school	329	8.2	219	4.9
Incomplete elementary school	318	7.8	155	3.5
Smoking*				
Never smoked	2,109	52.3	2,778	62.6
Former smoker	1,284	32.2	1,039	23.4
Current smoker	636	15.5	622	14
Physical activity*,**				
None	1,535	38.6	2,225	50.9
Light intensity	1,450	36.4	1,352	30.9
Moderate intensity	636	15.8	576	13.0
High intensity	359	8.9	221	5.0
BMI (kg/m²)*,**				
Eutrophic (< 25)	1,594	38.8	2,066	46.5
Overweight (≥ 25.0 to 29.9)	1,767	44.4	1,516	34.1
Obese (≥ 30.0)	665	16.7	855	19.2
CRP level (mg/l)***	1.20	0.64-2.5	1.47	0.72-3.39
Energy contribution from ultra-processed foods (kcal)***	638.2	427.3-936.6	566.7	384.9-808.8

*Data expressed as absolute numbers and percentages. The percentages are rounded, making the total percentage for each characteristic not always equal to 100%. **There may be differences in totals due to loss of information. ***Continuous variables. Data expressed as medians and interquartile ranges. BMI = body mass index; CRP = C-reactive protein.

disappeared after adjustment for BMI. Among men, there was an inverse association between consumption of ultra-processed foods and CRP levels in the crude analysis and after age adjustment. This association ceased to be significant after adjusting for sociodemographic factors.

This direct association between higher consumption of ultra-processed foods and CRP levels, independent of the total energy intake, corroborates previous studies that pointed out a relationship between unhealthy dietary patterns and higher CRP levels.[28,40] Nonetheless, the association observed was specific for women and, after adjusting for BMI, it lost statistical significance. This suggests that the relationship between ultra-processed foods and higher serum CRP levels was completely mediated by adiposity. It is important to highlight that in the present study, consumption of ultra-processed foods was corrected according to the total energy of the diet, i.e. the association found was independent of the total energy intake.

The difference regarding sex that we observed in this analysis is intriguing. Although previous studies have suggested that a sex-specific relationship between diet and CRP level exists, the results have not been consistent. In a Japanese study, the bread pattern (high in bread, margarine and coffee; low in rice and miso soup) and the dessert pattern (high in Western/Japanese confections and fruit) showed inverse associations with CRP levels

Table 2. Median C-reactive protein level and interquartile range (IQR) according to sociodemographic characteristics, behaviors, anthropometric measurements, health conditions and consumption of ultra-processed foods, ELSA-Brasil (2008-2010)

	C-reactive protein level (mg/l)					
	Male (n = 4,029) Median (IQR)		P-value	Female (n = 4,439) Median (IQR)		P-value
Age (years)						
35 to 44	0.98	(0.56-2.14)		1.25	(0.58-3.40)	
45 to 54	1.26	(0.68-2.66)	0.0001	1.46	(0.74-3.40)	0.0002
55 to 64	1.32	(0.70-2.55)		1.55	(0.78-3.37)	
65 to 74	1.24	(0.70-3.11)		1.78	(0.90-3.40)	
Race/skin color						
White	1.18	(0.64-2.37)		1.47	(0.71-3.29)	
Brown	1.29	(0.68-2.76)		1.43	(0.72-3.28)	
Black	1.22	(0.66-2.82)	0.0003	1.96	(0.83-4.45)	0.0001
Asian	0.77	(0.39-1.52)		0.92	(0.43-1.72)	
Indigenous	1.25	(0.68-2.54)		1.08	(0.81-2.26)	
Educational attainment						
University degree	1.05	(0.60-2.14)		1.33	(0.66-3.07)	
High school	1.30	(0.69-2.68)	0.0001	1.65	(0.77-3.82)	0.0001
Completed elementary school	1.33	(0.72-3.03)		1.93	(0.89-4.39)	
Incomplete elementary school	1.80	(0.83-3.63)		2.14	(1.03-5.16)	
Smoking						
Never smoked	1.05	(0.59-2.13)		1.41	(0.69-3.28)	
Former smoker	1.23	(0.68-2.64)	0.0001	1.55	(0.76-3.34)	0.0003
Current smoker	1.81	(0.93-3.65)		1.81	(0.79-3.95)	
Physical activity						
None	1.41	(0.71-3.02)		1.77	(0.81-3.98)	
Light intensity	1.17	(0.65-2.37)	0.0001	1.40	(0.71-3.03)	0.0001
Moderate intensity	1.03	(0.58-2.06)		1.11	(0.59-2.65)	
High intensity	0.99	(0.53-2.14)		1.03	(0.48-1.99)	
BMI (kg/m²)						
Eutrophic	0.86	(0.48-1.73)		0.92	(0.49-1.90)	
Overweight	1.30	(0.73-2.64)	0.0001	1.76	(0.93-3.34)	0.0001
Obese	1.97	(1.12-3.98)		3.91	(1.98-6.98)	
Percentage energy contribution from ultra-processed foods						
Tercile 1 (lowest)	1.22	(0.67-2.61)		1.45	(0.69-3.24)	
Tercile 2	1.20	(0.64-2.53)	0.09	1.47	(0.72-3.42)	0.3000
Tercile 3 (highest)	1.18	(0.62-2.32)		1.50	(0.74-3.59)	

Median (IQR): median and interquartile range. The differences between median C-reactive protein levels according to variables were tested using the Kruskal-Wallis test. Differences were considered significant at P-values < 0.05.
BMI = body mass index (kg/m²).

among men, while the Western pattern (high in meat, eggs, mayonnaise and deep or stir-fried foods) showed a positive association with CRP levels among women.[3] A multi-city cohort in South America showed that higher intakes of fruits, vegetables, fish, seafood, whole cereal and low-fat dairy products were associated with reduced CRP levels only in men.[4] On the other hand, a lack of association between ultra-processed foods and overweight and obesity among men has already been reported,[10] as has a stronger association between higher consumption of ultra-processed food and obesity among women.[29]

The positive association between consumption of ultra-processed foods and CRP that has been seen among women may be partly explained by the greater accumulation of body fat in women,[31] since BMI has been more strongly associated with CRP levels among females, whereas central adiposity seems to be more strongly related to CRP levels among men.[32,33] However, other studies have shown higher CRP levels in women than in men, irrespective of potential confounding factors such as race, BMI and estrogen use.[31,34] We also included waist circumference in the models, but the result did not change (results not shown). Moreover, a meta-analysis on longitudinal studies indicated that diets with high glycemic load and glycemic index, which are both characteristics of ultra-processed foods, were associated with metabolic changes among women, while the results for men were inconsistent.[35]

As in the present analysis, some studies have also shown that the association between the Western dietary pattern, consisting mostly of ultra-processed foods, and increased CRP levels, is attenuated after adjustment for BMI or waist circumference.[36,37] A direct relationship between consumption of ultra-processed foods and obesity has already been described.[9-11] Ultra-processed food consumption has also been correlated with increased BMI and waist circumference after simultaneous adjustment for these variables and other confounding factors in ELSA-Brasil.[13] It is well established that adipose tissue produces cytokines that induces CRP production.[38] Thus, the association between consumption of ultra-processed foods and the inflammatory response is expected to be largely dependent on adiposity.

However, it would be plausible to assume that part of this association is independent from adiposity, since some nutritional characteristics of ultra-processed foods, such as high energy density, high glycemic load and high content of saturated and trans fats,[39] may stimulate inflammatory markers[40] through promoting oxidative stress. This induces production of free radicals[19] or suppresses the antioxidant capacity of foods, and leads to hypersecretion of pro-inflammatory cytokines.[41] As mentioned earlier, the total energy intake was corrected through creation of the variable of percentage energy contribution from ultra-processed foods and, therefore, this factor did not influence the results. Our findings did not support this potential relationship between the contribution of ultra-processed foods towards total energy intake and the levels of a chronic systemic inflammation indicator, which in this case was CRP.

One point to be considered in the results from this study is the percentage energy contribution from ultra-processed foods. The NOVA classification proposes an indicator to measure the nutritional quality of a diet by grouping several foods into four groups, which are investigated in terms of energy consumption. It may be that other aspects of the diet that have pro-inflammatory and anti-inflammatory potential could add greater specificity to the diet and contribute towards better understanding of its adverse effects. Moreover, adding other biomarkers or a combination of

Table 3. Univariate and multivariate analyses on the association between the percentage energy contribution towards total energy intake that came from ultra-processed foods (in terciles) and the serum levels of C-reactive protein (CRP), ELSA-Brasil (2008-2010)

Males					
Ultra-processed foods	**Model 0**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
	ARM (95% CI)	**ARM (95% CI)**	**ARM (95% CI)**	**ARM (95% CI)**	**ARM (95% CI)**
Tercile 1 (lowest)	1.00	1.00	1.00	1.00	1.00
Tercile 2	0.95 (0.87-1.03)	0,97 (0.89-1.05)	0.99 (0.91-1.08)	0.98 (0.90-1.07)	0.98 (0.90-1.07)
Tercile 3 (highest)	0.85 (0.77-0.92)*** &	0,88 (0.81-0.96)** &	0.93 (0.85-1.02)	0.93 (0.84-1.02)	0.93 (0.84-1.02)
Females					
Ultra-processed foods	**Model 0**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
	ARM (95% CI)	**ARM (95% CI)**	**ARM (95% CI)**	**ARM (95% CI)**	**ARM (95% CI)**
Tercile 1 (lowest)	1.00	1.00	1.00	1.00	1.00
Tercile 2	1.04 (0.95-1.13)	1.04 (0.96-1.14)	1.07 (0.98-1.17)	1.06 (0.98-1.16)	1.01 (0.93-1.10)
Tercile 3 (highest)	1.08 (1.00-1.17)*&	1.09 (1.01-1.19)*&	1.14 (1.04-1.24)**&	1.14 (1.04-1.24)**&	1.00 (0.92-1.08)

Ultra-processed foods: percentage energy contribution towards total energy intake that came from ultra-processed foods, in terciles.
ARM (95% CI) = arithmetic mean ratio and 95% confidence interval estimated using a generalized linear model.
Model 0 = crude analysis; model 1 = adjusted for age (continuous); model 2 = model 1 + race/skin color and educational attainment; model 3 = model 2 + smoking and physical activity; model 4 = model 3 + body mass index (kg/m^2).
*P-value < 0.05; **P-value < 0.01; ***P-value < 0.001; &P-value < 0.05 for linear trend in the association between the percentage energy from ultra-processed foods (in terciles) and CRP.

inflammatory markers may contribute towards investigation of the association between ultra-processed foods and inflammation.

The strengths of this study include its sample size, the quality of data collection, the possibility of enabling adjustment for a large number of potential confounders and the use of a validated food frequency questionnaire (FFQ). Among its limitations, we emphasize that we used an FFQ that can overestimate consumption, especially given that it contained more than 100 food items.[42] It should also be noted that this FFQ was not designed to assess food consumption based on the level of processing, which may have led to erroneous classification of food items. It is also worth noting that classification of food items based on the level of processing is still a recent concept, and it may be subject to updates and future changes. Another limitation of this study was its cross-sectional design, which made it impossible to establish a temporal relationship between consumption of ultra-processed foods and CRP levels.

CONCLUSION

This study provides a contribution to the recent literature focusing on investigation of the relationship between consumption of ultra-processed foods and metabolic changes, especially those relating to chronic non-communicable diseases. Our findings suggest that there is a positive relationship between ultra-processed foods and CRP levels among women, irrespective of total caloric intake; however, this association appears to be totally dependent on adiposity. Thus, our results indicate that cutting back on ultra-processed foods can decrease chronic low-grade inflammation, even if through reducing obesity. This reinforces the importance of public policies aimed towards restricting the availability of ultra-processed foods.

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Respiratory evaluation through volumetric capnography among grade III obese and eutrophic individuals: a comparative study

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KEY WORDS:
Obesity.
Respiratory function tests.
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ABSTRACT

BACKGROUND: Excess trunk body fat in obese individuals influences respiratory physiological function. The aims of this study were to compare volumetric capnography findings (VCap) between severely obese patients and normal-weight subjects and to assess whether there is any association between neck circumference (NC), waist-hip ratio (WHR) and VCap among grade III obese individuals.

DESIGN AND SETTING: Analytical observational case-matched cross-sectional study, University of Campinas.

METHODS: This cross-sectional study compared VCap variables between 60 stage III obese patients and 60 normal-weight individuals.

RESULTS: In comparison with the normal-weight group, obese patients presented higher alveolar minute volume (8.92 ± 4.94 versus 6.09 ± 2.2; P = < 0.0001), CO_2 production (278 ± 91.0 versus 209 ± 60.23; P < 0.0001), expiratory tidal volume (807 ± 365 versus 624 ± 202; P = 0.005), CO_2 production per breath (21.1 ± 9.7 versus 16.7 ± 6.16; P = 0.010) and peak expiratory flow (30.9 ± 11.9 versus 25.5 ± 9.13; P = 0.004). The end-expiratory CO_2 ($PetCO_2$) concentration (33.5 ± 4.88 versus 35.9 ± 3.79; P = 0.013) and the phase 3 slope were normalized according to expired tidal volume (0.02 ± 0.05 versus 0.03 ± 0.01; P = 0.049) were lower in the obese group.

CONCLUSIONS: The greater the NC was, the larger were the alveolar minute volume, anatomical dead space, CO_2 production per minute and per breath and expiratory volume; whereas the smaller were the phase 2 slope (P2Slp), phase 3 slope (P3Slp) and pressure drop in the mouth during inspiration.

INTRODUCTION

Severely obese subjects develop various respiratory functional abnormalities, which may occur while awake, during sleep or while performing physical effort.[1,2] There are obese individuals who hypoventilate during wakefulness, and this hypoventilation may cause hypoxemia and hypercapnia. These events characterize the diagnosis of alveolar hypoventilation in obese people. Not all severely obese individuals hypoventilate when awake, and the factors that favor this situation are not entirely clear.[3-5] Among the respiratory abnormalities in obese patients that appear during sleep, the most common of these is obstructive sleep apnea caused by obstruction of the air inlet in the upper airway during inspiration.[4,5]

Obese subjects may also have difficulty performing physical effort because the accumulation of fat in the chest and abdomen may hinder the increased ventilation required by physical exertion.[4] Besides alveolar hypoventilation, obese patients can show abnormalities of respiratory patterns even when they are not exercising, and little is known about such patterns.[4,5]

Pulse oximetry and measurement of arterial blood gases during wakefulness make it possible to diagnose situations of obesity hypoventilation syndrome.[4,5] Polysomnography properly detects respiratory functional disorders that occur during sleep (obstructive apnea, central apnea and desaturation).[4] However, spirometry requires physical effort and can show restrictive defects that are not necessarily related to involvement of the lungs. These restrictions may be caused by excessive accumulation of fat in the chest and abdomen that precludes proper spirometry maneuvers, which require physical effort.[6-9]

Volumetric capnography (VCap), which consists of plotting the expired CO_2 concentration against expired volume, is a bedside-validated method for measuring airway and alveolar dead-space volumes, and ascertaining the pulmonary ventilation-perfusion relationships.[6-10] In addition to its application in surgical and anesthetic settings, this method may be used among outpatients with chronic respiratory diseases.[11,12] The examination is performed during spontaneous breathing, and breath-to-breath measurements are collected, including tidal volume, minute volume and end tidal CO_2. Besides these variables, each breath cycle produces a curve called a capnogram that has a shape similar to that of N_2 washout.

Our hypothesis was that VCap might help in understanding abnormalities in respiratory patterns and lung function during rest among obese individuals.[11-14]

The aims of this study were to compare the VCap variables between severely obese patients and normal-weight subjects and to evaluate the existence of any correlation between neck circumference (NC), waist/hip ratio (WHR) and VCap variables among obese patients.

METHODS

This was an analytical observational case-matched cross-sectional study in which the subjects enrolled were grade III obese (body mass index, BMI ≥ 40 kg/m^2) candidates for bariatric surgery at Hospital de Clínicas, University of Campinas (UNICAMP) and normal-weight controls (BMI 18.6-24.9) who were selected from the data bank of the Pulmonary Function Laboratory, UNICAMP. The subjects and controls were aged between 18 and 65 years old and were evaluated between August 2014 and July 2015. The study was approved by the local Research Ethics Committee.

The following potential participants were excluded: active smokers or former smokers who had quit less than one year previously; individuals with chronic respiratory diseases unrelated to obesity; vulnerable groups (individuals who were mentally ill, institutionalized or aged below 18 years); and individuals who opted not to take part in the study. Both the obese and the non-obese participants reported that they did not have any respiratory diseases (current or past) and were not on any respiratory medication.

The individuals selected were matched according to age, gender and height and were divided into two groups: obese (group 1) and non-obese (group 2). In both groups, the variables initially collected and analyzed were age, gender and anthropometric measurements (weight, height and BMI) (**Table 1**).

In the obese group, the variables of NC and WHR were also collected and analyzed. The obese patients also answered the Berlin questionnaire (BQ), which evaluates the risk of development of obstructive sleep apnea syndrome (OSAS). Occurrences of hypertension were assessed in accordance with the Eighth National Joint Committee (JNC 8) criteria, i.e. individuals were considered to present hypertension if at least three different blood pressure measurements were higher than 140/90 mmHg.[15] The presence of type 2 diabetes mellitus (T2DM) was assessed in accordance with the criteria defined by the current guidelines of the International Diabetes Federation (IDF). The presence of T2DM was defined as the presence of any of the following abnormalities: fasting plasma glucose ≥ 126 mg/dl; 75 g oral glucose tolerance test with fasting plasma glucose ≥ 126 mg/dl and/or two-hour plasma glucose ≥ 200 mg/dl; glycated hemoglobin (HbA1c) ≥ 6.5%; or random plasma glucose ≥ 200 mg/dl in the presence of classical diabetes symptoms.[16]

All the participants underwent VCap in the mornings at the Pulmonary Function Laboratory of UNICAMP. The device used was the oxy-capnograph and respiratory profile monitor (CO_2SMOS Plus 8100 Dixtal/Novametrix; Respironics, Murrisville, PA, USA).

VCap is a technique that analyzes the pattern of CO_2 elimination as a function of expired volume. It produces a curve called a capnogram, which represents the total amount of CO_2 eliminated by the lungs during each breath. As would be expected, capnograms have the same shape as other gas elimination curves, with the advantage that they are obtained using a gas that is produced normally by the body and is eliminated by the lungs.[15]

The VCap examinations took about 10 minutes each and were always performed by the same technician. Firstly, the participant was asked to sit in a comfortable position and rest for five minutes while instructions for the examination were provided. Before the examination, the patient was encouraged to drink water to prevent the discomfort that could be caused by mouth breathing

Table 1. Comparison of anthropometric variables between obese patients (group 1) and non-obese subjects (group 2), and data on frequencies of comorbidities, Berlin questionnaire (BQ) results, neck circumference and waist-hip ratio in group 1

	Obese (n = 60)	Non-obese (n = 60)	P-value
Women	45	45	1.0
Men	15	15	1.0
Age (years)*	36 ± 10	36 ± 11	0.92
Weight (kg)*	141 ± 27	67.3 ± 11	< 0.0001
Height (m)*	1.66 ± 0.09	1.66 ± 0.08	0.74
BMI (kg/m^2)*	50.9 ± 7	20.8 ± 3	< 0.0001
NC*	44.1 (4.43)		
WHR*	0.91 (0.11)		
Arterial hypertension	27(55%)		
Diabetes	49 (81%)		
BQ results	High risk 45	Low risk 15	

BMI = body mass index; NC = neck circumference; WHR = waist-hip ratio. *Data presented as mean ± standard deviation. Statistical difference when P < 0.05.

(e.g. dry throat, coughing, etc.). After this, a nose clip was put in place to avoid air escape through the nostrils and the subject was asked to breathe room air regularly through a mouthpiece that he or she held with his or her dominant hand, which was connected to the capnograph sensors. The participant was asked to breathe normally for some seconds to adapt to this situation.

Online digital recording of respiratory cycles was then started (Analysis Plus software), and this continued for five minutes. A pulse oximetry sensor was installed on the index finger. At the end of data collection, an offline sequence of the subjects' respiratory cycles was selected to accommodate variation of < 15% for expiratory tidal volume and < 5% for partial pressure of CO_2 concentration ($PetCO_2$). Furthermore, sequences that showed phases 2 and 3 slopes equal to zero were eliminated, along with outlier values.

Phases 2 and 3 slopes equal to zero can occur because, from time to time, the apparatus used removes the humidity from the sensor and, through this, the parameters are cleared. Outlier values occur because patients who are breathing spontaneously may make different respiratory efforts (e.g. sighing, coughing or speaking, etc.).

The patients were weighed using a digital scale that was appropriate for their size, with a maximum capacity of 300 kg and a resolution of 100 g, and height was ascertained using a wall-mounted stadiometer. From these measurements, BMI in kg/m^2 was calculated.

Waist circumference was determined using a measuring tape around the individual at the natural waist line, i.e. in the narrowest area between the chest and hip, at the midpoint between the last rib and the iliac crest. The readings were made at the end of expiration. Hip circumference was determined in the horizontal plane at the level of the greatest posterior protuberance of the buttocks. The waist/hip ratio (WHR) was calculated using the formula: WHR = waist circumference (cm)/hip circumference (cm). Both of these measurements were made with the patient standing, using a flexible measuring tape. Neck circumference was also measured using a flexible tape at the level of the laryngeal prominence.

Statistical analysis

The baseline characteristics of the sample were presented in frequency tables encompassing the categorical variables, as absolute (n) and percentage (%) frequencies. Continuous variables were presented as mean values with their respective standard deviations (SD). Bivariate analyses on categorical variables were carried out through the chi-square and Fisher's exact tests. For comparisons of continuous measurements, the Mann-Whitney test was used. To study the relationship between the capnography measurements and, respectively, the neck circumference and the waist-to-hip ratio of the obese individuals, Spearman's correlation coefficient was used. The significance level used was 5% ($P < 0.05$). A Bonferroni adjustment was used for pairwise comparisons, to identify the significance within mean differences between correlations for each outcome (Bonferroni adjusted $\alpha = 0.0015625$ for Mann-Whitney comparisons and $\alpha = 0.0045$ for Spearman's correlations). To perform the analyses, the Statistical Analysis System (SAS) software for Windows, version 9.2, was used.

Sample size estimation was performed through a single-proportion formula with a 95% confidence interval. Precision was set at 10% and the calculated sample size was determined to be 60.

RESULTS

In the obese group, there were 45 women (75%) and 15 men (25%). Their mean age was 36 years, mean weight 141 kg, mean height 1.66 m, mean BMI 50.9 kg/m^2, NC 44 cm and WHR 0.91. These two last anthropometric parameters were only measured in the group of obese individuals.

In this group, 27 (55%) had hypertension and 49 (81.7%) were diabetic. In the Berlin Questionnaire, 45 individuals (75%) presented a high risk of having OSAS and 15 (25%) presented a low risk.

In the non-obese group, 45 (75%) were women and 15 (25%) were men, with a mean age of 36 years, mean weight 67.3 kg, mean height 1.66 m and mean BMI 20.8 kg/m^2. **Table 1** summarizes the baseline characteristics of all the patients.

The obese patients presented alveolar minute volume (MV alv) (ml), production of CO_2 per minute (VCO_2) (ml/min), partial pressure of end-tidal carbon dioxide ($PetCO_2$) (mmHg), expiratory volume (Ve) (ml), peak expiratory flow (PEF) (l/min), production of CO_2 per breath (VCO_2/br) (ml/breath) and phase 3 slope normalized according to end-tidal partial pressure of CO_2 (P3Slp/Ve) that were statistically different ($P < 0.05$) from those of the normal-weight controls. After applying the Holm-Bonferroni correction, MV alv (ml) and VCO_2 (ml/min) remained significantly higher in the obese group ($P < 0.0015625$). The capnography variables are shown in **Table 2**.

In the obese individuals, WHR did not present any correlation with VCap measurements. On the other hand, in correlation analyses between NC measurements and capnography variables (**Table 3**), there were significant correlations for the following variables: the greater the NC was, the larger were the alveolar minute volume (MV alv), the anatomical dead space (V_D), the production of CO_2 per minute (VCO_2), the inspiratory volume (Vi), the expiratory volume (Ve), the peak expiratory flow (PEF) and the production of CO_2 per breath (VCO_2/br); whereas the greater the NC was, the smaller were the phase 2 slope (P2Slp), the phase 3 slope (P3Slp) and the pressure drop in the mouth during negative inspiratory pressure (NIP). After applying the Bonferroni adjustment ($P < 0.0045$), NIP, P3Slp and VCO_2/br no longer presented significant correlations, while the other variables remained significant.

DISCUSSION

The obese patients in this study had significantly greater alveolar minute volume (MV alv) and expired volume of CO_2 (average per minute) or VCO_2. These results (greater MV alv with equal respiratory rate) suggest that obese patients possibly have more efficient ventilation during tidal breathing, since the VCap measurements are made during several minutes of quiet breathing. These measurements do not require forced expiration, as spirometry does. Tidal volume and alveolar minute ventilation may be higher in order to match the higher needs of a greater body mass. Nevertheless, the low mean $PetCO_2$ and P3Slp/Ve may indicate that the obese group presented a larger alveolated area. The comparison between the two groups (obese versus non-obese subjects) revealed that there were no statistical differences regarding age and height. The respiratory rate and the dead volume of the airways were similar in the two groups.

The reductions in forced vital capacity that are detected in obese patients through spirometry may, at least in part, be related to the difficulties in using expiratory abdominal muscles due to fat accumulation in this area. The obese patients in the present study did not perform spirometry because this was not part of the study protocol.

Wei et al. found that the lungs of obese patients had higher capacity to diffuse carbon monoxide and attributed this result to the higher blood flow to the lungs that obese subjects may have.[14] However, our results may suggest that their greater capacity for diffusion may be due to a real increase in alveolar surface area.

The peripheral airspaces have been termed the silent lung zone because conventional lung function tests are unable to detect their involvement in disease processes. Inert gases such as helium (He), nitrogen (N_2) and sulfur hexafluoride (SF_6) have been used to study these areas and the elimination curves that they produce during each expiration depict concentrations of the gas at different volumes until all the expiratory volume has been expired. Irrespective of the gas used, all curves have the same shape and, on each of them, three phases can be identified: phase 1, with very low concentrations of the gas, corresponds to the elimination of the air from the anatomical dead space; phase 2, which is generally a steep upward line, represents the growing concentration of the gas that is eliminated from proximal alveolated air spaces; and phase 3, which is almost a plateau line, represents the elimination

Table 2. Distribution of the variables of age, anthropometry and volumetric capnography (VCap) among patients with and without obesity

Variables	Obese			Non-obese			P-value
	Average	SD	Median	Average	SD	Median	
RR (cpm)	14	4.94	14.1	13	3.76	13.4	0.365
HR (bpm)	74	13.7	74.7	77	11.3	76.5	0.198
SpO_2 (%)	97	1.02	97.4	97	0.64	97.8	0.155
VD (aw) (ml)	134	35.5	134	137	28.4	131	0.639
$PeCO_2$ (mmHg)	24.2	3.56	24.3	24	3.49	24.1	0.661
Vi (ml)	760	349	717	622	203	590	0.053
Ti (sec)	1.91	0.66	1.66	1.87	0.56	1.72	0.950
Te (sec)	2.66	0.98	2.46	2.87	0.97	2.81	0.129
PIF (l/min)	35.1	13.3	32.8	31.8	8.7	31.3	0.307
RSBI (VT/RR)	26.4	21.9	21.2	25.7	14.2	23.4	0.430
P2Slp (mmHg/l)	333	156	297	337	82.5	331	0.224
P3Slp (mmHg/l)	10.2	9.19	7.32	10.9	15.0	8.16	0.286
$P3Slp/PetCO_2$ (mmHg)	0.3	0.24	0.24	0.31	0.48	0.23	0.803
NIP (cmH_2O)	-0.36	0.65	-0.05	-0.7	4.27	-0.02	0.243
MV alv (ml)	8.92	4.15	8	6.09	2.2	5.3	**< 0.0001**
VCO_2 (ml/min)	278	91.0	268	209	60.2	199	**< 0.0001**
$PetCO_2$ (mmHg)	33.5	4.88	33.9	35.9	3.79	35.8	**0.013**
Ve (ml)	807	365	763	624	202	587	**0.005**
PEF (l/min)	30.9	11.9	28.6	25.5	9.13	23.3	**0.004**
VCO_2/br (ml/breath)	21.1	9.7	19.3	16.7	6.16	15.7	**0.010**
P3Slp/Ve	0.02	0.05	0.01	0.03	0.09	0.01	**0.049**

RR = respiratory rate; HR = heart rate; SpO_2 = oxygen saturation; VD (aw) = anatomical dead space; $PeCO_2$ = mean end-tidal partial pressure of CO_2; Vi = inspiratory tidal volume; Ti = inspiratory time; Te = expiratory time; PIF = peak inspiratory flow; RSBI = Tobin index; VT = tidal volume; P2Slp = phase 2 slope; P3Slp = phase 3 slope; $P3Slp/PetCO_2$ = phase 3 slope normalized according to end-tidal partial pressure of CO_2; NIP = negative inspiratory pressure; MV alv = alveolar minute volume; VCO_2 = CO_2 production; $PetCO_2$ = end-tidal partial pressure of CO_2; Ve = expiratory tidal volume; PEF = peak expiratory flow; VCO_2/br = CO_2 production per breath; P3Slp/Ve = phase 3 slope normalized according to expired tidal volume. Results are presented as means, medians and standard deviations. P-value for the Mann-Whitney test comparing group 1 (obese) with group 2 (non-obese) after the Bonferroni adjustment; $P < 0.0015625$.

Table 3. Analysis on correlations between neck circumference (NC) and volumetric capnography (VCap) variables among obese individuals (Group 1)

VCap variables	r	P
MV alv (l)	0.43	0.0006
VD (aw) (ml)	0.45	0.0003
VCO_2 (ml/min)	0.48	< 0.0001
Vi (ml)	0.36	0.0045
Ve (ml)	0.36	0.0041
PEF (l/min)	0.40	0.0017
VCO_2/br (ml/breath)	0.34	0.0082
P2Slp (mmHg/l)	-0.38	0.0027
P3Slp /Ve	-0.29	0.0242
PIF (l/min)	0.47	< 0.0001
NIP (cmH_2O)	-0.33	0.0100

MV alv (L) = alveolar minute volume; VD (aw) (ml) = anatomical dead space; VCO_2 (ml/min) = CO_2 production; Vi (mL) = inspiratory tidal volume; Ve (ml) = expiratory tidal volume; PEF (l/min) = peak expiratory flow; VCO_2/br (ml/breath) = CO_2 production per breath; P2Slp (mmHg/l) = phase 2 slope; P3Slp (mmHg/l) = phase 3 slope; PIF (l/min) = peak inspiratory flow; NIP (cmH_2O) = negative inspiratory pressure. P-value results regarding the Spearman correlation test are from correlations between NC and WHR measurements and the VCap variables of the obese individuals, adjusted in accordance with the Bonferroni correction: $P < 0.0045$.

of the gas from most of the alveoli in the lungs. The phase 3 slope (mmHg/l) is an important feature of gas washout curves and contains information about gas transportation in the alveolated airways of the lung periphery. It varies in many pathological conditions of the lungs.[14-21]

Phase 3 (mmHg/l) of the VCap represents the elimination of CO_2 from most of the alveoli and, in normal individuals, it is almost a plateau, with a slight upward slope. The phase 3 slope (P3Slp) should therefore be small.

Because of the very small convective velocities in the lung periphery, gas transportation through diffusion is the dominant mechanism in acinar air spaces. Steepened phase 3 slopes may represent increased diffusional resistance in the peripheral lung. These steepened slopes occur when breathing involves a smaller-than-normal maximum interfacial area between the tidal volume and the functional residual capacity (FRC) during a breathing interval. Small tidal volumes produce steeper slopes because the inhaled air penetrates to shallower-than-normal depths in the lung and therefore encounters smaller-than-normal maximum interfacial areas and longer gas-phase diffusion paths.[22-24] Hence, there is a need to normalize phase 3 slopes when comparing subjects with significantly different expired volumes.[11,12]

In a paper on VCap in children, Ream et al.[25] postulated that the observed decrease in normalized phase 3 slopes of CO_2 washout curves with increasing age was due to an increase in the interface between functional residual capacity (FRC) and tidal volume (VT), with lung growth in children.

It seems that, taking into account the significantly smaller normalized values of phase 3 slopes in obese patients, a hypothesis can be put forward: obese patients may have larger or more efficient alveolated airspaces than do non-obese subjects. The correlations between NC values and capnography variables that were found to be significant are in agreement with the hypothesis put forward here, i.e. that the greater the body mass was (reflected in this analysis by greater NC), the larger were the lungs of the obese subjects who participated in this study.

Human leptin is a 16-kDa protein of 167 amino acids and was the first fat cell-derived hormone to be discovered.[26,27] Leptin is produced primarily in the adipocytes of white adipose tissue. In the fetal lungs, leptin is induced in a special phenotype of alveolar interstitial fibroblasts, called lipofibroblasts, through the action of the parathyroid hormone-related protein (PTHrP), which is secreted by the alveolar epithelium under moderate stretching. The leptin from the mesenchyme, in turn, acts back on the epithelium at the leptin receptor carried in the alveolar type II pneumocytes and induces surfactant expression, which is of paramount importance for lung function.[28-30] Leptin-deficient mice show altered postnatal lung development. They have reduced lung volume and alveolar surface area and the alveolar size does not increase with age.[31]

Leptin levels are paradoxically increased in situations of obesity.[32] Although, as a circulating signal, leptin reduces appetite, obese individuals generally exhibit higher circulating concentrations of leptin than do normal-weight individuals, because of their higher percentage of body fat. The expected responses to high levels of leptin are decreased calorie intake and increased energy expenditure. Most obese humans are probably insensitive to this action by leptin, and behave similarly to type 2 diabetic patients who show resistance to the action of insulin.

The excess leptin present in obese subjects may at least partly explain the apparently larger lungs detected through VCap in these patients. Fat deposits in the neck and abdomen may display a mechanical effect on the chest and may hinder chest mobility during forced expiration and possibly also during spontaneous ventilation, with consequences for lung function. This has also been observed in other studies,[33-37] such as the increased risk of developing lung-base atelectasis in obese individuals due to mechanical compression exerted by the abdomen in the region.[38] Greater NC can cause increased airflow resistance, especially when NC is greater than 40 cm, and this can result in hypoventilation.

None of the obese patients in the present study, whose BMI was greater than 52, had obesity hypoventilation syndrome (OHS), although 45 of them showed a high-risk result from the Berlin questionnaire for obstructive sleep apnea syndrome (OSAS).[39] The scores in the Berlin questionnaire were positively correlated with neck circumference. No sleep studies were available for these individuals.

The hypothesis that these individuals may have had a larger alveolar-capillary membrane might serve as a possible reason for the absence of CO_2 retention. Recent reports have shown that alveolar growth continues from childhood into adolescence in humans and other mammals.[33-35] The lungs of obese patients who were obese children may have been exposed to higher levels of leptin during a period when the alveoli were actively growing. Obesity hypoventilation syndrome might perhaps be more commonly found among obese subjects whose weight gain occurred later in life, a hypothesis that awaits further investigation.

Ferreira et al.[40] analyzed obese and normal-weight children without asthma and reported that the obese children had greater lung volumes, shown through volumetric capnography, and lower values for the ratio between the phase 3 slope of the volumetric capnogram and the expired volume (P3Slp/Ve). These findings were consistent with the results obtained by Ream et al.[25] who evaluated infants, children and adolescents and found lower values for P3Slp in individuals with higher Ve, and a negative association between P3Slp, body weight and body surface area. Growth increased the number of alveoli in the lungs and reduced the phase 3 slope on capnograms. The obese children in the study by Ferreira et al. seemed to have larger lungs.

Limitations and strength

This study has some limitations. Carbon monoxide diffusion was not performed on the patients of the present study because we did not have the equipment to do this. This measurement could have helped to rule out alterations in carbon monoxide diffusion as the cause of our findings. The NC and WHR data relating to the controls were not available because the data were collected from a database. Spirometry data were not available because the obese patients were in the process of losing weight and would undergo spirometry after achieving a predetermined goal. It was not possible to evaluate whether exposure to toxic agents such as tobacco might have influenced respiratory function in the two groups, since we did not have this information in the database relating to the non-obese group.

Our findings may contribute towards understanding the complex range of alterations to respiratory function that are seen in very obese patients. They also raise the intriguing possibility that some obese individuals may undergo changes to the alveolar-capillary membrane that enable greater efficiency of CO_2 elimination. Knowing the leptin levels in these patients might have contributed towards investigating this hypothesis.

CONCLUSION

Volumetric capnography was capable of detecting particular characteristics of lung structure and function in morbidly obese patients, among which some had not previously been shown. It identified changes to various respiratory parameters, in comparison with a normal-weight control group. The greater the NC was, the larger were the alveolar minute volume, anatomical dead space, CO_2 production per minute and per breath and expiratory volume; whereas the smaller were the phase 2 slope (P2Slp), phase 3 slope (P3Slp) and pressure drop in the mouth during inspiration. Some of these changes were related to possibly larger lungs in obese patients and others to their larger NC. The combination of larger lungs and absence of hypoventilation makes us speculate that these two occurrences may be linked.

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What do Cochrane systematic reviews say about telemedicine for healthcare?

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KEY WORDS:
Telemedicine.
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Telephone.
Delivery of health care.

ABSTRACT

BACKGROUND: Telemedicine has emerged as a tool for overcoming the challenges of healthcare systems and is likely to become increasingly viable, since information and communication technologies have become more sophisticated and user-friendly.

OBJECTIVE: We aimed to identify all Cochrane systematic reviews (CSRs) on telemedicine within healthcare and to summarize the current evidence regarding its use.

DESIGN AND SETTING: Review of CSRs, developed at the Discipline of Emergency and Evidence-Based Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo.

METHODS: We searched for studies that compared use of telemedicine with conventional treatment or management of diseases within healthcare. Diagnostic telemedicine studies or studies using automatic text, voice-text or even self-managed care were excluded. The main characteristics and the certainty of evidence were synthetized and critically discussed by all authors.

RESULTS: We included 10 CSRs that investigated a broad range of diseases. There is still insufficient evidence to determine what types of telemedicine interventions are effective, for which patients and in which settings, and whether such interventions can be used as a replacement for the standard treatment. Harm relating to telemedicine technologies needs to be better investigated and addressed.

CONCLUSION: Telemedicine might be an excellent way to facilitate access to treatment, monitoring and dissemination of important clinical knowledge. However, given the recognition of systematic reviews as the best evidence resource available for decision-making, further randomized controlled trials with stricter methods are necessary to reduce the uncertainties in evidence-based use of telemedicine.

INTRODUCTION

Telemedicine is the use of information and communication technologies to provide healthcare services, especially when distance is a critical factor in accessing the healthcare provider.[1] Since 1879, the year in which the first medical telephone consultation was documented in an article published in the Lancet journal,[2] telemedicine and its use as a tool for improving healthcare have been continually expanding.

Although telemedicine is not a novel activity, it has over the past few years emerged as an alternative tool for addressing the challenges of universal healthcare systems, such as expansion of access to specialized healthcare services in regions that lack these resources.[3] This type of technology not only has the direct impact of improving access to treatment but also positively affects the environment while decreasing emissions of pollutants through reduction of staff and patients' need to travel. This is favored through remote care,[4] given that the physical distance between the patient and the provider of the intervention always exists.[5]

Telemedicine provides a virtual environment that enables remote interaction between healthcare professionals and their patients, and among healthcare professionals themselves. This particular characteristic, which goes beyond conventional standards, changes paradigms and has ethical and legal implications in each country where it is used, especially in relation to the confidentiality of patients' data.[6] The role of telemedicine within healthcare professionals' continuing education, research and evaluation is emphasized. This not only improves healthcare access for patients but also enables access to high-quality information for healthcare professionals located in remote settings.[7]

In the United States, it has been estimated that more than a quarter of consultations are undertaken through telephone calls.[8] Telemedicine has been evolving and progressing through the

advent of mobile phone applications such as Doctor On Demand, HealthTap and Pingmd.

The territorial extent of Brazil is huge, with thousands of isolated, difficult-to-access places and unequal distribution of good-quality medical resources. These characteristics put the right to universal, comprehensive and equitable healthcare services at risk and indicate that there is great potential for expansion of telemedicine in this country.[1] On the other hand, the benefits and harm relating to its use have not yet been established.

OBJECTIVE

The aim of this study was to identify all Cochrane systematic reviews (CSRs) on telemedicine within healthcare and to summarize the current evidence regarding its use.

METHODS

Design

Review of Cochrane systematic reviews (SRs).

Setting

Discipline of Urgency and Evidence-Based Medicine, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), Brazil.

Criteria for including reviews

Types of studies

We considered the latest versions of the published Cochrane SRs. We did not include any protocols or any SRs that had been withdrawn from the Cochrane Database of Systematic Reviews.

Types of participants

We considered all patients who made use of any category of telehealth intervention, without any restriction relating to type of intervention or the age or sex of the participants.

Types of interventions

We considered any category of telemedicine intervention for treatment or management of diseases within healthcare. We excluded studies that assessed the effect of telemedicine for diagnostic purposes or studies that used automatic text or voice-text or even self-managed care.

Types of outcomes

We considered any outcomes that had been assessed and reported by the authors of the SRs included.

Search strategy

We conducted an unrestricted systematic search within the Cochrane Database of Systematic Reviews (via Wiley) on February 26, 2019. The search strategy is presented in **Table 1**.

Selection of systematic reviews

The selection phase consisted of reading of all the abstracts retrieved, by three researchers independently (APR, ACPNP, KMM), to check their eligibility in relation to the inclusion criteria. Any disagreement was resolved through reaching a consensus among these three authors or by consulting a fourth author (CDQF).

RESULTS

Out of the 326 reviews that had been included in the primary analysis, we selected 10 SRs (published between 2011 and 2016) containing data on 53 randomized controlled trials (RCTs) with 6,836 participants, which had assessed the effectiveness and safety of telemedicine within healthcare. These SRs addressed the effects of telemedicine regarding heart-failure patients (n = 1),[7] chronic obstructive pulmonary disease (n = 1),[9] treatment and management of asthma (n = 2),[10,11] low vision (n = 1),[12] multiple sclerosis (n = 1),[13] stroke (n = 1),[14] parents of high-risk newborns (n = 1),[15] HIV patients (n = 1),[16] and children and adolescents with chronic pain (n = 1).[18] The main results are shown in **Table 2**.

Home telemonitoring and remote feedback for asthma

This review[11] included 18 parallel RCTs with a total of 2,268 participants. The results from this review showed that there was no difference between home telemonitoring and the usual monitoring relating to exacerbations that would require use of oral corticosteroids (odds ratio [OR] 0.93; 95% confidence interval [CI] 0.60 to 1.44; 466 participants; four studies; $I^2 = 0\%$; low quality of evidence). In relation to exacerbations requiring hospitalization, there was uncertainty regarding the benefit or harm, compared with the standard monitoring procedure (OR 0.56; 95% CI 0.21 to 1.49; 1,042 participants; 10 studies; $I^2 = 45\%$; moderate quality of evidence).

Overall, the evidence relating to asthma control was very weak due to the inconsistency of outcomes. The patients in the

Table 1. Search Strategy in Cochrane Library

Cochrane Library (26/02/2019)
#1 Mesh: [Telemedicine] = 1,982
#2 (Mobile Health) OR (Health, Mobile) OR mHealth OR Telehealth OR eHealth = 4,596
#3 #1 OR #2 = 5,946
#4 #3 in Cochrane Reviews = **326**

Table 2. Characteristics of studies included

Intervention	Comparison	Population	Benefits and harms	Certainty of evidence
Telehealthcare with input from a professional[9]	Standard care	Patients of any age, gender, ethnicity or language with COPD diagnosed by a clinician (n = 1,004)	– Total number of exacerbations recorded showed borderline statistical significance – Significantly fewer episodes of exacerbation per month. – Number of days free from exacerbations after one year was higher within the intervention group (30%) – There was a minimally clinically significant change regarding quality of life. – Fewer visits to the emergency service – Lower hospital admission rate – No difference in mortality rate between the groups.	– not assessed
Remote check-ups for asthma[10]	Standard check-up	Adults or children with asthma (n = 2,100)	– Greater need for oral corticosteroid intake in comparison with the control group – Fewer exacerbation than in face-to-face check-up group. – No difference in score relating to the Asthma Control Questionnaire – Lung function improvement (reported in one study) – Higher number of serious adverse events reported. Exacerbation requiring hospital admission was the most frequent of the events – Quality of life score similar to that of the control group (Asthma Quality of Life Questionnaire)	– low level – low level – moderate level – moderate level – not assessed – not assessed
Home telemonitoring and remote feedback between clinic visits for asthma[11]	Standard care	Adults or children with a diagnosis of asthma (n = 2,268)	– Number of episodes of exacerbation requiring oral corticosteroids was similar to that of standard care – No difference between telemonitoring and usual monitoring, regarding exacerbations requiring hospital admission – Improvement in the asthma quality of life score – Improvement of lung function – Telemonitoring did not lead to any clear increase or decrease in the number of unscheduled healthcare visits	– low level – moderate level – low level – moderate level – very low level
Telerehabilitation[12]	Standard rehabilitation	People with low vision or visual function loss due to any ocular condition	– Not assessed (no studies included)	– not assessed
Telerehabilitation[13]	Standard rehabilitation	Patients diagnosed with multiple sclerosis (> 18 years old) (n = 531)	– Reduction of short-term disability and symptoms such as fatigue – Long-term improvement in functional activities and impairments (such as fatigue, pain and insomnia) – Social re-integration measured through quality of life and psychological outcomes. – No adverse events relating to telerehabilitation were reported	– low level
Telerehabilitation[14]	Standard care	Patients diagnosed with stroke (n = 933)	– No difference in independence regarding activities of daily living and upper-limb function. – Insufficient data to draw conclusions regarding the effects of the intervention on mobility, health-related quality of life or participant satisfaction. – No adverse events relating to telerehabilitation were reported.	– not assessed
Baby Carelink[15]	Standard care	Parents of high-risk newborns in NICU (n = 56)	– No difference between groups regarding the length of hospital stay	– very low
Interventions delivered by telephone[16]	Standard care	HIV-infected patients (n = 1,381)	– No difference in adherence to antiretroviral medication – No difference in depressive symptoms	– low quality – low quality
Non-invasive telemonitoring[17]	Standard care	Patients with heart failure (n = 3,860)	– Reduction in all-cause mortality rates – Reduction in heart failure-related hospitalizations – No difference in reduction of risk of all-cause hospitalizations	– moderate level – moderate level – very low level
Structured telephone[17]	Standard care	Patients with heart failure (n = 9,332)	– Reduction in all-cause mortality rates – Reduction in heart failure-related hospitalizations – No difference in reduction of risk of all-cause hospitalizations	– moderate level – moderate level – very low level
Psychological therapies delivered remotely[18]	Face-to-face psychological therapy or waiting list	Children and adolescents (0 to 18 years old) with chronic pain (n = 371)	– Severity of headache pain reduced post-treatment – Pain intensity reduced post-treatment in mixed pain conditions (i.e. recurrent abdominal pain or musculoskeletal pain) – At follow-up: no difference in headache conditions – No difference in depression in headache group	– not assessed

NICU = neonatal intensive care unit; COPD = chronic obstructive pulmonary disease; n = number of participants.

telemedicine groups scored better in the Asthma Quality of Life Questionnaire than did those who were monitored using standard protocols (median difference [MD] 0.23; 95% CI 0.01 to 0.45; 796 participants; six studies; I^2 = 54%; low quality of evidence). Adverse events, whether serious or non-serious, were not reported in any of the studies included in this review. Small benefits regarding quality of life were observed, although the studies were unblinded. Some benefits regarding lung function were reported, but the effects were uncertain due to possible attrition bias.

The quality of evidence was downgraded by the SR authors because of imprecision, inconsistency, publication bias and the risk of bias. The authors of the review[11] concluded that the current evidence did not support widespread implementation of telemonitoring, with feedback between visits to asthma clinics.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011714.pub2/full.

Remote check-ups for asthma

Six RCTs with 2,100 participants were included in this review.[10] These RCTs compared remote check-ups using various forms of telehealth technology (telephone calls or video-conferencing) versus standard face-to-face check-ups. The results from a cluster study and an oral steroid tapering study were also included, but they were reported separately.

The effects from use of telehealth among people who required oral corticosteroids to treat exacerbations were greater in the telehealth group than in the control group, although the confidence intervals were very wide due to the small number of events (OR 1.74; 95% CI 0.41 to 7.44; 278 participants; low quality of evidence). Moreover, the cluster study showed that there were positive effects in the face-to-face check-up groups (OR 1.43, 95% CI 1.04 to 1.97).

The effect of exacerbation events that needed emergency department visits favored the face-to-face check-up groups, but this was uncertain due to the small number of events (OR 2.60; 95% CI 0.63 to 10.64; 651 participants; three studies; low quality of evidence). However, neither the RCTs (Peto OR 0.63; 95% CI 0.06 to 6.32; 651 participants; three studies; low quality of evidence) nor the cluster implementation study (Peto OR 2.18; 95% CI 0.83 to 5.69; 1,213 participants; one study) showed any statistically significant benefits, compared with face-to-face check-ups, regarding exacerbations that required hospital admission.

The authors of this review reported that there were no differences relating to the scores obtained in the Asthma Control Questionnaire between the remote and face-to-face groups (MD 0.07; 95% CI −0.35 to 0.21; 146 participants; one study; moderate quality of evidence). There were no differences between the two groups regarding asthma-related quality of life, as determined through the Asthma Quality of Life Questionnaire (MD 0.08; 95% CI −0.14 to 0.30; 544 participants; three studies; moderate quality of evidence).

The results relating to unscheduled healthcare visits were imprecise with few events and, therefore, it was impossible to draw a conclusion. Lung function assessed by means of forced expiratory volume in the first second (FEV1) was only reported in one study. The authors of this review[10] identified enhancement of lung function in the remote check-up group, compared with the face-to-face group (MD 166.76; 95% CI 78.03 to 255.50; 253 participants; one study; moderate quality of evidence). No adverse events, whether serious or non-serious, were recorded in any of the studies included in this review.

All the available evidence was based on small RCTs. Outcomes relating to lung function, asthma control and exacerbations requiring oral corticosteroids were only reported in one study. The evidence was downgraded by the SR authors to moderate quality regarding asthma-related quality of life and asthma control because of the lack of blinding of the participants and outcome assessments. The evidence regarding the lung function was downgraded because of imprecision relating to the small sample size. The data on the other outcomes were of low quality due to the wide CIs, small number of events and risk of bias.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011715.pub2/full.

Telehealthcare for chronic obstructive pulmonary disease (COPD)

This review[9] included 10 RCTs comparing telehealth with the usual care among 1,004 patients who had been diagnosed with COPD.

Total number of exacerbations was only analyzed in one RCT, with borderline statistical significance (P = 0.06). In another trial, it was reported that the mean number of exacerbations per month was significantly higher among the controls than in the telehealthcare group (0.78 ± 0.77 and 0.23 ± 0.38, respectively; P < 0.0001). The number of days that were free from exacerbation after one year was higher in the intervention group (30%) than in the control group (5%).

Quality of life was assessed through scores from the validated St George Respiratory Questionnaire (SGRQ), and improvement of quality of life showed slight clinical significance with very wide confidence intervals (MD -6.57; 95% CI -13.62 to 0.48; 253 participants; two studies). The patients who received telehealthcare were much less likely to attend the emergency department than were the individuals in the control group (OR 0.27; 95% CI 0.11 to 0.66; 449 patients; three studies), and the number of patients with one or more hospital admissions was lower in the telehealthcare group (OR 0.46; 95% CI 0.33 to 0.65; P < 0.00001; 604 patients; four studies). There was no difference in mortality rate between the

groups (OR 1.05; 95% CI 0.63 to 1.75; P = 0.86; 503 patients; three studies). There were no differences between the groups regarding lung function or patient satisfaction. The authors of this review encouraged support for telehealthcare, even though the evidence came from very heterogeneous studies.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007718.pub2/full.

Telerehabilitation for people with low vision

This review[12] did not find any RCTs that had evaluated the effectiveness and/or safety of telerehabilitation for people with low vision. However, given the growing interest in telemedicine and the burden of low vision, it was recommended that pilot studies should be conducted in the future in order to explore the potential for telemedicine to provide rehabilitation for people with low vision.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011019.pub2/full?highlightAbstract=telerehabilit%7Cwithdrawn%7Ctelerehabilitation.

Telerehabilitation for patients with multiple sclerosis

This review[13] included nine RCTs (n = 531 participants) that assessed a wide variety of telerehabilitation methods among adults with multiple sclerosis. The patients' ages ranged from 41 to 52 years (mean of 46.5 years). The mean number of years since the patients received their diagnosis ranged from 7.7 to 19 years (mean of 12.3 years).

The telerehabilitation interventions included physical activity and educational, behavioral and symptom management programs. The duration of the interventions ranged from one to six months (median of 12 weeks). The main outcomes evaluated were the following: functional activities; improvement in symptoms or impairments (pain, fatigue, spasms frequency, spasticity and others); quality of life; and psychosocial outcomes.

No quantitative analysis could be conducted in this review,[13] due to clinical and methodological heterogeneity. Overall, the review found that there was a low level of certainty regarding telerehabilitation interventions for reducing short-term disability and symptoms, such as fatigue in patients with multiple sclerosis. In longer-term follow-ups, there was also a low level of certainty regarding telerehabilitation for improving functional activities and impairments (such as fatigue, pain and insomnia); and regarding participation, as measured in terms of quality of life and psychological outcomes. Regarding safety, the studies included did not report any adverse event relating to telerehabilitation.

Multiple sclerosis is a complex condition and the range of telerehabilitation interventions and their prescription requirements can vary from person to person and are difficult to standardize. Factors such as the patients' functional abilities, personal characteristics and comorbidities and the characteristics of the healthcare system may influence patients' outcomes. The interaction of these factors with rehabilitation strategies and their impact on patients' outcomes is still little understood. However, because the multiple sclerosis population is young and has high rates of internet use, these patients are likely to be receptive to telerehabilitation.

In addition to the limited number of studies in this review and the high heterogeneity among these studies, methodological weaknesses were identified in them (underpowered data due to small sample sizes, high risk of bias, short follow-up periods, lack of rigorous methodology and differences in outcome measurements).

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010508.pub2/full?highlightAbstract=telerehabilit%7Cwithdrawn%7Ctelerehabilitation.

Telerehabilitation for stroke

Ten RCTs (n = 933) were included in this review.[14] Regarding age, the patients were in their 50s to 70s. All interventions were delivered in the patients' own homes. The patients were generally in the chronic phase following a stroke.

The telerehabilitation interventions included use of telephones, videoconferencing hardware and software, desktop videophones, in-home messaging devices, video recordings, emails, online chat programs and online resource rooms. The intervention approaches included upper limb training, lower limb and mobility retraining, case management and caregiver support. Several outcomes were evaluated, such as physical function, independence in activities of daily living, quality of life and participant satisfaction.

Pooled data from 661 participants did not show any statistically significant results regarding independence in activities of daily living when a case management intervention was evaluated (standardized mean difference [SMD] 0.00; 95% CI -0.15 to 0.15). No statistically significant results regarding upper limb function (based on two studies with 46 participants: MD 3.65; 95% CI -0.26 to 7.57) were observed when computer software was used to remotely retrain upper limb function.

Insufficient evidence was found to draw any conclusions regarding the effects of the intervention on mobility, health-related quality of life or participant satisfaction with the intervention. No adverse events were reported within the studies.

Overall, telerehabilitation offers great potential as an intervention to be used in addition to current therapies or as a therapy for patients with difficulty in accessing places where face-to-face rehabilitation can be provided. However, it is still important to investigate whether there are any differences in the same therapy between delivery face-to-face and delivery via telecommunication.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010255.pub2/full?highlightAbstract=telerehabilit%7Cwithdrawn%7Ctelerehabilitation.

Telemedicine for supporting parents or caregivers of high-risk newborns while hospitalized in an intensive care unit

The aim of this review[15] was to assess the effects of use of telemedicine (Baby Carelink) to support the families of newborns, regarding the newborn's length of hospital stay and the family's satisfaction while the newborn was hospitalized in an neonatal intensive care unit (NICU), compared with those that received standard care without access to this telemedicine program. The study included one RCT (n = 56 newborn infants). The Baby Carelink program consisted of use of multimedia and videoconference devices that provided the families with the infant's daily clinical progress and also enabled provision of clinical information, communication through a message center, release preparation, viewing of the infant and a family room.

The results from the review showed that the lengths of hospital stay were similar in the telemedicine group (68.5 days; standard deviation [SD] 28.3 days) and the control group (70.6 days; SD 35.6 days; MD -2.10 days; 95% CI -18.85 to 14.65 days). The quality of the evidence was very low due to the small sample size and imprecision of the effect estimates.

The participants formed a very specific group: families living within the urban area, with good internet access, who were competent in English and had higher economic status than other possible candidates. There was a withdrawal rate of 20% within the control group, since these newborns were transferred back to level-2 nurseries. The data regarding family satisfaction and other outcomes were insufficient for conducting proper analysis.

Thus, so far, there is not enough evidence to promote use of telemedicine to support parents or caregivers of newborns receiving intensive care as an effective procedure. However, this study dates back to the year 2000 and many technological resources have been developed since then. For this reason, we cannot rule out the idea that application of telemedicine to this kind of population now could have a different outcome.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006818.pub2/epdf/full.

Telephone-delivered interventions for HIV-infected patients:

The aim of this review[16] was to assess the effectiveness of interventions delivered by telephone, compared with standard care for HIV-infected patients. It included 11 RCTs, with 1,381 participants.

The main findings were that there were no differences between the intervention and control groups regarding adherence to antiretroviral medication, with low quality of evidence (3 studies; 191 participants; SMD 0.49; 95% CI -1.12 to 2.11; P = 0.55), or regarding depressive symptoms, also with low quality of evidence (3 studies; 447 participants; SMD 0.02; 95% CI -0.18 to 0.21; P = 0.85). In relation to all other information (reduction of risky sexual behavior, virological outcomes and psychiatric symptoms other than depression), there was insufficient data to provide meta-analyses.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009189.pub2/full.

Structured telephone support or non-invasive telemonitoring for patients with heart failure

This review[17] addressed how telemonitoring and structured telephone support could help patients with heart failure in relation to undesirable outcomes such as hospitalization and death. The difference between these two interventions lay in the manner in which they were used: structured telephone support only used the technology of transmission by telephone to collect patient data; while telemonitoring involved multiple ways of transmission, such as Bluetooth, satellite and wireless technologies. For this review, 25 studies evaluated structured telephone support interventions (9,332 participants) and 18 studies assessed non-invasive home telemonitoring (3,860 participants).

The main findings from this review regarding non-invasive telemonitoring were that it gave rise to reductions in the all-cause mortality rates (17 studies; 3,740 participants; relative risk [RR] 0.80; 95% CI 0.68 to 0.94; P = 0.0057); and reductions in heart failure-related hospitalizations (8 studies; 2148 participants; RR 0.71; 95% CI 0.60 to 0.83; P = 0.000013). Structured telephone support also reduced all-cause mortality (22 studies; 9,222 participants; RR 0.87; 95% CI 0.77 to 0.98; P = 0.017) and had a positive impact regarding reduction of hospitalizations caused by heart failure (16 studies; 7,030 participants; RR 0.85; 95% CI 0.77 to 0.93; P = 0.00047). All of these outcomes were graded as presenting moderate quality of evidence.

This review did not show any difference regarding reduction of the risk of all-cause hospitalizations, (structured telephone support: 16 studies; 7,216 participants; RR 0.95; 95% CI 0.90 to 1.00; P = 0.055; and non-invasive telemonitoring: 13 studies; 3,332 participants; RR 0.95; 95% CI 0.89 to 1.01; P = 0.033), with very low quality of evidence. The outcomes of length of stay, quality of life related to the health condition, cost effectiveness and treatment adherence were not described consistently, which hindered development of a meta-analysis. The funnel plot analyses demonstrated that there was strong evidence of publication bias.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007228.pub3/full.

Psychological therapies (remotely delivered) for management of chronic and recurrent pain in children and adolescents

This review[18] examined the effectiveness of treatments performed remotely (via the internet, telephone and audiotapes, among other methods), in comparison with face-to-face psychological therapy or waiting-list control in a population from 0 to 18 years of age with chronic and recurrent pain. It included 8 studies, with 371 participants.

The severity of headache pain was reduced through remote psychological treatments (6 studies; 247 participants; RR 2.65; 95% CI 1.56 to 4.50; P = 0.00030; number needed to treat to benefit [NNTB] 2.88). For mixed pain conditions, i.e. musculoskeletal pain or abdominal pain with recurrence, there was a beneficial effect regarding reduction of pain intensity post-treatment (3 studies; 131 participants; standardized mean difference [SMD] -0.61; 95% CI -0.96 to -0.25; P = 0.00074).

At follow-up, however, no statistical difference in headache conditions was achieved (3 studies; 85 participants; RR 1.56; 95% CI 0.67 to 3.68; P = 0.30). This was also observed regarding the outcome of depression, when analyzed in the same headache groups (2 studies; 103 participants; SMD 0.02; 95% CI -0.38 to 0.43; P = 0.91). For headache and mixed conditions, there were no beneficial effects from the therapies included as interventions in this review (2 studies; 94 participants; SMD -0.50; 95% CI -1.02 to 0.02; P = 0.06). No data were available in relation to any other outcomes, or in relation to adverse events.

The authors of this review did not use GRADE (the grading of recommendations, assessment, development and evaluations recommended by Cochrane) in the assessment of risk of bias because of the lack of information in the studies included. However, they classified most of the studies as presenting "low risk" or "unclear risk" of bias.

For further details, the full content of this review can be accessed through: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011118.pub2/full.

DISCUSSION

The use of telemedicine is likely to become increasingly viable as information and communication technologies within healthcare become more sophisticated and user friendly. The driving force behind this is the need for an alternative to face-to-face interventions that enables service delivery in the natural environment, i.e. in patients' homes.

For pulmonary care, telemedicine has become an important alternative to the standard care. Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide.[19,20] Moreover, it has been estimated that around 300 million people around the world are affected by asthma. Thus, there is a need to explore the available evidence regarding the benefits or harm from telemedicine care. Telemedicine seems to reduce hospitalization and emergency department visits, and it possibly has an impact on the quality of life of patients with COPD.[21,9]

Telerehabilitation is an emerging method that extends rehabilitative care beyond the hospital, using telecommunication technology at home or in the community.[22] Overall, a wide range of telerehabilitation methods have been studied, but the evidence for their effectiveness remains unclear. In this review, we found that the telerehabilitation interventions evaluated were complex, with various rehabilitation components that included physical activity and educational, behavioral and symptom management programs. These interventions had different purposes and used different technologies, and therefore no single definitive overall conclusion was possible.

We also performed a broad search in the Medline database via PubMed on March 12, 2019, in order to find other reviews. The PubMed search strategy is provided in **Appendix A**. Our search retrieved 1,274 reviews. We looked for SRs on asthma, chronic obstructive pulmonary disease, stroke, low vision, multiple sclerosis, parents of high-risk newborns, HIV patients, heart-failure patients or children and adolescents with chronic pain, in order to make comparisons with our Cochrane database findings.

In general, the Cochrane reviews had broader searches and identified greater numbers of randomized trials than were described in other reviews[23,24] published within the same period as the Cochrane SRs (2011-2016). However, it seems that the Cochrane and non-Cochrane reviews came to similar conclusions: namely, that the evidence is currently insufficient to draw any conclusions regarding the effectiveness of telemedicine.[25] Nonetheless, a recent review (found in Medline) that was published after 2016 showed that telemedicine was a promising alternative tool for improving motor function in patients who had suffered a stroke.[26]

Furthermore, although the purpose of telemedicine is to reduce costs and overcome some barriers such as availability of transportation, hospital costs and ability to make visits to healthcare professionals, no Cochrane reviews have identified any trials on its cost-effectiveness. Establishment of telemedicine services can be expensive due to the costs of equipment, training and ongoing technical support. Therefore, it is important to determine whether, once telemedicine services have been established, they should be used as an alternative or as a supplement to the conventional therapy that is delivered face-to-face.

It is also relevant to note that the use of technology to facilitate communication may, on the other hand, lead to miscommunication. For example, healthcare professionals may make errors relating to their assessments of patients, or these patients may misunderstand the advice or instructions provided by the healthcare professional. Therefore, not only the benefits, but also the harm associated with telemedicine needs to be addressed.

Overall, there is still insufficient evidence regarding what types of telemedicine interventions are effective, and for which patients in which setting. Here, we can also highlight the lack of robust, methodologically strong studies evaluating the effectiveness of the different technologies relating to telemedicine interventions. Researchers should ensure that trials are adequately powered, developed with high methodological quality and reported in compliance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

CONCLUSION

In the data universe of the Cochrane Library, we found 10 Cochrane systematic reviews relating to the use of telemedicine within healthcare. The quality of the evidence reported was too low to support or refute the use of this technology within clinical practice as an effective intervention for replacement of standard treatment. The best evidence available was of moderate quality, relating to the effectiveness of telemedicine among patients with heart failure, for reducing the risks of heart failure-related hospitalization and all-cause mortality.

Given the growing interest in telemedicine and the recognition of the Cochrane Library as the best evidence resource available for decision-making, further RCTs with stricter methods are necessary in order to address many structured clinical questions and inform better systematic reviews. Such RCTs will be able to evaluate the efficacy, effectiveness, efficiency and safety of telemedicine. In this manner, the uncertainties regarding the therapeutic, managerial, ethical and economic aspects of evidence-based telemedicine could be reduced. Moreover, telemedicine may be an excellent way to facilitate access to treatment and monitoring and to disseminate important clinical knowledge among healthcare professionals.

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Appendix A. MEDLINE via PubMed search strategy

(((“Telemedicine”[Mesh]) OR (mobile health) OR (health, mobile) OR telehealth OR ehealth))) AND ((((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE[subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt])

Objective structured teaching examination (OSTE): an underused tool developed to assess clinical teaching skills. A narrative review of the literature

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Education, medical.
Educational measurement.
Professional competence.

ABSTRACT

BACKGROUND: There are plenty of options for evaluating medical students and medical residents' clinical skills. Objective structured clinical evaluations (OSCEs) have emerged as a powerful and reliable tool for assessing multiple cognition domains of clinical expertise. In the same way as OSCEs have emerged to assess clinical skills, objective structured teaching evaluations (OSTEs) have come to light as promising and unbiased interventions for evaluating the act of clinical teaching.

DESIGN AND SETTING: Narrative review developed at Universidade Federal de Uberlândia, Brazil.

METHODS: We searched the literature regarding OSTEs using the MEDLINE (via PubMed) and LILACS (via Biblioteca Virtual em Saude) databases. The SciELO library was also searched for Brazilian papers. Systematic reviews, reviews and randomized controlled trials specifically assessing how OSTEs performed in relation to development of academic staff and medical residents were then selected.

RESULTS: Our search retrieved 178 papers, of which 40 were considered eligible for intensive review. Most of the studies selected reported positive effects from OSTE activities. However, there was little quantitative data to gauge the impact of OSTEs on improvement of teaching skills.

CONCLUSIONS: Considering that OSCEs have become a widely used tool for assessing medical students' and residents' clinical skills, it is high time to incorporate OSTEs for evaluating teaching skills in Brazil. Encouraging data to support implementation of this assessment tool in this country is available from abroad. The net benefit from this would possibly encompass medical students, residents and academic staff, through bringing awareness about the importance of excelling in teaching skills.

INTRODUCTION

Teaching is a complex activity for which multiple methods are needed in order to properly evaluate it. Teaching performance can be directly examined and students' results can be highlighted. All assessment methods have their strong and weak points and any method used in isolation will provide an incomplete image of academic staff members' teaching skills.

Goe et al.[1] described five measurable aspects of teaching efficacy. They asked whether the teaching was doing the following: (1) helping with learning; (2) contributing towards enhancement of academic, social and attitudinal performance; (3) using multiple resources to engage students in learning opportunities; (4) promoting civic values and respect for diversity; and (5) collaborating with the institution, peers and families to help students succeed, particularly those with a higher chance of failing.

The method most used for assessing the act of teaching comprises direct observation of the activity. This can be done by directors, other academic staff members (supervisors) or external evaluators (locally or with the aid of video-recorded performances). These evaluations are, in general, more time and resource-consuming than are estimates centered on tests that are based on teaching efficacy, such as national and international examinations on students' performance. Standardized tests provide a more economical and efficient way of making reliable measurements of the content acquired by students.[2]

Evaluations are routine events in the lives of university students worldwide. Their methods take different shapes, but one of the methods within medical education consists of assessments of simulated situations that have been developed specifically to assess clinical skills. Since the famous neurologist Howard Barrows[3] used trained actors to evaluate his residents' examination

skills in a simulated environment in the 1960s, use of this assessment method has spread fast in the academic community.

Nowadays, medical schools are not alone in using simulated events. Training courses for a wide diversity of careers, especially health-related courses, have embraced this resource as a means of evaluation.

The authors of the present narrative review are working on the development of residents as teachers, using OSTE as a means of evaluation. Considering the need for refinement in academic staff development and the importance of medical residents' teaching skills awareness, we judged it to be of utmost interest to introduce, report on and disseminate the concept of assessment of clinical teaching skills. In this paper, we describe the main evidence that provides support for implementing the OSTE method as an objective, summative and formative tool.

OBJECTIVE

The main objectives of this narrative review were to introduce the concept of evaluating the act of teaching, through systematic observation of a simulated activity; and to summarize the evidence that provides support for dissemination of the "objective structured teaching examination/evaluation/exercise/encounter" method (OSTE).

METHODS

We conducted a review of the literature using the MEDLINE database (via PubMed) and the LILACS database (via Biblioteca Virtual em Saúde) to extract relevant articles that describe simulated activities that were performed with the specific aim of evaluating teaching skills. We also searched the SciELO library for Brazilian papers. The key words used in the literature search included "objective structured teaching examination", "objective structured teaching evaluation", "objective structured teaching encounter", "objective structured teaching exam", "observed structured teaching examination" and teaching AND evaluation. The MeSH terms used in the search were educational measurement/methods, professional competence, teaching/methods and teaching/standards.

The relevant publications included original articles, systematic reviews, critical reviews, randomized controlled trials, guidelines from medical education experts and material from pioneering authors in this field. Attention was given to papers focusing on pre and post-OSTE intervention designs, validity and reliability assessments, experimental work and publications describing the process of creating OSTE scenarios.

RESULTS

Of all identified papers, 40 contained information regarding the specific topic of evaluating clinical teaching skills through objective and structured simulated activities. Searches for primary publications referenced in other articles were also included. These 40 articles with relevant information were selected for intensive review and were analyzed by two authors (SAF and MPTN). The search in LILACS and SciELO using Portuguese key words did not yield any results regarding the specific topic of interest. **Table 1** describes the number of texts extracted from each database.

The majority of the studies included in this review reported that the participants (academic staff members and residents alike) gave positive responses regarding the activities involving OSTEs. There was a trend towards lack of robust quantitative data on these activities. Nonetheless, overall, these studies recommended dissemination of OSTEs as a means of assessing clinical teaching skills. **Table 2** describes the most relevant studies included in this review and summarizes their main objectives and results.

DISCUSSION

Defining the instrument

In medical education, simulated assessments of clinical skills, known as "objective structured clinical evaluations" (OSCEs) are routinely conducted. At our institutions, OSCEs are used with summative, formative and selective purposes, such as in entry contests for medical residency. In the same way in which clinical skills can be placed under scrutiny through simulated experiences, some authors have hypothesized that teaching skills could also be assessed using the same principles.[4-7]

Clinical training is vital for producing medical staff who are capable of delivering high quality assistance. Successful clinical

Table 1*. Evolution of objective structured teaching examinations (OSTEs) over time

Year	Author	Name attributed to activity	Target audience
1992	Simpson et al.[4]	SATS: standardized ambulatory teaching situations	Academic staff member
1994	Orlander et al.[5]	CFE: clinical feedback exercise	Residents
1994	Lesky et al.[6]	OSTE: objective structured teaching exercise	Academic staff member
1997	Kachur et al.[9]	Multiple-station exam/teaching exercise	Academic staff member
1998	Dunnington et al.[10]	OSTE: objective structured teaching evaluation	Residents
1998	Prislin et al.[7]	OSTE: objective structured teaching evaluation	Academic staff member
2001	Schol et al.[11]	MSTAT: multiple-station teaching assessment test	Academic staff member

*Inspired by the timeline developed by Elizabeth Kachur.

teachers actively engage their students in patient care and provide constructive counseling and feedback.

Objective structured teaching examinations/encounters/evaluations/exercises (OSTEs) have emerged as promising and unbiased interventions for assessing the act of teaching. The reasons that are commonly given for using OSTEs as a means of assessing the teaching skills of teachers and facilitators are that this method promotes rapid and rigorous assessment and that it enables practicing of specific skills in a realistic atmosphere with immediate feedback and potential benefits for raters.[8]

The first studies using OSTEs were started during the 1990s. **Table 3** details how simulated activities designed to assess teaching skills have evolved over the years.[4-7,9-15] This table presents a modified version of material that was produced in a workshop conducted by Wamsley et al.,[8] at the University of California, in 2006. These authors specifically described OSTEs as a novel tool that was designed to enhance teaching skills and techniques.

OSTEs consist of simulated scenarios of teaching environments with students and have the aim of providing immediate objective feedback to the teacher or medical resident participating in the activity.[16] Most of the literature has described OSTEs as 10 to 15-minute encounters in which the students interact with a teacher in video-recorded sessions that are then discussed in large debriefing groups.[17] They provide an opportunity for teachers to show how they teach and interact with standardized students in a controlled and thus protected scenario. There is the possibility of enacting daily situations and repeating them as necessary.

During an OSTE activity, the participants go through sequential stations, each consisting of a different clinical teaching situation. Standardized students are used (trained to present a prototypical teaching challenge consistently across many meetings with different teachers), and a simulated patient can be included, depending on the purpose of the specific station. Both verbal and non-verbal communication skills are evaluated. Feedback is given about different aspects of the teacher's performance. Feedback from the standardized student can also be given. The materials needed for performing the activity include descriptions of the situations in every detail, good training and precise orientations for the standardized student and instructors, and a reliable and validated instrument for rating the OSTE. Standardization is expected to occur because the real students or trained actors follow a script with predefined objectives.

Instrument applications

Teaching evaluations in OSTE scenarios are used with distinct purposes in American academic institutions. Some authors have used OSTEs to evaluate the teaching skills of medical preceptors, academic staff members at multiple schools and residents.[7,10,11,18,19]

McSparron et al.[20] developed an OSTE with the specific aim of assessing academic staff members' skills in orienting a procedure. The task consisted of guiding a standardized student who was required to place a central line in a model that had been developed for this purpose. These authors named their activity "prOSTE" and they reported that the performance of standardized students was better when the instructors offered positive feedback and suggestions for improvement and when the procedure was explained step by step. Another use for this method was to observe medical teachers or residents' teaching skills and try to enhance them through effective feedback.

Cerrone et al.[21] described an activity in which the aim was to use OSTEs as a means of evaluating and promoting chief residents as emotionally intelligent leaders. These authors cited emotional intelligence as a core competence of leadership that was required from these residents. The OSTE scenarios for this activity addressed professionalism, confidentiality, teamwork and escalation issues (resolution of conflicts with team members who were at a higher hierarchical level). The chief residents were divided into pairs and participated in simulations of authentic incidents that were not identified. These authors concluded by affirming that OSTEs combined with post-activity debriefing sessions provided a powerful platform through which individuals undergoing evaluation (teachers or residents) would be able to demonstrate competencies in areas that were frequently ignored, omitted or even considered

Table 2. Literature search in medical databases, search strategies used for each database and number of articles extracted

Database	Search strategies	Papers found
MEDLINE (via PubMed)	#1- ("objective structured teaching evaluation"[Title/Abstract]) OR ("objective structured teaching examination"[Title/Abstract]) OR ("objective structured teaching encounter"[Title/Abstract]) OR ("objective structured teaching exam"[Title/Abstract]) OR ("observed structured teaching examination"[Title/Abstract])	15
	#2- ("educational measurement/methods"[Mesh Terms]) OR ("professional competence"[MeSH Terms]) OR ("teaching"[MeSH Terms]) OR ("teaching/standards"[Mesh Terms])	175,601
	#3- #1 AND #2	13
LILACS (via Biblioteca Virtual em Saúde)	#1- (tw:(internato e residência)) AND (tw:(capacitação em serviço)) AND (tw:(treinamento por simulação)) AND (instance:"regional") #2- (tw:(modelos educacionais)) AND (tw:(avaliação educacional)) AND (tw:(treinamento por simulaçao)) AND (instance:"regional")	0

Table 3. Studies of relevance to the objective structured teaching examination (OSTE) method, included in the present review

Authors	Year	Study type	Participants (n)	Specialty	Objectives	Conclusions
Orlander et al.[5]	1994	Qualitative/ experimental	23 residents and 47 interns	Internal medicine	To obtain residents' and interns' opinions after participating in a clinical feedback exercise	Residents reported better attitudes towards clinical teaching skills and contact with interns
Lesky et al.[6]	1994	Qualitative/ experimental	Ambulatorial preceptors and standardized students (sample not informed)	Not informed	To develop an ambulatorial preceptorship program and help preceptors to adopt a student-centered teaching approach	Preceptors who participated in the activity reported better comprehension of their clinical teaching competencies
Schol et al.[11]	2001	Validity and reliability	35 residents acting as preceptors	General practice	To evaluate the validity and reliability of an evaluation with seven OSTE scenarios	This type of assessment provides important information about the levels of competency in clinical teaching
Morrison et. al[13]	2002	Validity and reliability	23 second-year residents	Internal medicine, pediatrics and family medicine	To evaluate the validity and reliability of an eight-station OSTE that was developed specifically for residents involved in teaching activities	Cronbach's alpha > 0.9 for all eight stations; 92% of the residents reported that the stations realistically reflected important clinical teaching skills
Stone et al.[14]	2003	Pre and post-intervention design	40 teachers	Family medicine, pediatrics and family medicine	To develop and implement an OSTE to assess an academic staff development module	OSTEs can be more sensitive for detecting skills that are more readily applicable to daily practice
Sturpe et al.[17]	2014	Descriptive	NA	NA	To describe how to develop a scenario to evaluate clinical skills	When used together with other teaching strategies, OSTEs can enhance academic staff members' teaching strategies
Cerrone et al.[21]	2017	Non-randomized intervention	80 chief-residents	15 specialties	To develop a program capable of enhancing chief-residents' emotional intelligence	There was a statistically significant improvement in OSTE scores after the intervention
Zackoff et al.[23]	2015	Prospective, with intervention group and blinded raters	49 residents	Pediatrics	To create an OSTE capable of detecting changes in residents' teaching skills after participation in a teaching skill development program	The OSTE showed efficacy in detecting changes in clinical teaching skills
Steinert et al.[24]	2006	Systematic review	NA	Multiple	To describe the evidence that gives support to programs aimed towards developing teaching skills	Participants generally reported positive changes after specific interventions, but methodological limitations remain and need to be addressed
McAndrew et al.[25]	2011	Descriptive	12 teachers	Dentistry	To describe the creation of an OSTE to assess an academic staff development program within dentistry	Use of OSTEs not only enhances the levels of academic staff development programs, but also enriches efforts to foster teaching within dentistry
McCutcheon et al.[26]	2017	Pilot, qualitative, pre and post-OSTE	23 preceptors	Pharmacy	To evaluate interprofessional teaching skills	Pharmacy preceptors demonstrated better teaching skills and self-confidence after participating in OSTEs
Wamsley et al.[31]	2005	Qualitative/ experimental	16 teachers	Internal medicine, pediatrics and family medicine	To develop teaching skills among academic staff members in different specialties	Teachers reported that they would change their teaching styles after participating in OSTEs; standardized students reported more interest in teaching after the activity
Trowbridge et al.[33]	2011	Systematic review	NA	Multiple	To describe the use of OSTEs and the evidence that gives support for their use	OSTEs are a promising innovation with potential application in assessment and promotion of clinical teaching; new research is necessary to define the designs of appropriate stations

NA = not applicable.

"hidden". Lastly, the strategy was also used to evaluate interventions that were designed to enhance the teaching skills of academic staff members and medical residents at different institutions.[14,22,23]

Steinert et al.[24] reviewed 303 articles on academic staff member development programs. They specifically emphasized the importance of using OSTEs to measure the scores before and after the interventions.

Using the instrument beyond medicine

OSTEs are nowadays not restricted to medicine or to preceptors and residents working in large university hospitals. McAndrews et al.[25] developed an activity based on OSTEs to measure the response of academic staff members in the dentistry department of New York University, to a development program for teaching skills. Sixteen academic staff members participated in a study measuring scores before and after the intervention. Three stations were created to evaluate 15 domains of teaching. There was a statistically significant improvement in the scores from all the domains tested, after exposure to an intervention based on academic staff member development.

McCutcheon et al.[26] described a study in which the aim was to training pharmacy preceptors in interprofessional educational activities. One OSTE station was created in such a way that two standardized students (one from nursing and one from pharmacy) interacted with a patient who had been diagnosed with asthma. Analysis on the data obtained showed that there were statistically significant improvements in all the 15 self-confidence items for which the participants gave responses. These authors highlighted the following items as resulting in significant improvements in students' abilities: guiding students from different specialties, facilitating a simulated activity, leading a debriefing session and discussing the core competencies in interprofessional education.

Rating OSTE participants

OSTEs provide highly versatile evaluations. They can be used for either educational or assessment purposes. Currently, OSTEs form the gold-standard instrument for assessing medical residents' teaching skills.[25] They have also become the most accurate measurement method for evaluating academic staff member development programs.[24]

To provide unbiased, valid and reliable scores, activities such as OSTEs require appropriate measurement instruments. It is imperative that these instruments should have highly accurate measurement properties, so that they can contribute reliable and relevant feedback regarding the qualities and deficiencies demonstrated by the individuals who are undergoing evaluation.

Review studies have identified more than 32 different instruments that were developed to score simulated activities within clinical teaching. These instruments are an essential part of the process of continuous qualification in medical education and development of clinical teaching competencies.[27]

Two scoring instruments have been validated and are widely used by the academic community: (1) the "Stanford Faculty Development Program" (SFDP26);[28] and (2) the "System for Evaluation of Teaching Qualities" (SETQ).[29] The SFDP26 was originally developed in the United States and evaluates the following teaching skills: (1) establishment of the learning environment; (2) session control; (3) communication of learning goals; (4) facilitation of retention and understanding; (5) evaluation of previous knowledge, (6) promotion of self-directed learning; and (7) giving feedback.

Instrument advantages:

Irby et al.[30] described the main reasons for using OSTEs: (1) rapid and rigorous evaluation of clinical teaching skills; (2) provision of time for practicing of specific teaching skills; (3) creation of a practical and realistic atmosphere; (4) provision of immediate feedback; and (5) potential for benefiting the standardized students, who acquire additional knowledge while they rehearse for the stations and while they give feedback to the person undergoing evaluation.

According to Wamsley et al.,[31] teaching skills are deemed to be of good quality, in most scenarios, through students' personal opinions. This type of evaluation is susceptible to the teacher's charisma and to her/his communication skills. In this circumstance, the picture of what constitutes a good teacher can be contaminated by personal interactions in daily activities, either in a classroom or in hospital wards. This interaction bringing a positive or negative bias. OSTEs have the advantage of attenuating this potential contamination through specifically assessing the teacher's professional performance. This can be achieved using standardized situations, instruments, students and even patients.

Another attractive feature of OSTEs is that they provide the opportunity for an immediate debriefing session after the activity. The debriefing process is considered by many researchers to be the most important component of any learning experience based on simulation. It relates directly to the learner's capacity to reflect on his/her performance in the activity.

Decker et al.[32] stated that the learning process is dependent on the interaction between experience and reflection. Regarding the reflection process, these authors took the view that this comprised conscious consideration of the meanings and implications that arise from an action. All these processes would lead to assimilation of knowledge, skills and attitudes that did not exist before the intervention. These authors concluded by citing the necessary conditions for an effective debriefing session: (1) facilitated by a competent individual; (2) conducted in an environment that favors knowledge acquisition and that guarantees confidentiality, trust, open communication, self-analysis and reflection; (3) facilitated by someone who directly observed the simulation experience; (4) based on a work plan specifically structured for that task; and (5) congruent with the participants' objectives and the previously established results.

Instrument limitations

According to the literature reviewed here, the main limitations on developing OSTEs are the scarcity of financial and human resources for implementing the activities and the lack of time that can be attributed to tasks that are deemed "less important". Training standardized students or hiring professional actors for the activities can be a limiting factor in institutions in which simulations are not part of the local culture. There are also no data on the financial impact of this kind of activity or on its cost effectiveness.

A systematic review on the use and efficacy of OSTEs, published in 2011, did not find much evidence in the form of quantitative data to gauge the impact that this method might have in relation to improvement of teaching skills.[33] Nonetheless, most participants reported that they benefited from the activities. The same authors also cited the lack of uniformity in the scripts for the scenarios that were used. The reliability of the rating instruments was moderate to high in most of the studies and the rating scores appeared not to be related to rater background, i.e. academic staff member or student. Only four studies specifically evaluated station validity and, thus, little evidence regarding OSTE validity up to the date of that review was available.[11,13,18,34]

Brazilian studies

Our search using Portuguese key words in the LILACS and SciELO databases did not yield any results. To our knowledge, there has been no experience of using the OSTE method in Brazil. The present review demonstrates that there is little or no knowledge about how to apply the OSTE method in Brazil, despite all the positive remarks regarding this activity. We have now managed to successfully develop OSTE scenarios within a doctoral project that is still in progress. Four scenarios were created, in which discussion of cases in emergency, ambulatory and surgical ward settings was simulated and a simple procedure was taught. We translated the SFDP26 instrument into Portuguese and then validated it using a specialists' panel; we trained arts students as standardized medicine pupils; and finally, we received voluntary help from medical residents who performed in the proposed simulations (data not yet published).

This narrative review forms part of a doctoral project that is still in progress. Its aim is to assess residents' clinical teaching competencies before and after an intervention based on the one-minute preceptor technique.[35] The OSTE method was presented, based on our previously cited experience, at the Brazilian Congress of Medical Education in 2017, as a workshop.

Adequate assessment of teachers' performance gives them the opportunity to reflect on their teaching skills and consequently evolve during the process of knowledge acquisition. Teachers desire and need feedback, not only in relation to the time that they spend in the classroom, but also in relation to how this enhances the educational results. Evaluation systems directed towards teachers are frequently proposed, in order to provide feedback and guide the evolution of professional practice.[36]

Assessment of academic staff members, preceptors and medical residents is a subject of major controversy not only in Brazil. We believe that most teachers with well-consolidated careers would feel uneasy about having their skills put under scrutiny from their peers or students. This may explain why the word evaluation, contained in the acronym OSTE, is frequently changed to encounter, exercise or situation.

In the same way in which OSCEs have been brought into Brazilian settings as a tool for assessing medical students and residents, it is also proving possible to develop the dynamics of OSTEs within our practice. Some useful papers have dealt specifically with the process of creating OSTE stations, and these form an excellent starting point. Boillat et al.[16] presented 12 tips for constructing activities based on simulation, for assessing clinical teaching skills (**Table 4**). There are potential benefits from OSTEs at all educational levels, given that evaluation of reactions (the lowest level on the Kirkpatrick scale[37]) is being superseded, such that the level of understanding of attitudes and behavioral change is now being reached.

Table 4*. Tips for producing an objective structured teaching examination (OSTE) scenario

1	Establish specific goals for the activity in advance
2	Determine context and target audience for the activity
3	Identify specific teaching skills to be evaluated
4	Set the scenario: use real cases based on situations that occurred in the place where the activity is being performed
5	Develop the assessment tool: checklists, self-evaluations and those to be performed by standardized students or peers
6	Choose the standardized student: medicine or other pupils, trained actors, academic staff members or other institutional staff
7	Train the standardized student according to the scenario and teaching skill to be assessed
8	Test the scenario before the main event to correct potential errors and maximize case fidelity
9	Protect the teacher undergoing evaluation: strictly follow the principles of effective debriefing and feedback to reduce stress from the activity
10	Incorporate this simulation method into academic staff development programs in the specific context of your institution
11	Emphasize the positive aspects of the method to enhance adherence by academic staff members or residents
12	Evaluate the activity after concluding the simulations: use pre and post-activity interviews, written evaluations or qualitative comments

*Modified from Boillat et al.[16]

CONCLUSIONS

Teaching is a complex activity that requires multiple methods for complete assessment. In the present review, we elected to examine a standardized observational method: OSTEs. Considering that OSCEs have become a widely used tool for assessing medical students' and residents' clinical skills, it is high time to incorporate OSTEs for evaluating teaching skills in Brazil. Encouraging data to support implementation of this assessment tool in this country is available from abroad. The net benefit from this would possibly encompass medical students, residents and academic staff, through bringing awareness about the importance of excelling in teaching skills.

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Solitary pancreatic metastasis from breast cancer: case report and review of literature

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KEY WORDS:
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ABSTRACT

CONTEXT: Pancreatic metastases from primary malignant tumors at other sites are rare, constituting about 2% of the neoplasms that affect the pancreas. Pancreatic metastasis from breast cancer is extremely rare and difficult to diagnose, because its clinical and radiological presentation is similar to that of a primary pancreatic tumor.

CASE REPORT: A 64-year-old female developed a lesion in the pancreatic tail 24 months after neoadjuvant therapy, surgery and adjuvant radiation therapy for right-side breast cancer (ductal carcinoma). She underwent distal pancreatectomy with splenectomy and left adrenalectomy, and presented an uneventful outcome. The immunohistochemical analysis on the surgical specimen suggested that the lesion originated from the breast.

CONCLUSION: In cases of pancreatic lesions detected in patients with a previous history of breast neoplasm, the possibility of pancreatic metastasis should be carefully considered.

INTRODUCTION

Pancreatic metastases from primary malignant tumors at other sites are rare, constituting about 2% of the neoplasms that affect the pancreas.[1] In most cases, the involvement occurs through hematological and lymphatic dissemination, as in cases of kidney and lung carcinomas. It can also occur through contiguous invasion of neighboring organs such as the liver, stomach and spleen. Pancreatic metastasis from breast cancer is extremely rare and difficult to diagnose, because its clinical and radiological presentation is similar to that of a primary pancreatic tumor.[2-5] The objective of the present study was to report on a case of pancreatic metastasis of breast cancer, along with the treatment that was proposed.

CASE REPORT

A 64-year-old female underwent neoadjuvant chemotherapy consisting of doxorubicin, cyclophosphamide and paclitaxel, with subsequent quadrantectomy and axillary lymph node dissection due to a right-side breast neoplasm. Histopathological examination revealed a ductal carcinoma classified as T2N2M0, consisting of a 4-cm tumor with spreading to six axillary lymph nodes but without distant spreading to bones, liver, brain or lungs). It was triple-negative, for estrogen, progesterone and human epidermal growth factor receptor 2 (HER2) receptors. Radiation therapy was subsequently implemented. The patient was then followed up with serial investigations (mammogram, bone scintigraphy scan and computed tomography scans of the cranium, thorax and abdomen) for locoregional and distant relapses every six months.

Twenty-four months after receiving the diagnosis, she evolved with a complaint of left-flank pain, inappetence and loss of seven kilograms in four months. She presented dyspeptic symptoms characterized by early satiety and pain in the upper abdomen after feeding. On physical examination, the abdomen was painful to deep palpation. There was no evidence of relevant laboratory abnormalities.

Abdominal computed tomography demonstrated a hypervascularized solid lesion of 6.6 cm x 6.0 cm x 7.0 cm in the tail of the pancreas. It had an irregular outline and partially defined borders, presented a central area of necrosis and was in contact with the anterior margin of the spleen and greater gastric curvature. It was not possible to determine any cleavage plane. A small amount of free liquid was present (**Figure 1**). Cancer antigen (CA)-19.9, carcinoembryonic antigen (CEA) and CA-125 levels

were within the normal ranges. No other sites with suspected lesions were detected through positron-emission computed tomography.

Because the hypothesis of pancreatic neoplasia needed to be clarified and no endoscopic ultrasound-guided biopsy was available, prompt surgery was warranted given that there was no evidence of other sites of active disease. The patient underwent distal pancreatectomy with splenectomy and left adrenalectomy (**Figure 2**), with uneventful postoperative outcomes. She had good evolution in the postoperative period, with complete remission of symptoms.

The histopathological diagnosis consisted of metastasis from breast carcinoma. The results from the immunohistochemical analysis were positive for the cytokeratin-7 (CK7) marker and negative for the mucin 5AC (MUC-5AC), CEA, CA-19.9, estrogen receptor (ER), progesterone receptor (PR) and Breast-2 (BRST-2) markers. Although negativity for ER, PR and BRST-2 does not favor a breast origin, these markers do not preclude this origin. On the other hand, negativity for the MUC-5AC, CEA and CA-19.9 markers does not favor a pancreatobiliary origin and favors the breast as the primary site. A chemotherapy regimen consisting of paclitaxel was administered for 12 weeks following the patient's recovery from the operation, and currently she is being followed up with serial screenings for locoregional and distant spreading of disease every six months. As of 18 months after the diagnosis was made, there is no evidence of active disease.

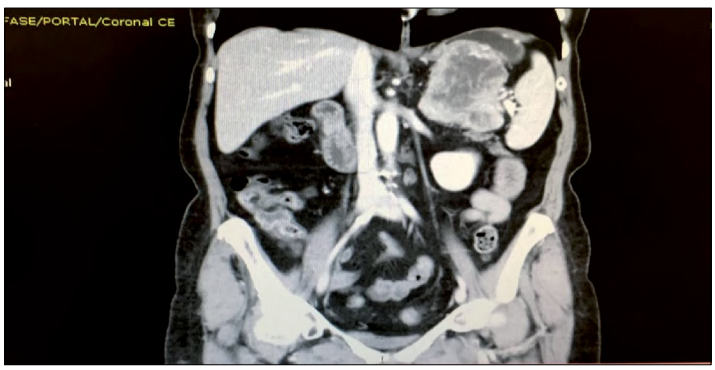

Figure 1. Computed tomography showing a lesion in the tail of the pancreas.

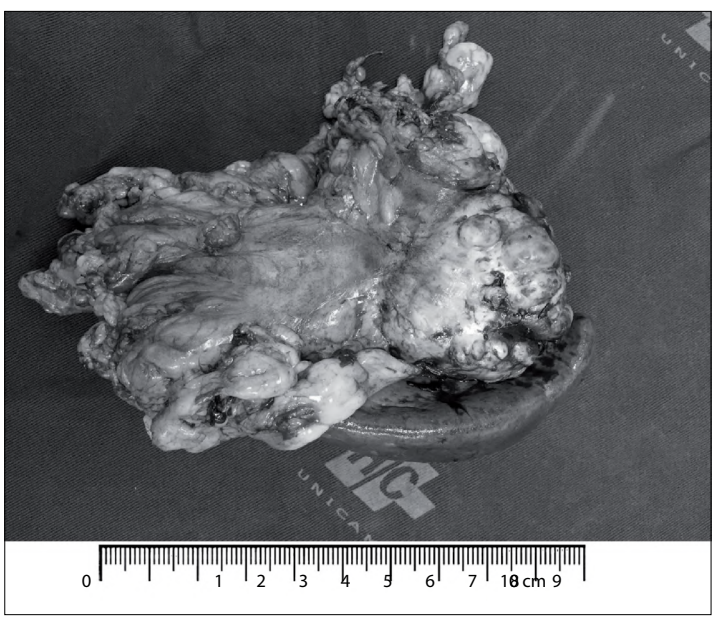

Figure 2. Surgical specimen (distal pancreatectomy with splenectomy and left adrenalectomy).

DISCUSSION

Breast cancer causes metastases especially to bones, liver and lungs. Pancreatic involvement in solitary metastases from a primary breast neoplasm is rare, occurring in less than 3% of the cases. A review of the literature was conducted through an online search for the Medical Subject Headings (MeSH) terms "breast neoplasms", "pancreas" and "neoplasm metastasis" in MEDLINE (via PubMed) and LILACS (via BVS) (**Table 1**). We included original studies that reported single cases or case series of this disease or correlated conditions. All the papers were checked according to their titles and abstracts (screening). Full papers were obtained from journals available on the website of the Commission for Improvement of Higher Education Personnel (Comissão de Aperfeiçoamento de Pessoal de Nível Superior, CAPES) (Ministry of Education, Brazil). Unavailable articles were requested from their authors. Articles presenting potentially relevant studies were read and analyzed to assess the inclusion criteria. We excluded articles that consisted of *in vitro* or animal studies, articles in which the participants' characteristics did not match those mentioned above, poster session abstracts, review articles and other types of publications. Other papers were used for contextualization and discussion.

After extensive online research, we identified 23 studies, 17 case reports and 6 case series, totaling 28 reported cases of pancreatic metastases from breast cancer. **Table 2**[2,3,6-8,10-27] summarizes the main articles found and their reported outcomes. **Figure 3** presents a flow diagram of the articles selected. In the majority of the cases described, spreading to the head of the pancreas was more

Table 1. Database search results for pancreatic metastasis arising from primary breast cancer

Electronic databases	Search strategies	Results
MEDLINE (PubMed)	(Breast neoplasms) AND (Pancreas) AND (Neoplasm Metastasis)	17 case reports 6 case series
LILACS (BVS)	(((Breast neoplasms) OR (Neoplasias da mama) OR (Neoplasias de la mama)) AND ((Pancreas) OR (Pâncreas) OR (Páncreas)) AND ((Neoplasm Metastasis) OR (Metástase Neoplásica) OR (Metástasis de la Neoplasia)))	1 case report

Table 2. Reported cases of pancreatic metastases arising from primary breast cancer

Authors	Breast cancer subtype	Age (years)	Disease-free interval (months)	Presenting symptoms	Location of metastases at diagnosis	Profile of the metastatic disease at diagnosis	Clinical management	Overall survival (months)
Akashi et al.[6]	Lobular	47	41	NR	Head of pancreas	Solitary	Pancreaticoduodenectomy	28
Azzarelli et al.[7]	Lobular	49	43	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, radiation therapy	72
Bednar et al.[8]	Lobular	75	96	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	48
	Phyllodes	57	48	Abdominal pain	Head of pancreas, lung	Widespread disease	Chemotherapy	15
Bonapasta et al.[2]	Ductal	51	24	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	36
Crippa et al.[10]	Lobular	46	60	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy	22
	Lobular	70	36	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	38
	Lobular	57	84	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	26
Dar et al.[11]	Ductal	76	108	NR	Pancreas, liver	Widespread disease	Palliative bypass	6
Engel et al.[12]	Signet-ring cells	59	46	Pruritus, choluria	Head of pancreas	Solitary	Palliative bypass, Chemotherapy	15
Estraviz et al.[13]	Ductal	56	36	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy	6 (still alive at the time of report)
Haque et al.[14]	Lobular	85	168	Jaundice, pain	Head of pancreas	Solitary	Palliative bypass	NR
Kitamura et al.[15]	Ductal	55	117	Jaundice	Head of pancreas	Solitary	Percutaneous drainage	1
Le Borgne et al.[16]	Lobular	48	Synchronous	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy	12
Mehta et al.[17]	Comedo type	30	36	Jaundice, pruritus	Head of pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy, hormonal therapy	27
Molino et al.[3]	Lobular	68	Synchronous	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, hormonal therapy	12 (still alive at the time of report)
Mountney et al.[18]	Lobular	57	16	Jaundice	Head of pancreas	Solitary	Palliative bypass, hormonal therapy	24
Moussa et al.[19]	Ductal	53	132	Acute pancreatitis	Head of pancreas	Solitary	Radiation therapy, chemotherapy, hormonal therapy	50
	Lobular	35	45	Abdominal mass	Body of pancreas	Solitary	Total pancreatectomy, chemotherapy	7
Nomizu et al.[20]	Lobular	46	80	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy, hormonal therapy	18
Odzak et al.[21]	Lobular	48	Synchronous	Jaundice, ascites	Head of pancreas	Widespread disease	Palliative care	NR
Pan et al.[22]	Lobular	59	182	Jaundice	Head of pancreas	Solitary	Chemotherapy, hormonal therapy	21
Pappo et al.[23]	Lobular	52	24	Jaundice	Pancreas, gallbladder	Widespread disease	Palliative bypass, hormonal therapy	16
Pérez Ochoa et al.[24]	Lobular	60	1	Jaundice	Head of pancreas, bone	Widespread disease	Biliary stent, pancreaticoduodenectomy, chemotherapy	2
	Ductal	55	108	None	Tail of pancreas	Solitary	Distal pancreatectomy, splenectomy, chemotherapy	2

Continues...

Table 2. Continuation

Authors	Breast cancer subtype	Age (years)	Disease-free interval (months)	Presenting symptoms	Location of metastases at diagnosis	Profile of the metastatic disease at diagnosis	Clinical management	Overall survival (months)
Razzetta et al.[25]	Lobular	51	Synchronous	Jaundice, pain, diarrhea	Head of pancreas, bone	Widespread disease	Pancreaticoduodenectomy, neoadjuvant chemotherapy, mastectomy	5
Tohnosu et al.[26]	Scirrhous type	54	52	None	Tail of pancreas	Solitary	Distal pancreatectomy, chemotherapy, hormonal therapy	5
Z'graggen et al.[27]	Lobular	NR	96	Jaundice	Head of pancreas	Solitary	Biliary and gastric bypass, chemotherapy	54
Current study	Ductal	64	24	Pain	Tail of pancreas	Solitary	Distal pancreatectomy, chemotherapy	18 (still alive at the time of report)

NR = not reported.

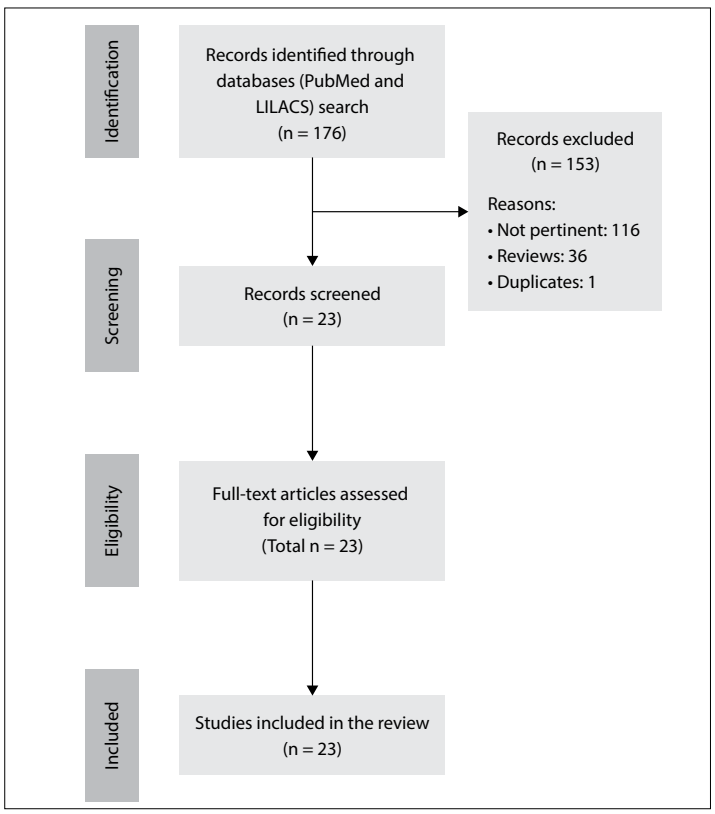

Figure 3. Flow diagram of the review of the literature.

common than to the tail, and the most common histological type was lobular carcinoma; the predominant metastatic pattern was solitary. The average interval between the diagnoses of primary breast neoplasm and pancreatic metastasis was 43.3 months.[2] In our case, the patient presented metastasis to the region of the tail of the pancreas, with a histopathological diagnosis of ductal carcinoma, and the asymptomatic interval was 24 months.

The clinical signs of this condition are unspecific, with abdominal pain and obstructive jaundice as the main findings.[4] The absence of characteristic clinical signs and symptoms leads to investigation by means of imaging tests. Ultrasonography, computed tomography and magnetic resonance imaging are frequently used for making this diagnosis; however, the radiological features of primary pancreatic tumors and pancreatic metastases are difficult to differentiate. Use of serum markers such as CA-15.3 may help in making the diagnosis, although in some cases its serum elevation is not relevant.[2,5-9,28] The most accurate diagnostic method is pancreatic biopsy. Some studies have suggested that fine-needle biopsies guided by endoscopic ultrasound or percutaneously should be used.[3] The unavailability both of tests for this marker and of endoscopic ultrasound at our service precluded their use in the present case; however, this should not prevent the oncology and surgery teams from recommending operative treatment in cases without widespread disease.

The prognosis for patients with pancreatic metastatic disease is usually better than for patients with primary pancreatic tumors.[2] Masetti et al. analyzed the prognostic factors relating to metastatic tumors in the pancreas and found two and five-year survival rates of 57.1% and 34.3% in cases of pancreatic metastasis due to breast cancer, respectively.[28] Surgical resection in cases with disease limited to the pancreas is considered to be the main form of treatment, despite its morbidity.[3]

CONCLUSION

Based on this study and the evidence available to date, it may be concluded that in cases of pancreatic lesions detected in patients with previous histories of breast neoplasms, the possibility of pancreatic metastasis should be carefully considered.

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Recurrence of retroperitoneal localized perivascular epithelioid cell tumor two years after initial diagnosis: case report

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KEY WORDS:
Perivascular epithelioid cell neoplasms.
Retroperitoneal neoplasms.
Antineoplastic protocols.

ABSTRACT

CONTEXT: Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors. Adjuvant radiotherapy and/or chemotherapy are administered according to the patient's clinical characteristics.

CASE REPORT: A 42-year-old female patient was operated to treat a retroperitoneal mass. The diagnosis was established as PEComa with benign behavior. Two years after the diagnosis, chest and abdominal computed tomography scans showed intra-abdominal recurrence and lymphangioleiomyomatosis in the lung. Treatment with everolimus was started. The disease stabilized in the third month of treatment, according to the response evaluation criteria in solid tumors.

CONCLUSION: PEComas are tumors with unpredictable behavior. Therefore, these patients require long-term follow-up, even in cases of correct diagnosis and benign PEComa.

INTRODUCTION

Perivascular epithelioid cell tumors (PEComas) are mesenchymal tumors consisting of perivascular epithelioid cells that can be histologically and immunohistochemically distinguished and are rarely seen. In general, these tumors are seen in women aged around 50 years. The most common location is the retroperitoneum.[1,2] However, these tumors have been reported in several anatomical regions, including the visceral organs, soft tissues, prostate and broad ligament. Tumors located in the retroperitoneum grow insidiously and manifest as huge lesions. In 2002, the World Health Organization (WHO) reclassified tumors involving PEComas such that they included angiomyolipoma, clear-cell "sugar" tumor, lymphangioleiomyomatosis, clear-cell myomelanocytic tumor of the ligamentum teres/falciform ligament and PEComa not otherwise specified. Primary PEComas may be benign, malignant or otherwise specified with unknown potential for malignancy. The majority of these tumors are benign with a good prognosis.[1-3]

In this report, we present a patient who was operated to treat a retroperitoneal mass that was diagnosed as a benign PEComa, and who developed abdominal recurrence and pulmonary lymphangioleiomyomatosis.

CASE REPORT

A 42-year-old female patient was seen in October 2014, with complaints of abdominal pain and nausea/vomiting that had been occurring for the last three months. In her medical history, she had been using colchicines for 15 years with the diagnosis of familial Mediterranean fever (FMF).

Abdominal ultrasonography (USG) showed a lesion of cystic appearance that measured 8 cm x 3 cm, starting from the lower pole of the left kidney, which was located anteriorly to the iliopsoas muscle. Computed tomography (CT) scans showed a hypodense lesion that measured 5.5 cm x 9.0 cm x 3.0 cm and was located retroperitoneally. It had a smooth outline, started from the level of the left renal artery and expanded from anterior to the iliopsoas muscle towards an inferior position. The backgrounds of the lesion and iliopsoas muscle were not clearly visible (**Figure 1**).

The patient underwent local mass excision. Histopathological examination showed PEComa (lymphangioleiomyomatosis). No atypia or necrosis was observed. Onemitosis was present and Ki67 proliferation in 2% of cells was observed. The diagnosis was established as PEComa with benign behavior. Chemotherapy and radiotherapy were not recommended for this patient.

The patient returned with complaints of shortness of breath and back pain two years after the diagnosis and was diagnosed as presenting pneumothorax. Chest and abdominal CT scans

showed intra-abdominal recurrence and lymphangioleiomyomatosis in the lungs. The pneumothorax was treated by means of chest tube placement.

The patient was also evaluated for a biopsy. However, the intra-abdominal lesions were small and difficult to biopsy. Treatment with everolimus at 10 mg/day was started. This was well tolerated, except that a grade 1 acneiform rash occurred on the patient's back, which was relieved by means of topical steroid.

Positron emission tomography (PET)-CT indicated minimal regression at the third month of treatment (**Figure 2A** and **B**). However, the disease had become stable according to the response evaluation criteria in solid tumors (RECIST).[4] Everolimus has been continued for nine months.

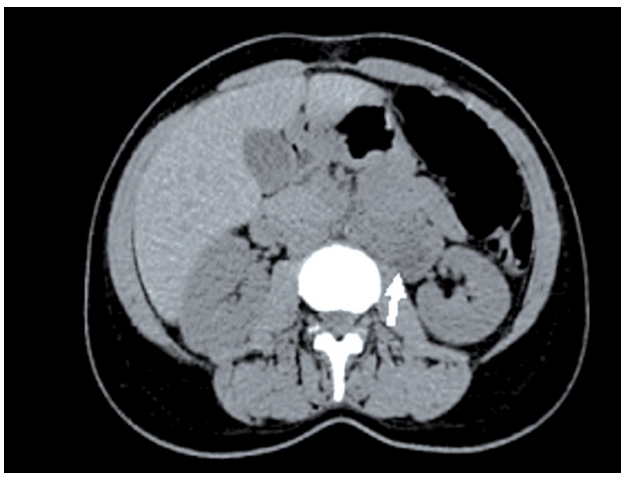

Figure 1. Axial abdominal computed tomography image showing hypodense mass lesion in the left anterior pararenal space with well-defined borders.

DISCUSSION

No optimal treatment approach has been standardized for PEComas. The standard treatment is surgery plus chemotherapy. It is important to reach negative surgical margins. Chemotherapy forms the basis for treatment and can be combined with radiotherapy. Recently, developments towards targeted treatments have shown promise.[2-5]

PEComas show evidence of mammalian target of rapamycin (mTOR) activation, but the mechanisms for its activation remain unclear. Tuberous sclerosis complex (TSC) 1 or 2 tumor suppressor genes regulate mTOR kinase. Defects in mTOR kinase lead to an increased signal pathway, transduction and cell proliferation. mTOR inhibitors, such as everolimus block this signal pathway and decrease cell proliferation. There have been several reports of treatment of metastatic PEComa with mTOR inhibitors. In a case series, mTOR inhibitors were reported to be reliable and effective, especially for treating unresectable recurrent tumors and cases with distant metastases.[3]

Because the number of reported cases is limited (**Table 1**), there are no consistent criteria for diagnosing and treating benign or malignant PEComas. Aggressive progression is observed in malignant cases presenting two or more of the following criteria: marked atypia and mitosis, vascular infiltration, infiltrative growth, high nuclear grade, tumor diameter greater than 5 cm, high mitotic activity (> 1 mitotic figure/50 high power fields), tumor necrosis and increased cellularity. Despite postoperative radiotherapy, chemotherapy and/or immunotherapy (which may be implemented separately or in combination), the prognosis is poor in cases of

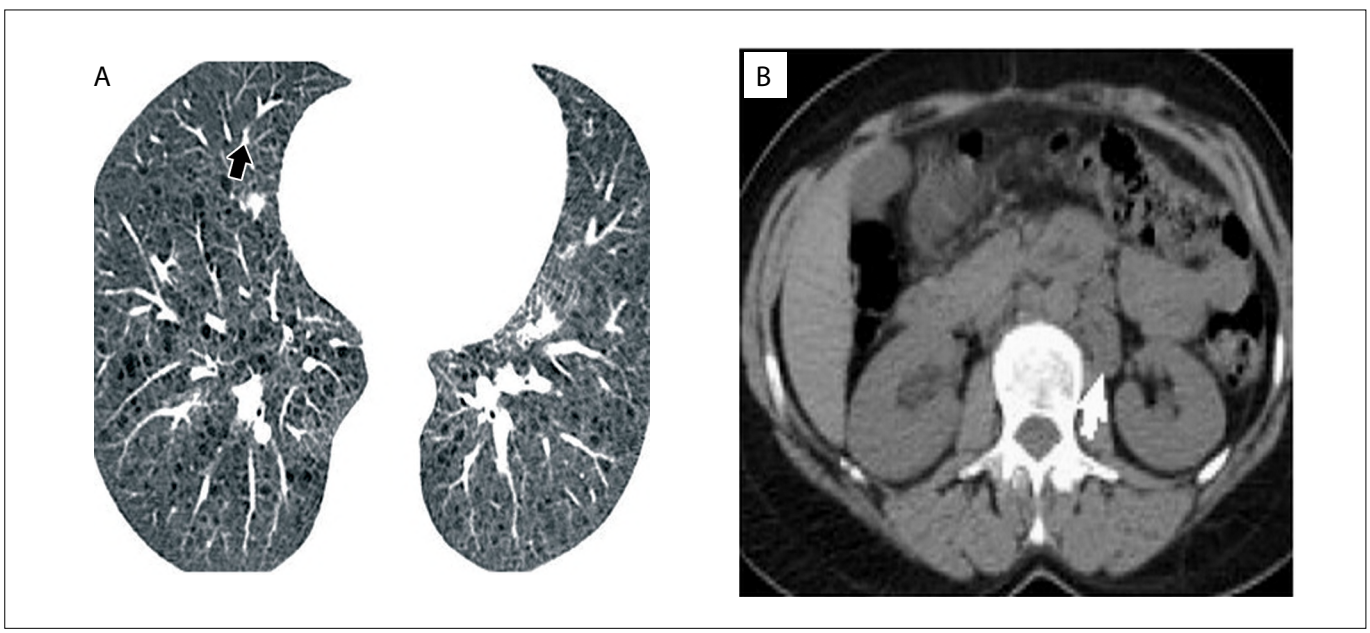

Figure 2. A) Axial abdominal computed tomography image showing residual tumor (arrow). B) Lung computed tomography image showing tiny diffuse parenchymal cystic air spaces.

these tumors with a malignant course. There was only one criterion for malignancy in our patient (tumor diameter > 5 cm). This case was then considered to be one of benign PEComa, since no other criterion was found.[2,3]

To the best of our knowledge, only 20 cases of retroperitoneal PEComa have been reported in the literature so far,[1,6-10] some of them commented below. Our case is the only one in which there was local recurrence and pulmonary metastasis, two years after the initial diagnosis of benign PEComa.

Pata et al.[1] performed total resection in a 66-year-old female patient with synchronous diffuse pulmonary lymphangioleiomyomatosis with a large retroperitoneal PEComa. Their patient was followed up without adjuvant therapy. They did not detect any local recurrence or metastasis at the end of the first year.[1] Benson et al. conducted a retrospective study on ten cases and observed partial response in five patients and stable disease in one patient.[4] Gennatas et al. obtained a significant response over the course of the follow-up on a patient who received 10 mg of everolimus for 10 months and subsequently reached survival of 37 months after surgery.[5] Wagner et al. reported a case of recurrent retroperitoneal PEComa and started administration of another mTOR inhibitor, sirolimus (8 mg/day). At the end of the first year, the tumor had regressed almost completely, while at the end of the 16th month they reported that both the treatment and the response remained the same.[3] In our case, we achieved minimal regression with everolimus.

CONCLUSION

PEComas located retroperitoneally are rarely seen. These lesions are generally confused with stromal tumors. PEComas are tumors with unpredictable behavior. Therefore, these patients require long-term follow-up, even in cases of correct diagnosis and benign PEComa.

Table 1. Results from search of the literature

Database	Search strategy	Results	
		Found	Related
MEDLINE (via PubMed, July 14, 2017)	#1 ("Perivascular epithelioid cell neoplasms"[MeSH]) #2 ("Retroperitoneal neoplasms"[MeSH]) #3 #1 AND #2 Filters: Case Reports	214	9
LILACS (via Bireme)	#1 mh:(Perivascular epithelioid cell neoplasms) #2 mh:(Retroperitoneal neoplasms) #3 #1 AND #2	0	--

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Bilateral subconjunctival hemorrhage secondary to abciximab use: case report

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KEY WORDS:
Conjunctivitis, acute hemorrhagic.
Abciximab [supplementary concept].
Coronary disease.

ABSTRACT

CONTEXT: There are no reports on cases of subconjunctival hemorrhage due to use of glycoprotein IIb/IIIa inhibitors. In this report, we present the case of a patient with bilateral subconjunctival hemorrhage after receiving abciximab.

CASE REPORT: A 40-year-old male patient underwent coronary angiography after acute anterior myocardial infarction and a coronary stent was placed. Abciximab was added to the therapy because of stent thrombosis. Bilateral subconjunctival hemorrhage was observed after the administration of the abciximab treatment. We treated our patient by stopping abciximab and administering artificial tears.

CONCLUSİON: For the first time in the literature, we presented the case of a patient with bilateral subconjunctival hemorrhage after receiving abciximab, which was managed conservatively.

INTRODUCTION

Abciximab, a Fab fragment of the chimeric human-murine monoclonal antibody 7E3, interferes with platelet aggregation by binding to the glycoprotein IIb/IIIa receptors of platelets.[1] Although no randomized trial has tested the use of abciximab as a bailout therapy in cases of ST-elevated myocardial infarction (STEMI), it has been found to be beneficial in cases of large intraluminal thrombus, slow reflow or no reflow, and in relation to other thrombotic complications during angiography.[2]

The major side effect of abciximab is bleeding. The EPIC trial included patients undergoing high-risk angioplasty procedures, among whom 14% suffered major bleeding after receiving a bolus followed by infusion of abciximab, compared with 7% of the patients receiving placebo.[3]

For the first time in the literature (**Table 1**), we present the case of a patient with bilateral subconjunctival hemorrhage after receiving abciximab.

CASE REPORT

A 40-year-old man was brought to the emergency department of our hospital with a history of chest pain for the last two hours. His past history was notable only for smoking as a cardiovascular risk factor. His vital signs included arterial blood pressure of 120/80 mmHg and a pulse rate of 66 bpm. His electrocardiogram was consistent with ST elevation in leads V1 to V6. His echocardiogram was notable for anterior and apical hypokinesia, with an ejection fraction of 40%. All his biochemical and blood count parameters were within normal limits.

The patient was diagnosed as presenting anterior myocardial infarction and was transferred to the catheter laboratory for primary percutaneous coronary intervention (PCI). He was administered

Table 1. Strategies used for search in electronic databases on June 11, 2017

Database	Search strategy	References retrieved
MEDLINE (via PubMed)	("Conjunctivitis, Acute Hemorrhagic"[Mesh]) AND ("abciximab" [Supplementary Concept])	0
Embase (via Elsevier)	(Abciximab OR Tirofiban OR Eptifibatide) AND (Subconjunctival Hemorrhage)	0

loading doses of 600 mg, 300 mg and 8000 U of clopidogrel, acetylsalicylic acid and unfractionated heparin, respectively. A coronary angiogram showed 99% stenosis in the proximal portion of the left anterior descending artery (LAD) (**Figure 1A**). The left circumflex artery was free of any stenosis and the right coronary artery had a 30% non-significant lesion in its mid-segment. A 3.0 mm x 24 mm drug-eluting stent was placed at a pressure of 12 atm in the severely stenotic LAD segment, without predilatation (**Figure 1B**).

The patient was then transferred to the coronary care unit for further observation. Thirty minutes later, the patient was defibrillated at 270 J due to an episode of ventricular fibrillation. Because his chest pain intensified, he was taken back to the catheter laboratory for a check on stent patency. Coronary angiography showed a thrombus in the LAD stent (**Figure 1C**).

A decision was made to administer abciximab to prevent further thrombosis inside the stent lumen or elsewhere in the coronary circulation. Abciximab was administered as a bolus at a dose of 0.25 mg/kg, followed by infusion at a dose of 0.125 mcg/kg/min intravenously. However, 20 minutes after the start of the infusion, the patient developed subconjunctival hemorrhage in both eyes (**Figure 2**). Therefore, infusion of the drug was stopped, but administration of acetylsalicylic acid and clopidogrel was continued.

An ophthalmology consultation was obtained for the patient, and it was recommended that he should receive conservative treatment consisting of artificial tears. The chest pain did not recur in the coronary intensive care unit after administration of abciximab was stopped. He was transferred to the cardiology ward, and a few days later, a coronary angiogram showed absence of thrombus and the patient was discharged.

He returned to the cardiology outpatient clinic for a follow-up visit, at which it was noted that his conjunctival hemorrhage had been completely eliminated. He was asymptomatic, while continuing to take acetylsalicylic acid and clopidogrel two months later.

DISCUSSION

Anticoagulants and antiaggregant medications that prevent thrombosis and clot formation are central to management of patients undergoing percutaneous coronary intervention. Nevertheless, the risk of bleeding is inevitably increased through use of powerful antiplatelet and anticoagulant agents. Subconjunctival hemorrhage is one of the most common eye disorders, especially among individuals over the age of 50 years. Hypertension is one of the major risk factors of this condition. Anticoagulants in the form of low-dose heparin and warfarin have been linked to subconjunctival hemorrhage at an incidence of 1.5% to 5%.[4,5] Dabigatran, a novel direct thrombin inhibitor with anticoagulant properties, has been reported to cause subconjunctival hemorrhage.[6]

Our patient suffered bilateral subconjunctival hemorrhage. So far, no study has reported such an association for abciximab, tirofiban or eptifibatide. Our patient may have developed this

Figure 2. Bilateral subconjunctival hemorrhage secondary to use of abciximab.

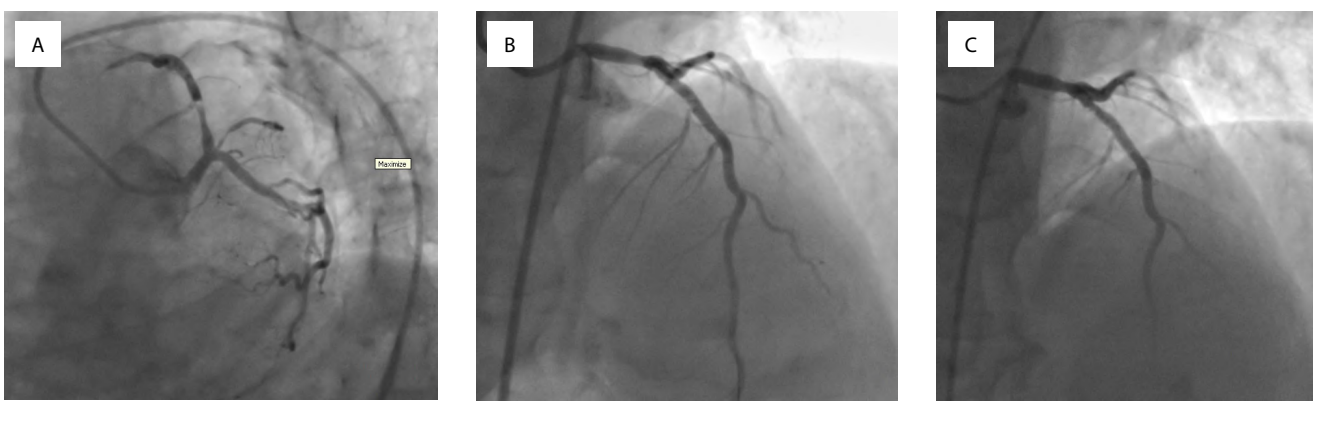

Figure 1 A. Coronary angiogram showing 99% stenosis in the proximal portion of the left anterior descending artery (LAD). B. A 3.0 mm x 24 mm drug-eluting stent was placed at a pressure of 12 atm in the severely stenotic LAD segment, without predilatation. C. Coronary angiography showing thrombus in LAD stent.

complication due to abciximab, acetylsalicylic acid, clopidogrel or combined use of these three medications. We have not come across any report in the literature on a case of conjunctival hemorrhage due to use of clopidogrel. There has only been one case of conjunctival hemorrhage due to a high dose of aspirin.[7] We used the usual doses of acetylsalicylic acid and clopidogrel. Since our patient's subconjunctival hemorrhage regressed after abciximab was withdrawn, despite continuation of use of clopidogrel and acetylsalicylic acid during the follow-up, we consider that this complication was due solely to use of abciximab. Our patient suffered a rare bleeding complication due to abciximab, i.e. bilateral spontaneous subconjunctival hemorrhage. Even though subconjunctival hemorrhage may also occur as a result of rupture of small subconjunctival blood vessels, either idiopathically or after trauma or the Valsalva maneuver, our patient had neither of these causes.

Subconjunctival hemorrhage usually has a benign course and is self-limiting. It is minimally symptomatic and does not necessitate any specific therapy; and this is particularly true for patients who are not using anticoagulants.

CONCLUSION

Bilateral subconjunctival hemorrhage due to use of abciximab has not been previously reported in the literature. Bilateral subconjunctival hemorrhage was seen after abciximab use in our case for the first time in the literature. Bilateral subconjunctival hemorrhage was a rare complication due to use of abciximab in our patient. We treated our patient by stopping his use of abciximab and administering artificial tears and followed him up conservatively on an outpatient basis. We achieved the outcome of complete spontaneous healing. In cases of subconjunctival hemorrhage due to abciximab use, abciximab treatment must be discontinued and full recovery can be achieved by artificial tearing and conservative treatment.

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

São Paulo Medical Journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Editorial policy

Papers with a commercial objective will not be accepted: please review the Journal's conflicts of interest policy below.

São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

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Transparency and integrity: guidelines for writing

The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

All studies published in *São Paulo Medical Journal* must be described in accordance with the specific guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

Conflicts of interest

Authors are required to describe any conflicts of interest that may exist regarding the research or the publication of the article. Failure to disclose any conflicts of interest is a form of misconduct.

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Acknowledgements and funding

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." Any financial support should be acknowledged, always with the funding agency name, and with the protocol number whenever possible. Donation of materials used in the research can and should be acknowledged too.

This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing or reviewing the study, and whose contributions to the publication do not constitute authorship.

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When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

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Articles will be rejected without peer review if:

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- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. This is done in order to ensure transparency and integrity of publication.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;

2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports;
4. a brief description of the contributorship of each author;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number in the PROSPERO database. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

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

Abbreviations, acronyms and products

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

Interventions

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

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

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Short communications

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

Case reports, case series, narrative reviews and letters to the editor

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

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

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

search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

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

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

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

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
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8. Place or institution where the work was developed, city and country.
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10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
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Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
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- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
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References

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

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For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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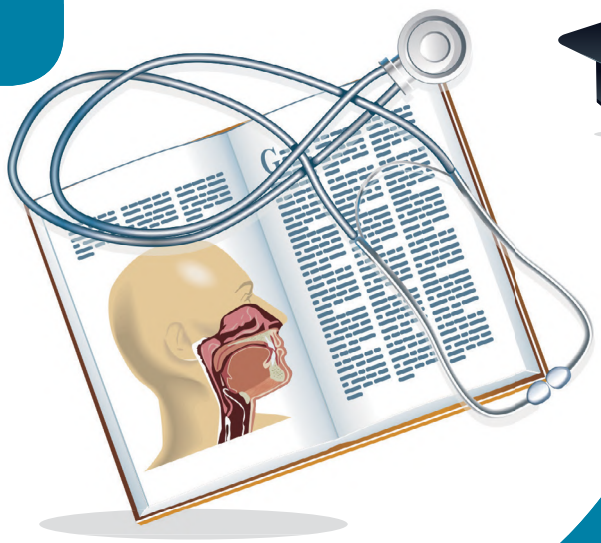

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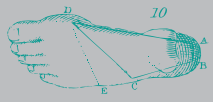

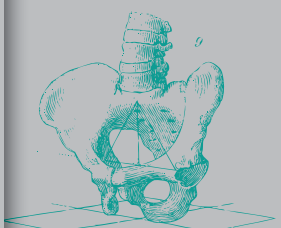

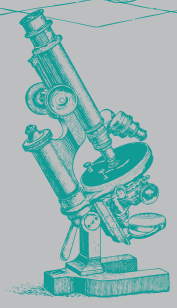

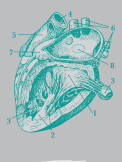

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