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Trends in cardiovascular diseases and heart disease death rates among adults aged 45-64: Brazil, 2000-2017

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In a previous editorial in this Journal this year, I addressed the question of whether the risk of death due to cancer in Brazil will surpass the risk of death due to cardiovascular diseases at some point over the next decades. The conclusion was that "the risks of death due to cardiovascular diseases, independent of aging, are higher than the numbers and risks relating to cancer, for both sexes."[1] This result differed from what was observed recently in the United States.[2]

One criticism of approaches in which all age strata are analyzed is that the older that people are when they die, the more frequent it is that comorbidities will be present, especially coexistence of heart disease and cancer. Consequently, among elderly people, mortality data based on the underlying cause of death do not reflect the primary determinant of death, as occurs in cases of death among young people. A second concern is that the impact of death among middle-aged individuals has much greater social, economic and psychological implications than does death among elderly people.

The differences between rates of occurrence of circulatory diseases and neoplasm among people aged 45 to 64 years for the whole of Brazil from 2000 to 2017 were analyzed using the Ministry of Health mortality databank. The first approach consisted of comparison of proportional mortality; the second step was to determine the annual percentage change (APC) in the mortality rates, calculated using Poisson regression, thereby revealing the inflection points of the mortality rate curves.

Cardiovascular diseases and cancer are the cause of more than half of deaths among adults in Brazil. The excess of deaths for men (67%) was constant over this entire period. Comparison of proportional mortality for each sex between the periods 2000-2002 and 2015-2017 showed that the proportion of deaths due to cardiovascular diseases decreased both for men (from 30.1% to 27.6%) and for women (31.1% to 29.9%), and that the proportion of deaths due to cancer increased both for men (16.6% to 19.9%) and for women (14.4% to 17.9%). The rise in the proportion of or men, the percentage of deaths due to circulatory diseases was 30.1%, and for cancer, 16.6% in 2000-2002 and changed to 27.6% for circulatory disorders

Figure 1 shows different temporal trends of the mortality rates (per 100,000 inhabitants) due to cardiovascular diseases and cancer for each sex, for people aged 45 to 64 years. For men, the risk of death due to all cardiovascular diseases declined year by year at a relatively constant pace. In contrast, the temporal trends regarding death due to cancer among men had a peak in 2010 and has been declining since then.

For women, there was a shift in the risk of death after 2012. In that year, the rates due to cancer and cardiovascular diseases matched. The reason for the shift was a downward trend regarding cardiovascular diseases and an upward trend regarding neoplasm since 2000.

Table 1 shows the temporal trends for coronary heart diseases (CHD), stroke and other cardiovascular diseases (most of them are myocardiopathy). All of these categories presented significant reductions in their rates over 2000-2017. Despite an initial, lower rate of cardiovascular diseases among women than among men, the annual decline was faster for women.

Table 2 shows the patterns of mortality rates due to different types of cancer for women and men, calculated according to the annual percentage change. The most notable difference

according to gender was in relation to lung cancer. Women presented an alarming yearly increase in deaths of 2.4%; in contrast, men had an annual reduction of 1.3%. The mortality rates due to upper aerodigestive cancers (mouth, nose, pharynx, larynx and esophagus), which along with lung cancer are closely associated with the smoking habit, climbed for women but declined for men from 2008 onwards. The combination of those diseases did not materially change the trend according to gender.

Cancers of the colon, rectum, liver, biliary tract and pancreas, myelomas and neoplasms of the central nervous system showed annual increases for both sexes (except myelomas, only for women). Declines in rates were observed for stomach cancer for both genders, and for leukemias and lymphomas for men. The risk of death due to prostate cancer did not change significantly. Breast and ovarium cancer showed an upward trend, but deaths due to endometrial and uterine cervical cancer showed a downward trend.

This description of the mortality rates among middle-aged women and men in Brazil in this century reveals some crucial issues relating to medical and public health:

1. The excess of premature male deaths due to cardiovascular diseases and cancer was constant, with a male-to-female ratio of 2:1.
2. The reduction in cardiovascular diseases among middle-aged men and women was impressive, and this means that the influence of weight gain was not still observed. The death rate due to diabetes also declined (data not shown).
3. The risk of death due to cancer among women surpassed the risk due to circulatory diseases after 2012.
4. The impact of smoking-associated cancer differed according to gender. It can be speculated that, over the next five to ten years, the number of deaths due to lung cancer will be higher among women.
5. The death rates due to neoplasms located in the colon, rectum, liver, biliary tract and pancreas are rising steadily for both sexes. In contrast, stomach cancer deaths are declining.
6. Occurrences of neoplasms located in the central nervous system are rising, as also are occurrences of leukemias, lymphomas and myelomas.

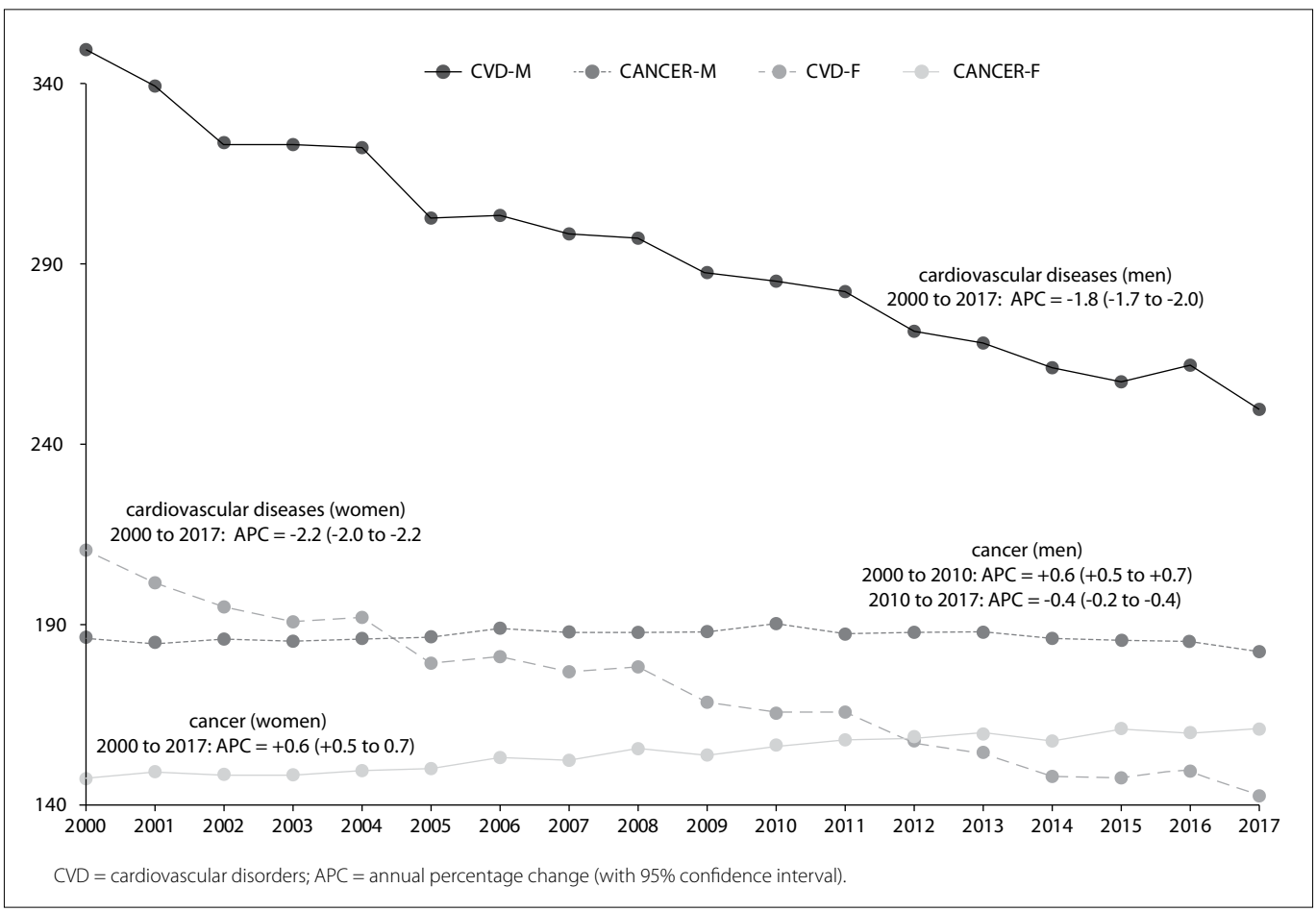

Figure 1. Mortality rates due to cardiovascular diseases and cancer in Brazil from 2000 to 2017, for men and women aged 45 to 64 years.

Table 1. Annual percentage change (APC) and 95% confidence interval (95% CI) for death rates due to cardiovascular disorders (CVD) in Brazil from 2000 to 2017, for women and men aged 45 to 64 years

	Women		Men	
	period	APC (95% CI)	period	APC (95% CI)
Coronary heart disease	2000-17	-1.3 (-1.5 to-1.1)	2000-17	-1.1 (-1.3 to -1.0)
Stroke	2000-17	-3.4 (-3.5 to -3.2)	2000-08	-2.9 (-3.7 to -2.1)
Other CVD	2000-17	-1.8 (-2.0 to -1.6)	2000-17	-1.4 (-1.6 to -1.3)

Table 2. Annual percentage change (APC) and 95% confidence interval (95% CI) for death rates due to cancer in Brazil from 2000 to 2017, for women and men aged 45 to 64 years

	Women			
	period	APC (95% CI)	period	APC (95% CI)
Lung		2.4 (2.2 to 2.7)	2000-17	-1.3 (-1.4 to -1.1)
UAD	2000-07	1.5 (0.6 to 2.4)	2000-09	0.2 (-0.1 to 0.5)
	2007-17	-0.6 (-1.0 to -0.1)	2009-17	-0.7 (-1.0 to -0.4)
Lung + UAD	2000-17	1.7 (1.5 to 1.9)	2000-08	-0.2 (-0.5 to 0.0)
			2008-17	-1.0 (-1.2 to -0.8)
Stomach	2000-17	-0.7 (-1.0 to -0.5)	2000-17	-2.0 (-2.1 to -1.8)
Colon + rectum	2000-17	2.1 (1.9 to 2.4)	2000-17	2.6 (2.4 to 2.8)
Liver + biliary tract	2000-017	0.5 (0.3 to 0.7)	2000-12	1.9 (1.4 to 2.5)
			2012-17	-0.4 (-2.0 to 1.3)
Pancreas	2000-17	1.9 (1.6 to 2.2)	2000-17	2.0 (1.8 to 2.2)
CNS	2000-11	1.4 (1.1 to 1.8)	2000-17	0.7 (0.4 to 1.0)
	2011-17	0.2 (-0.6 to 0.9)		
Lymphoma	2000-17	-0.4 (-0.8 to 0.0)	2000-17	-0.7 (-1.1 to -0.3)
Leukemia	2000-17	-0.2 (-0.6 to 0.2)	2000-17	-0.4 (-0.8 to -0.1)
Myeloma	2000-17	0.7 (0.2 to 1.2)	2000-17	1.2 (0.7 to 1.8)
Prostate	N/A		2000-17	-0.2 (0.3 to 0.0)
Breast	2000-17	0.8 (0.7 to 0.9)		
Ovarium	2000-17	0.9 (0.7 to 1.2)		
Endometrium	2000-09	-2.7 (-3.5 to -1.8)		
	2009-17	0.2 (-0.8 to 1.2)		
Uterine cervix	2000-14	-1.5 (-1.7 to -1.3)		
	2014-17	1.8 (-0.5 to 4.1)		

UAD = upper aerodigestive neoplasm (in mouth, nose, pharynx, larynx and esophagus); CNS = central nervous system.

7. Despite successive annual campaigns against breast and prostate cancer, no impact can be seen. The prostate cancer rate is flatlining and the breast cancer rate is increasing.

Full comprehension of these patterns will require more analysis, including to verify the patterns of mortality due to other non-communicable diseases such as chronic obstructive pulmonary disease, hepatic cirrhosis and chronic kidney failure. Moreover, the impact of external causes of deaths among men as competitive risks needs to be further addressed.

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Health professionals' perception of patient safety culture in a university hospital in São Paulo: A cross-sectional study applying the Hospital Survey on Patient Safety Culture

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KEY WORDS:
Patient safety.
Organizational culture.
Surveys and questionnaires.
Hospitals.
Safety management.

ABSTRACT

BACKGROUND: Patient safety culture is part of the organizational profile of healthcare institutions and is associated with better quality of care.

OBJECTIVE: To assess patient safety culture in a university hospital.

DESIGN AND SETTING: Hospital-based cross-sectional study conducted in a public university hospital in São Paulo, Brazil, between September and December 2015.

METHODS: We randomly selected 68 sectors of the hospital, to include up to 5 employees from each sector, regardless of length of experience. We used the validated Brazilian version of the Hospital Survey on Patient Safety Culture (HSOPS) via an electronic interface. We calculated the percentage of positive responses for each dimension of the HSOPS and explored the differences in age, experience, occupation and educational level of respondents using the chi-square test.

RESULTS: Out of 324 invited respondents, 314 (97%) accepted the invitation and were surveyed. The sample presented predominance of women (72%), nursing staff (45%) and employees with less than six years' experience at the hospital (60%). Nine out of the 12 dimensions showed percentages of positive responses below 50%. The worst results related to "nonpunitive response to errors" (16%). A better safety culture was observed among more experienced staff, nurses and employees with a lower educational level. In the previous year, no events were reported by 65% of the participants.

CONCLUSIONS: The patient safety culture presented weaknesses and most of professionals had not reported any event in the previous year. A policy for improvement and cyclical assessment is needed to ensure safe care.

INTRODUCTION

New technologies associated with increased knowledge regarding healthcare have changed the operation of hospital environments, such that they have become more complex.[1] Simpler treatments have been replaced by sets of procedures requiring continual training and supervision of healthcare professionals. The inherent risks of these more complex systems, combined with insufficient investment, professional overload, communication failures and inadequate supervision in hospital environments, can result in occurrences of adverse events.[2]

Since the 1999 publication of the report "To err is human: Building a safer health system"[2] by the Institute of Medicine, healthcare organizations have increased their focus on issues relating to patient safety.[3] Data on mortality due to adverse events have become available, especially in the United States, in addition to data on the social costs caused by irreversible harm to users and their families.[2]

An update of these data has shown that medical errors are the third leading cause of death in the United States.[4] In settings with lower resources, this risk may be higher. The incidence of adverse events in Brazil has been estimated to be 7.6% for hospitalized patients, and it has been shown that 66.7% could be avoided. These findings are similar to those from studies in other countries.[5]

Healthcare institutions are viewed as organizations that are based on a culture founded on values, attitudes, skills and standards of individual and group behavior, which define quality in healthcare. Patient safety culture is part of the organizational habits of hospital institutions,[1] and an assessment of patient safety culture makes it possible to obtain knowledge on the factors that

are involved in the professionals' routine and their perceptions, along with the strengths and weaknesses of the culture of patient safety. Such assessments also make it possible to identify the sectors and processes that generate risks.[6] Knowing the weaknesses in patient safety culture makes it feasible to establish interventions and improvements in the quality of care for users, thus changing the professionals' behavior.[7]

To assess patient safety culture, surveys with validated questionnaires are widely used.[8] The Hospital Survey on Patient Safety Culture (HSOPS) and the Safety Attitudes Questionnaire have been widely cited in research that aimed to assess patient safety culture in hospital settings worldwide.[6] The HSOPS, developed by the United States Agency for Healthcare Research and Quality (AHRQ) in 2004,[9] proposes 12 dimensions to assess patient safety culture from the professionals' perspective in a hospital setting (**Table 1**). This instrument has been translated and validated for use in several languages,[10-12] and in 2012, the Brazilian version was made available for use.[13] In 2013, the Brazilian government issued regulations on patient safety actions, including identification, reporting and system improvement.[14,15]

OBJECTIVE

Few studies have reported on use of the HSOPS in Brazil to characterize the level of patient safety culture in Brazilian hospitals. In this scenario, studies that estimate patient safety culture are necessary. The objective of this study was to assess perceptions of patient safety culture in a university hospital.

METHODS

Study design and context

This was a hospital-based cross-sectional study in which the HSOPS was used to assess patient safety culture from the professionals' perspective. It was conducted from September to December 2015 at Hospital São Paulo, the university hospital of Universidade Federal de São Paulo, located in the city of São Paulo, the largest city in Brazil. This hospital provides high-complexity care in all medical specialties and has more than 700 beds. The primary outcome was the percentage of positive responses for each dimension of the HSOPS.

Participants

All professionals who directly or indirectly were attending patients in the hospital, regardless of their length of experience at the institution, were eligible for participation in this study. Trainees, interns, dismissed employees and outsourced workers (cleaning, security and food service employees) were not eligible, because not including them would improve the homogeneity of the sample.

Sample size and sampling process

To calculate the sample size, we considered the population of approximately 5,000 employees at the hospital. We made a conservative estimate for the frequency of positive responses regarding the presence of patient safety culture ("strongly agree/agree" or "most of the time/always") of 50%. In the dimensions of the HSOPS, a precision rate of 7%, a value of 1.5 for the sampling effect and a possible loss rate of 10% were used. These parameters resulted in a need to survey a minimum of 312 professionals.

We randomly selected 60 primary and 20 secondary sectors out of the 106 sectors of the main building of the hospital and invited up to five employees who were present at the time of the visit to each sector, to be interviewed.

Data collection

The instrument used for data collection was the Brazilian version of the HSOPS.[13] The survey is composed of 42 items grouped

Table 1. Dimensions of the Hospital Survey on Patient Safety Culture: numbers of items and what is assessed[9]

Dimensions of patient safety culture relating to the work area or unit		
1. Teamwork within units	4 items	
2. Supervisor/manager expectations and actions that promote patient safety	4 items	
3. Organizational learning and continuous improvement	3 items	Assessment of teamwork, considering support by supervisors
4. Communication openness	3 items	and managers, open communication about mistakes and
5. Feedback and communication about error	3 items	continuous improvement of errors within teams
6. Staffing	4 items	
7. Nonpunitive response to errors	3 items	
Dimensions that explore aspects of safety culture in a hospital		
8. Management support for patient safety	3 items	Assessment of hospital management support for patient
9. Teamwork across units	4 items	safety and cooperation between units to maintain the
10. Handoffs and transitions (i.e. handovers)	4 items	quality of and information on patient care
Dimensions of outcome measurements		
11. Overall perceptions of patient safety	4 items	Assessment of the existence of procedures to avoid occurrences
12. Frequency of events reported	3 items	of errors and make rectifications before errors impact the patient

into 12 dimensions that measure different aspects of patient safety culture, including personal data relating to the professional and data on the unit and the hospital (**Table 1**). The HSOPS makes it possible to measure the beliefs, skills and behaviors involved in the safety culture of the organization from hospital staff perspectives.

Each dimension is composed of three to four items that are constructed in a positive or negative manner (**Table 1**). For each item, the respondent may choose a score on a five-point Likert scale with the response options of strongly agree, agree, neither agree nor disagree, disagree and strongly disagree, or response options of never, rarely, sometimes, most of the time and always, in relation to frequency.[9] Two other items assess individual assessments of patient safety: the "patient safety grade", with response options of excellent, very good, acceptable, poor and failing, and the "number of events reported", with response options of no events reported, 1 to 2 events reported, 3 to 5 events reported, 6 to 10 events reported, 11 to 20 events reported and 21 or more events reported.

After reversing the sentences that were negatively worded, we calculated the percentage of positive responses regarding the presence of patient safety culture in each dimension by dividing the number of positive responses ("strongly agree/agree" or "most of the time/always") by the total number of responses (positive, neutral and negative) in the dimension. A percentage of positive responses above 75% was considered strong, and a percentage below 50% showed that there were issues that needed improvement. For items with reverse wording and that had a negative connotation, disagreement indicated a positive response. Thus, to calculate the percentage of positive responses among the answers, we needed to consider the strongly disagree/disagree or never/rarely responses.

In the process of pretesting the survey, we modified the Portuguese-language wording of three items (A5 in the "staffing" dimension, C1 in the dimension of "feedback and communication about error" and G1 in the dimension of "number of events reported"), in accordance with previous recommendations, to improve comprehensibility (**Table 1**).[16] The research group that suggested this wording has, furthermore, validated a new version of the HSOPS in an electronic interface.[17]

The survey was developed using a suite of tools for field data called KoBo Toolbox (www.kobotoolbox.org, Cambridge, MA, USA) and was administered in the workplace. Notices invited hospital staff to participate in the study and, after agreeing to do so and signing an informed consent form, staff members completed the survey using tablet electronic devices (Samsung Galaxy Tab 3). The device recorded the data online or offline and, after connecting to the internet, the surveys were automatically uploaded to the online platform.

Two trained survey administrators performed the data collection: a pharmacy undergraduate student and a pharmacist.

Statistical methods

The negatively worded items were reverse-coded to calculate the percentage of positive responses for each dimension. The answers were recoded as follows: strongly disagree, disagree, neither agree nor disagree, always, most of the time and sometimes were assigned a score of 0; while agree, strongly agree, never and rarely were assigned a score of 1, in accordance with the HSOPS manual.[9]

The proportion of positive responses for each dimension was stratified according to respondent age, length of employment at the hospital (in years: less than 1; 1 to 5; 6 to 10; 11 to 20; or 21 or more), profession (doctor, nurse or other professional) and educational level (completion of high school, undergraduate level or postgraduate level). The differences were tested using the chi-square test and were considered significant if $P < 0.05$.

To assess the internal consistency of the survey, we calculated Cronbach's alpha for each dimension and item of the Brazilian version of the HSOPS. The calculations on the data were done using Stata 14.2.

Ethical issues

The present study was approved by the hospital's research ethics committee, under the number CAAE 48415315.3.0000.5505. All subjects signed an informed consent form.

RESULTS

We invited 324 employees from 68 sectors of the hospital to participate. A total of 314 professionals (97%) accepted the invitation and were included, while 10 (3%) refused to participate.

Most participants were women (72%); 41% had undergraduate and postgraduate educational levels. The majority had direct contact with patients (80%), 45% were nursing staff (nurses, nursing technicians and nursing assistants) and 60% had been working at the hospital for less than six years. As shown in **Table 2**, different professionals participated in the survey.

Nine out of the 12 dimensions showed positive response rates below 50% (**Table 3**). The dimension of "nonpunitive response to errors" had the worst result (16%). A total of 65% of the participants indicated that they had reported no events in the past 12 months. The internal consistency was adequate for eight dimensions and the other four showed lower consistency (Cronbach's alpha < 0.6).

Greater age and length of work experience were associated with higher perceptions of patient safety culture in the dimensions of "supervisor/manager expectations and actions promoting patient safety", "organizational learning and continuous improvement", "frequency of events reported", "feedback and communication about error", "staffing" and "management support for patient safety". On the other hand, the dimension of "nonpunitive response

to errors" was only associated with age (**Table 4**). The dimension of "frequency of events reported" was significantly different according to professional category (higher perception among nurses than among other professionals and physicians) and educational level (lower perception among employees with higher education). The dimension of "management support for patient safety" was also inversely proportional to educational level.

Table 2. Characteristics of the respondents (n = 314)

Characteristics	Sample (n)	Frequency (%)
Age (years)		
18-34	145	46.2
35-44	84	26.8
45-70	85	27.1
Gender		
Female	226	72.0
Male	88	28.0
Educational level		
Elementary and high school	104	33.1
Undergraduate level at college/ university	82	26.1
Postgraduate level	128	40.8
Length of employment at the hospital (years)		
Less than 1	59	18.8
1 to 5	94	29.9
6 to 10	25	8.0
11 to 20	98	31.2
21 or more	38	12.1
Professional experience in the work area/unit (years)		
Less than 1	67	21.3
1 to 5	123	39.2
6 to 10	29	9.2
11 to 20	69	22.0
21 or more	26	8.3
Working hours per week		
Less than 40	126	40.1
40 to 59	140	44.6
60 or more	48	15.3
Staff position		
Physician	53	16.9
Nurse	142	45.2
Other professional (pharmacists, therapists, etc.)	35	11.2
Technicians (laboratory, radiology)	19	6.1
Management/secretary	26	8.3
Other	39	12.4
Direct patient interaction		
Yes	252	80.3
No	62	19.8
Professional experience in the same position or specialty (years)		
Less than 1	37	11.8
1 to 5	100	31.9
6 to 10	25	8.0
11 to 20	104	33.1
21 or more	48	15.3

DISCUSSION

Patient safety culture in this hospital was fragile, considering that 9 of the 12 dimensions of HSOPS were rated at below 50%. Two-thirds of the respondents did not report any events in the last 12 months, thus indicating that potential safety problems may be going unrecognized and are not being addressed properly. The low rate of positive responses for the dimension of "nonpunitive response to errors" has also been found in other studies,[18-20] and this may also explain the behavior of not reporting events.

The dimensions with higher levels of positive responses, i.e. "supervisor/manager expectations and actions promoting patient safety", "organizational learning and continuous improvement" and "teamwork within units", did not represent strengths in patient safety culture, since they fell below 75%.[9] Within their work units, professionals may seek to carry out their activities in a team with supervised support and to look for improvements to patient safety.[21] Teamwork is a critical point and is important because it relies on collaboration and mutual respect.[21] Such values lead to opportunities to adopt improvement programs. Investigations conducted by different researchers have found similar results.[18,22,23]

A study that applied the HSOPS to 26 hospitals in Iran[20] observed that there was better perception in the dimension of "organizational learning and continuous improvement". In teaching hospitals, professionals are willing to improve their understanding and knowledge. It has been observed that in the dimension of "organizational learning and continuous improvement", the percentage of positive responses improves as the amount of work experience increases.[24]

Table 3. Percentage of positive responses according to dimension (n = 314)

Dimensions	%	95% CI	Cronbach's alpha
Supervisor/manager expectations and actions promoting patient safety	53.0	49.2-56.8	0.75
Organizational learning and continuous improvement	51.5	47.9-55.1	0.56
Teamwork within units	51.0	47.5-54.5	0.62
Frequency of events reported	43.8	39.2-48.5	0.89
Communication openness	40.0	36.1-43.9	0.68
Feedback and communication about error	35.7	31.8-39.6	0.70
Overall perceptions of patient safety	34.7	31.7-37.8	0.48
Staffing	28.0	25.2-30.8	0.53
Handoffs and transitions (i.e. handovers)	26.8	23.6-29.9	0.66
Teamwork across units	24.8	22.6-27.1	0.61
Management support for patient safety	23.0	19.4-26.7	0.76
Nonpunitive response to errors	15.6	13.2-18.1	0.37

CI = confidence interval.

The "staffing" dimension needs improvement, which may be an effect caused by a situation of an insufficient number of professionals with heavy workloads. This imbalance increases the risk relating to the assistance provided.[10] In units that perform activities under unfavorable conditions, professionals feel that the level of support that they can count on to carry out their tasks safely when they are confronted by a high volume of responsibilities is lower.[25]

The number of working hours can also be related to the results, since tiredness decreases attention and increases the incidence of errors.[26] A number of factors affect the safety and quality of patient care, such as the organization of nursing units, structure, communication, stress and workload.[27] A better distribution of professionals and appropriate working hours are paramount for improving healthcare quality.

The dimensions of "communication openness" and "feedback and communication about error" indicated that there was a need for to improve priorities. Ineffective communication increases the occurrence of adverse events.[24] As observed in other studies, failure in communication is directly related to worsening of quality of care.[28,29] Hospitals in which there is a channel for free communication between supervisors and employees to exchange suggestions, questions and feedback on improvements in patient safety tend to have better scores for quality and motivation, with regard to learning from errors.[18]

Professionals with greater experience had a better perception of safety culture. Usually, such professionals have more responsibility or occupy leadership positions within their teams. This may positively influence their perception of patient safety, as observed in a study conducted in Finland that compared the perceptions of managers and registered nurses.[30] The experience of a professional can positively influence the results, as shown in a Palestinian study in which the number of adverse events reported increased with a professional's length of experience.[19] The participants in the present study were mostly composed of early-career professionals, which may explain the low rate of errors reported. More events were reported by nurses than by the medical team, which is similar to what was seen in a study conducted in the United States.[31]

Given that contextual limitations may have influenced the present results, we need to highlight that an employee strike had ended just before the time of data collection and that budget cuts occurred during the survey period. Despite the difficulties faced by these professionals, a good acceptance rate

Table 4. Frequency of positive responses in the dimensions of patient safety culture, stratified according to subgroups (n = 314)

Variables	Dimensions of patient safety culture											
	1	2	3	4	5	6	7	8	9	10	11	12
Age group (years)												
18-24	44.6	51.8	44.0	16.7	25.9	25.0	34.5	22.6	17.9	20.5	29.5	15.5
25-34	49.8	52.6	47.9	17.4	29.5	30.5	34.5	39.0	23.7	25.0	25.6	12.3
35-54	56.8	53.6	59.1	20.6	40.5	40.1	49.2	48.8	26.8	31.0	25.3	14.7
55-70	59.7	66.1	64.5	46.2	48.4	51.6	44.1	68.8	33.1	39.5	33.1	29.0
P-value	0.132	0.135	0.012	< 0.001	0.003	0.001	0.083	< 0.001	0.095	0.020	0.571	0.009
Length of experience (years)												
< 1	52.1	58.1	45.2	21.5	31.8	32.2	37.3	32.8	24.2	22.9	30.9	13.0
1-5	49.7	50.5	50.4	25.2	31.6	32.6	36.2	42.9	23.4	25.0	26.3	15.6
6-10	43.0	48.0	50.7	8.0	35.0	33.3	34.7	52.0	17.0	34.0	25.0	14.7
11-15	57.1	50.7	55.4	20.3	35.8	35.1	45.5	43.2	29.4	28.7	26.7	13.5
16-20	57.3	62.5	55.6	20.8	36.5	44.4	48.6	58.3	26.0	28.1	25.0	18.1
≥ 21	55.3	67.1	68.4	43.0	52.6	55.3	51.8	61.4	31.6	45.4	30.9	27.2
P-value	0.304	0.037	0.027	< 0.001	0.023	0.003	0.059	< 0.001	0.227	0.008	0.864	0.076
Staff position												
Physician	55.7	62.3	48.4	18.2	31.6	30.8	34.6	31.4	25.0	25.9	26.9	15.7
Nurse	55.5	53.0	56.3	25.1	37.3	38.7	47.4	51.2	28.7	31.3	33.1	17.6
Other	51.2	52.7	52.1	23.4	35.3	37.5	39.3	46.3	25.3	28.3	25.0	14.2
P-value	0.771	0.299	0.535	0.474	0.692	0.454	0.175	0.013	0.804	0.698	0.413	0.804
Educational level												
High school or less	54.3	59.9	60.3	36.9	39.9	46.8	43.3	58.7	26.7	32.5	34.6	18.3
Undergraduate	50.9	51.8	49.6	17.5	33.2	31.7	37.4	38.2	25.0	24.7	23.8	15.4
Postgraduate	52.3	52.3	49.7	17.2	34.2	32.0	42.2	38.8	25.2	28.7	24.4	14.8
P-value	0.890	0.435	0.219	0.001	0.566	0.041	0.666	0.004	0.956	0.475	0.158	0.772

Note: Dimensions: (1): Teamwork within units; (2): Supervisor/manager expectations and actions promoting patient safety; (3): Organizational learning and continuous improvement; (4): Management support for patient safety; (5): Overall perceptions of patient safety; (6): Feedback and communication about error; (7): Communication openness; (8): Frequency of events reported; (9): Teamwork across units; (10): Staffing; (11): Handoffs and transitions (i.e. handovers); (12): Nonpunitive response to errors.

was obtained for the survey. The participants were a diverse group of professionals who were either directly or indirectly involved with patient care. Examining the hospital as a whole improves the representativeness of the results.[32] We also chose to approach employees in person instead of via remote strategies, which are more prone to give rise to a less diverse sample population and a lower response rate. The institution surveyed here is a university hospital and its staff include a wide variety of professionals for the purposes of undergraduate education, residency and specialization. These data may suggest that high turnover exists,[33,34] and this may have been related to the low perception of safety among these professionals.

The reliability of the HSOPS version used in the present study was fair. Changes that had been made to improve comprehensibility[16] resulted in better consistency in the "staffing" dimension, such that it improved from 0.20 in the first Brazilian validation of the HSOPS[13] to 0.53 in the present study. A new validation of the HSOPS that featured better wording of these questions was performed and published after our survey was conducted and had high instrument reliability.[17]

The negative results found in the present study may be viewed as demotivating with regard to patient safety in the hospital. Measuring safety culture is the first step towards identifying the priorities that need to be addressed if a change in patient safety is to be achieved. In Brazil, the regulations in this field are still evolving, and greater investment in patient safety strategies is required.[14,15] In addition to ameliorating assistance, improvement of patient safety culture in university hospitals enriches undergraduate and postgraduate education.

CONCLUSION

Patient safety culture in this Brazilian hospital was shown to be fragile, and improvement is necessary in order to ensure safe care. Implementation of enhancement measures and further assessment of patient safety culture should be a cyclical process to drive effective changes in patient safety forward.

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Secondary prevention of coronary heart disease: a cross-sectional analysis on the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Risk factors.
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ABSTRACT

BACKGROUND: Coronary heart disease (CHD) remains a major cause of mortality worldwide and in Brazil. Use of standard medications after CHD has been proven to avoid new events and reduce early mortality.

OBJECTIVES: This study aimed to analyze secondary prevention of CHD and its association with the baseline characteristics of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

DESIGN AND SETTING: Cross-sectional analysis on ELSA-Brasil data.

METHODS: Secondary prevention of CHD recommended in standard guidelines (antiplatelet plus beta-blocker plus lipid-lowering drug, with or without angiotensin-converting enzyme inhibitors, ACEI, or angiotensin receptor blockers, ARB) was evaluated in relation to sociodemographic data and the time since the coronary event. The chi-square test, one-way analysis of variance (ANOVA) and Mann-Whitney test were performed, as necessary.

RESULTS: Among 15,094 participants, 2.7% reported a previous diagnosis of CHD. Use of recommended drugs for secondary prevention was reported by almost 35% of the participants. Medication use for secondary prevention was generally more frequent among high-income participants than among low-income participants. Use of ARB and ACEI was different between participants who had private health insurance and those who only used the public healthcare system. Men were more likely to use medication than women. The frequency with which participants used the recommended drugs was similar in all time periods after CHD, but use of only one drug increased progressively across time periods.

CONCLUSION: The use of medication for secondary prevention of CHD was lower than what is recommended in standardized guidelines, especially among women and lower-income participants.

INTRODUCTION

Coronary heart disease (CHD) remains a major cause of mortality worldwide and in Brazil. As life expectancy has increased in low-middle income countries, including Brazil, and people start to live long enough to develop CHD, there has been an increase in the years of life lost (YLL) that possibly presents a correlation with suboptimal access to healthcare in these areas.[1] In Brazil, late case-fatality in occurrences of CHD is a very important problem that has been found to be associated with poor follow-up after an acute coronary event.[2]

In this context, secondary prevention of CHD, especially using pharmacological therapy, has been effective in reducing recurrence of events, decreasing morbidity and mortality and improving quality of life.[3] National and international guidelines recommend long-term use of evidence-based medication for management of CHD, such as use of acetylsalicylic acid (ASA), beta blockers, angiotensin-converting enzyme inhibitors (ACEI) and statins, as first-line therapy; or other antiplatelet medication, angiotensin receptor blocker (ARB) or fibrate when first-line therapy is contraindicated.[3-8] Despite this well-established knowledge, not all patients with CHD are able to obtain the standard treatment endorsed by the guidelines. Lack of adherence to these medications is associated with higher risk of adverse outcomes. Furthermore, sociodemographic factors are known to influence medication use and prescription, and all these factors need to be taken into consideration when developing interventions and public policies that are aimed towards improving adherence.[9-12]

OBJECTIVE

We sought to analyze secondary prevention of CHD and its association with the baseline characteristics of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

METHODS

Participants

ELSA-Brasil is a cohort study on 15,105 civil servants aged 35 to 74 years living in six cities (Salvador, Vitória, Belo Horizonte, Rio de Janeiro, São Paulo and Porto Alegre). It was designed to investigate cardiovascular diseases and diabetes, and their associated factors.[13] The exclusion criteria were current or recent pregnancy (< 4 months prior to the first interview), intention to leave employment at the institution in the near future, severe cognitive or communication impairment or living outside of the study center's corresponding metropolitan area. The baseline assessment was made between August 2008 and December 2010 and included application of validated questionnaires and clinical and laboratory examinations.[13-16]

All the participants in the study were invited to visit the research center to answer a detailed questionnaire on their sociodemographic and clinical risk factors, along with their medication use. The training for all interviewers was centralized, with certification and recertification every six months for all interviewers and for all the people who performed measurements and laboratory tests. Also, during data collection, periodic staff meetings were held to discuss problems and to check whether standardized procedures were correctly performed.[13]

The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki. Approvals were granted by the institutional review boards of all centers [Ethics Committees of Hospital de Clínicas de Porto Alegre (under the registration number 194/06), Hospital Universitário da Universidade de São Paulo (669/06), Fundação Oswaldo Cruz (343/06), Universidade Federal de Minas Gerais (186/06), Universidade Federal da Bahia (027/06) and Universidade Federal do Espírito Santo (041/06)] and all participants provided written informed consent.[17]

In this cross-sectional baseline analysis, we included all participants for whom self-reported information about CHD was available (N = 15,094).

Variables

Coronary heart disease

CHD was considered to be present if it was self-reported at the baseline assessment, through reports of a medical history of myocardial infarction and/or percutaneous coronary intervention, including balloon angioplasty with or without stent placement, or myocardial revascularization.

Medication use

All participants were asked about their continuous and non-continuous use of prescription and nonprescription medication over the previous two weeks. They were instructed to bring all medications to the study center. Seven different categories were created for medication use: ASA, any beta blocker, ACEI, statins, other antiplatelet medications, ARB and fibrates. A description of the drugs included is provided in **Supplemental File 1**.

Time since CHD

The time that had elapsed since the occurrence of CHD was defined as the difference between the date of the interview and the date of the event, as reported by the participants. When both infarction and coronary intervention were reported, the oldest event was used. This variable was divided into the following categories: ≤ 4, 5-9, 10–14 and ≥ 15 years.

Covariates

This study considered the following sociodemographic variables: age (years), sex, self-declared race (white, mixed, black, Asian or indigenous), education (less than high school, completed high school and some college/university, or completed college/university or more), mean monthly family income (≤ USD 1245, USD 1246–3319 or ≥ USD 3320) and whether the participants had private health insurance. Local currency (Brazilian reais, BRL) was converted to U.S. dollars (USD) at the prevailing rate in December 2008, of BRL 2.00 = USD 1.00.

Anthropometric measurements were obtained using standard protocols.[18] Body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in meters).

A family history of premature cardiovascular disease was taken to mean a diagnosis of CHD, including myocardial infarction, revascularization or sudden death in a first-degree relative before the age of 60 years. Smoking and alcohol use were categorized as never, past or current. Presence of hypertension was defined as use of antihypertensive medication, or systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg.

Presence of diabetes mellitus was defined as a previous medical diagnosis, use of medication to treat diabetes, fasting plasma glucose ≥ 7.0 mmol/l (≥ 126 mg/dl), two-hour plasma glucose after an oral glucose overload as part of an oral glucose tolerance test ≥ 11.1 mmol/l (≥ 200 mg/dl) or glycated hemoglobin (HbA1c) ≥ 6.5% (≥ 47.5 mmol/mol). Presence of dyslipidemia was defined as an LDL-cholesterol level ≥ 130 mg/dl or use of lipid-lowering medication. Presence of chronic kidney disease (CKD) was defined as a glomerular filtration rate (calculated by means of CKDEpi) < 60 ml/min/1.73 m^2. The strategies used for collection, processing and quality control of the blood and urine tests in ELSA-Brasil have been published previously.[19]

Depression was assessed through the Clinical Interview Schedule-Revised (CIS-R), which is a structured interview used to diagnose current common nonpsychotic conditions.[20,21]

Dietary quality was assessed using the Brazilian Healthy Eating Index Revised (BHEI-R), via a score ranging from 0 to 100.[22] Physical activity during leisure time and commuting was assessed through the International Physical Activity Questionnaire (IPAQ) long form,[23-25] and the participants were categorized as active, insufficiently active or inactive, as recommended by the World Health Organization (WHO).

Adherence to medication was assessed using the four-item Morisky Medication Adherence Scale (MMAS-4). This method consisted of asking four questions about the use of continuous medication: (1) Sometimes if you feel worse when you take the medicine, do you stop taking it? (2) When you feel better, do you sometimes stop taking your medicine? (3) Are you careless at times about taking your medicine? and (4) Do you ever forget to take your medicine? The participants were considered to be adherent if they answered "no" to all questions. Nonadherence consisted of at least one positive answer.[26]

Statistical analysis

Categorical variables were compared using the chi-square test, and were presented as absolute numbers and proportions. Continuous variables were tested for normality using the Kolmogorov-Smirnov goodness-of-fit test. They were compared either using one-way analysis of variance (ANOVA), with presentation as means and standard deviations; or using the Mann-Whitney test, with presentation as medians and interquartile ranges, as appropriate. In addition, associations of sociodemographic variables and medication use (antiplatelet drug plus beta blocker plus lipid-lowering drug, with or without ACEI or ARB) were assessed by means of logistic regression models. Crude models (univariate analysis) and an adjusted model (taking into account income, education, sex, race, age and private health insurance) were built and presented with the odds ratio (OR) and 95% confidence interval (95% CI).

All the analyses were performed using the Statistical Package for the Social Sciences software, version 22 (SPSS Inc., Chicago, Illinois, USA). P-values < 0.05 were considered statistically significant.

RESULTS

Among the 15,094 participants, 405 (2.7%) reported having a prior history of CHD. The frequency of CHD was higher among men and participants in the lower socioeconomic level (less education and lower mean family monthly income). The participants with CHD had higher BMI and, especially, larger waist circumference, as well as higher frequencies of hypertension, diabetes, dyslipidemia, CKD and depression. They presented lower HDL-cholesterol and LDL-cholesterol levels than those of non-CHD participants. In the case of LDL-c, the lower levels may be explained by reverse causation, with prescription of statins for patients with CHD. The participants with CHD presented slightly higher quality in their diets, but although this was statistically significant, the differences were not clinically relevant. They were less active during leisure time, but no difference was found in relation to commuting. The participants with CHD had higher frequency of adhering to continuous medication than did those without the disease (**Table 1**).

Tables 2 and 3 show the associations of medication use and sociodemographic characteristics among the participants who self-reported CHD (first and second-line therapy for secondary prevention, respectively). Older participants reported having higher frequencies of use of ASA, statins, other antiplatelet medications and ARB, but no differences were found in relation to beta blockers and ACEI. Except for ARB, medication use for secondary prevention of CHD was higher among men than among women. Use of ASA, other antiplatelet medications and statins was higher among whites and those with higher socioeconomic status (higher education and income), except for beta blockers, for which use was higher among individuals with high income but not among whites or individuals with higher education levels. Having private health insurance was associated with use of ASA, other antiplatelet medications, ARB and statins, and with no use of ACEI. No association was found between fibrate use and any sociodemographic characteristic. Adhering to continuous treatment was associated with use of all first-line medications, except ACEI.

After adjustment for sociodemographic variables through logistic regression, men and participants reporting higher income presented higher frequency of using the recommended drugs for secondary prevention of CHD (**Supplemental File 2**). We also analyzed differences in sociodemographic variables according to sex, in an attempt to explain the lower use of secondary prevention among women than among men. Women with CHD presented higher frequency of lower education and income than seen among men, and more frequently reported themselves as having black or mixed color, than as having white skin color (**Supplemental File 3**).

The proportion of the participants who were not using any of the recommended drugs was approximately 16% and this was similar among all the periods of time since the occurrence of CHD (≤ 4, 5-9, 10-14 and ≥ 15 years), although it was higher among those with four years or less and with 15 years or more since the event. Recommended combinations (antiplatelet medication plus beta blocker plus lipid-lowering drugs, with or without ACEI/ARB) were used by around 35% and this proportion was also similar among different time periods. However, the most common situation regarding use of secondary prevention was the use of only one drug, which was reported by 11.8% of the participants with four years or less since the event and 21.7% of those with 15 years or more since the event (**Table 4**).

Table 1. Characteristics of participants with self-reported coronary heart disease at the baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

	Coronary heart disease		P-value
	No n = 14,689 (%)	Yes n = 405 (%)	
Age (years)*	51.8 (9.0)	60.9 (8.1)	< 0.0001
Age stratum (%)			
35-44	3,333 (22.7)	7 (1.7)	< 0.0001
45-54	5,848 (39.8)	86 (21.2)	
55-64	4,060 (27.6)	172 (42.5)	
65-74	1,448 (9.9)	140 (34.6)	
Female (%)	8,065 (54.9)	148 (36.5)	< 0.0001
Race (%)			
White	7,574 (52.2)	212 (53.5)	0.199
Mixed	4,102 (28.3)	98 (24.7)	
Black	2,325 (16.0)	69 (17.4)	
Asian	364 (2.5)	9 (2.3)	
Indigenous	149 (1.0)	8 (2.0)	
Educational level (%)			
Less than high school	1,803 (12.3)	114 (28.1)	< 0.0001
High school and some college/university	4,108 (28.0)	94 (23.2)	
Completed college/university or more	8,778 (59.8)	197 (48.6)	
Mean monthly family income (%)			
≤ USD 1,245	3,868 (26.4)	121 (30.1)	0.026
USD 1,246 to 3,319	5,579 (38.1)	127 (31.6)	
≥ USD 3,320	5,178 (35.4)	154 (38.3)	
Private health insurance (%)	10,024 (68.2)	272 (67.2)	0.643
Smoker (%)			
Never	8,423 (57.3)	164 (40.5)	< 0.0001
Past	4,332 (29.5)	197 (48.6)	
Current	1,933 (13.2)	44 (10.9)	
Alcohol consumption (%)			
Never	1,545 (10.5)	66 (16.5)	< 0.0001
Past	2,927 (20.0)	104 (25.9)	
Current	10,195 (69.5)	231 (57.6)	
Dietary quality score*	69.7 (9.3)	71.3 (10.9)	0.004
Leisure-time physical activity (%)			
Inactive	9,129 (63.1)	286 (71.3)	0.003
Insufficiently active	1,830 (12.6)	42 (10.5)	
Active	3,517 (24.3)	73 (18.2)	
Commuting physical activity (%)			
Inactive	3,856 (26.7)	106 (26.4)	0.884
Insufficiently active	5,608 (38.8)	152 (37.9)	
Active	4,984 (34.5)	143 (35.7)	
Family history (%)	3,052 (21.1)	139 (35.9)	< 0.0001
Dyslipidemia (%)	8,331 (57.2)	326 (81.3)	< 0.0001
Hypertension (%)	5,090 (34.7)	304 (75.2)	< 0.0001
Diabetes mellitus (%)	2,796 (19.0)	171 (42.2)	< 0.0001
Chronic kidney disease (%)	902 (6.2)	75 (18.7)	< 0.0001
Depression (%)	607 (4.1)	29 (7.2)	0.003
Body mass index (kg/m^2)*	27.0 (4.8)	28.1 (4.6)	< 0.0001
Waist circumference (cm)*	91.1 (12.9)	97.0 (12.2)	< 0.0001
Triglycerides (mg/dl)**	114.0 (81;165)	127.0 (95;173)	< 0.0001
LDL cholesterol (mg/dl)*	131.5 (34.8)	114.1 (40.5)	< 0.0001
HDL cholesterol (mg/dl)*	56.8 (14.6)	51.54 (13.1)	< 0.0001
Medication adherence (%)			
Adherent	3,130 (37.0)	163 (44.3)	0.005
Non-adherent	5,321 (63.0)	205 (55.7)	

USD = United States dollars; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

*Presented as the mean (with SD); **Presented as the median (with interquartile interval).

DISCUSSION

In the baseline assessment of ELSA-Brasil, 2.7% of the participants self-reported having a previous diagnosis of CHD, with higher frequencies among men and older participants. As expected, lower educational and income levels, and presence of cardiovascular risk factors, such as hypertension, diabetes, central obesity, prior family history of CHD and sedentarism, were more common among participants reporting previous CHD at the baseline.

However, even though the ELSA-Brasil sample presented higher educational and income levels than those of the general population in Brazil, the use of recommended treatment for secondary prevention of CHD (antiplatelet plus beta blockers plus lipid-lowering drugs, with or without ACEI/ARB) was low. As expected, participants with CHD reported having greater adherence to continuous treatment than did those without the disease, and those who were using the first-line recommended drugs also reported better adherence.

Individuals with higher income reported having greater use of medication than did individuals with lower income. Moreover, access to private health insurance was associated with higher use of ARB and other antiplatelet drugs, and lower use of ACEI.

Men were more likely to use preventive drugs than women were, which may have reflected lower levels of prescription of secondary prevention for women. This highlights the importance of considering CHD among women to be a public health concern.

In Brazil, the national drug policy provides free-of-charge medication via the public healthcare system (Sistema Único de Saúde, SUS). The government has also created the Popular Pharmacy Program (Programa Farmácia Popular do Brasil), in which drugs are fully or partly financed by the government in order to increase access to medication. Initially, this program covered drugs for hypertension and diabetes. At the time of the ELSA-Brasil baseline evaluation (2008 to 2010), only two of the recommended drugs

Table 2. Sociodemographic variables associated with use of first-line therapy among participants with self-reported coronary heart disease

	ASA			Beta blockers			ACEI			Statins		
	No n = 184	Yes n = 220	P-value	No n = 189	Yes n = 215	P-value	No n = 263	Yes n = 141	P-value	No n = 163	Yes n = 241	P-value
Age (mean, SD)	59.3 (8.3)	62.2 (7.6)	0.0004	60.2 (8.4)	61.4 (7.7)	0.145	60.4 (8.4)	61.8 (7.3)	0.082	58.7 (8.5)	62.3 (7.4)	< 0.0001
Age stratum (%)												
35-44	7 (3.8)	0 (0.0)		6 (3.2)	1 (0.2)		7 (2.7)	0 (0.0)		7 (4.3)	0 (0.0)	
45-54	47 (25.5)	39 (17.7)	0.002	43 (22.8)	43 (20.0)	0.148	61 (23.2)	25 (17.7)	0.111	45 (27.6)	41 (17.0)	< 0.0001
55-64	78 (42.4)	94 (42.7)		80 (42.3)	92 (42.8)		106 (40.3)	66 (46.8)		71 (43.6)	101 (41.9)	
65-74	52 (28.3)	87 (39.5)		60 (31.7)	79 (19.6)		89 (33.8)	50 (35.5)		40 (24.5)	99 (41.1)	
Sex (%)												
Male	96 (52.2)	160 (72.7)	< 0.0001	109 (57.7)	147 (68.4)	0.026	156 (59.3)	100 (70.9)	0.021	78 (47.9)	178 (73.9)	< 0.0001
Female	88 (47.8)	60 (27.3)		80 (42.3)	68 (31.6)		107 (40.7)	41 (29.1)		85 (52.1)	63 (26.1)	
Race (%)												
White	79 (43.4)	133 (62.1)		88 (46.8)	124 (59.6)		133 (52.0)	79 (56.4)		64 (39.8)	148 (63.0)	
Mixed	48 (26.4)	50 (23.4)		50 (26.6)	48 (23.1)		68 (26.6)	30 (21.4)		45 (28.0)	53 (22.6)	
Black	47 (25.8)	22 (10.3)	0.0003	39 (20.7)	30 (14.4)	0.076	43 (16.8)	26 (18.6)	0.706	43 (26.7)	26 (11.1)	< 0.0001
Asian	5 (2.7)	4 (1.9)		5 (2.7)	4 (1.9)		7 (2.7)	2 (1.4)		4 (2.5)	5 (2.1)	
Indigenous	3 (1.6)	5 (2.3)		6 (3.2)	2 (1.0)		5 (2.0)	3 (2.1)		5 (3.1)	3 (1.3)	
Education (%)												
Less than high school	59 (32.1)	55 (25.0)		61 (32.3)	53 (24.7)		67 (25.5)	47 (33.3)	0.229	55 (33.7)	59 (24.5)	
High school and some college/ university	51 (27.7)	43 (19.5)	0.009	48 (25.4)	46 (21.4)	0.062	65 (24.7)	29 (20.6)		57 (35.0)	37 (15.4)	< 0.0001
Completed college/ university or more	74 (40.2)	122 (55.5)		80 (42.3)	116 (54.0)		131 (49.8)	65 (46.1)		51 (31.3)	145 (60.2)	
Income (%)												
≤ USD 1,245	66 (36.3)	55 (25.0)		64 (34.0)	57 (26.6)		78 (29.9)	43 (30.5)		71 (43.8)	50 (20.8)	
USD 1,246 to 3,319	68 (37.4)	59 (26.8)	< 0.0001	67 (35.6)	60 (28.0)	0.008	86 (33.0)	41 (29.1)	0.705	59 (36.4)	68 (28.3)	< 0.0001
≥ USD 3,320	48 (26.4)	106 (48.2)		57 (30.3)	97 (45.3)		97 (37.2)	57 (40.4)		32 (19.8)	122 (50.8)	
Private health insurance (%)	114 (62.0)	157 (71.4)	0.045	128 (67.7)	143 (66.5)	0.796	189 (71.9)	82 (58.2)	0.005	92 (56.4)	179 (74.3)	< 0.0001
Medication adherence (%)												
Adherent	49 (32.7)	114 (52.3)		57 (37.0)	106 (49.5)		95 (41.9)	68 (48.2)		35 (27.1)	128 (53.6)	
Non-adherent	101 (67.3)	104 (47.7)	0.0002	97 (63.0)	108 (50.5)	0.017	132 (58.1)	73 (51.8)	0.231	94 (72.9)	111 (46.4)	< 0.0001

ASA = acetylsalicylic acid; ACEI = angiotensin-converting enzyme inhibitor; SD = standard deviation; USD = United States dollars.

Table 3. Sociodemographic variables associated with use of second-line therapy among participants with self-reported coronary heart disease

	Other antiplatelet			ARB			Fibrate		
	No n = 349 (%)	Yes n = 55 (%)	P-value	No n = 332 (%)	Yes n = 72 (%)	P-value	No n = 398 (%)	Yes n = 6 (%)	P-value
Age (mean, SD)	60.3 (8.0)	64.4 (7.5)	< 0.0001	60.1 (8.0)	64.3 (7.4)	< 0.0001	60.9 (8.1)	60.3 (5.6)	0.873
Age stratum (%)									
35-44	7 (2.0)	0 (0.0)		7 (1.7)	0 (0.0)		7 (1.8)	0 (0.0)	
45-54	78 (22.3)	8 (14.5)	0.001	77 (23.2)	9 (12.5)	0.001	85 (21.4)	1 (16.7)	0.670
55-64	157 (45.0)	15 (27.3)		148 (44.6)	24 (33.3)		168 (42.2)	4 (66.7)	
65-74	107 (30.7)	32 (58.2)		100 (30.1)	39 (54.2)		138 (34.7)	1 (16.7)	
Sex (%)									
Male	214 (61.3)	42 (76.4)	0.031	215 (64.8)	41 (56.9)	0.212	252 (63.3)	4 (66.7)	0.866
Female	135 (38.7)	13 (23.6)		117 (35.2)	31 (43.1)		146 (36.7)	2 (33.3)	
Race (%)									
White	173 (50.4)	39 (73.6)		179 (54.7)	33 (47.8)		208 (53.2)	4 (40.0)	
Mixed	90 (26.2)	8 (15.1)		74 (22.6)	24 (34.8)		97 (24.8)	1 (20.0)	
Black	64 (18.7)	5 (9.4)	0.034	59 (18.0)	10 (14.5)	0.319	69 (17.6)	0 (0.0)	0.771
Asian	8 (2.3)	1 (1.9)		8 (2.4)	1 (1.4)		9 (2.3)	0 (0.0)	
Indigenous	8 (2.3)	0 (0.0)		7 (2.1)	1 (0.3)		8 (2.0)	0 (0.0)	
Education (%)									
Less than high school	112 (32.1)	2 (3.6)		90 (27.1)	24 (33.3)		112 (28.1)	2 (33.3)	
High school and some college/university	81 (23.2)	13 (23.6)	< 0.0001	84 (25.3)	10 (13.9)	0.108	93 (23.4)	1 (16.7)	0.917
Completed college/university or more	156 (44.7)	40 (72.7)		158 (47.6)	38 (52.8)		193 (48.5)	3 (50.0)	
Income (%)									
≤ USD 1,245	114 (32.8)	7 (13.0)		102 (30.8)	19 (26.8)		119 (30.1)	2 (33.3)	
USD 1,246 to 3,319	115 (33.0)	12 (22.2)	< 0.0001	102 (30.8)	25 (35.2)	0.712	126 (31.8)	1 (16.7)	0.716
≥ USD 3,320	119 (34.2)	35 (64.8)		127 (38.4)	27 (38.0)		151 (38.1)	3 (50.0)	
Private health insurance (%)	227 (65.0)	44 (80.0)	0.028	211 (63.6)	60 (83.3)	0.001	267 (67.1)	4 (66.7)	0.983
Medication adherence (%)									
Adherent	133 (42.4)	30 (55.6)	0.71	131 (44.3)	32 (44.4)	0.977	161 (44.5)	2 (33.3)	0.586
Non-adherent	181 (57.6)	24 (44.4)		165 (55.7)	40 (55.6)		201 (55.5)	4 (66.7)	

ARB = angiotensin receptor blockers; SD = standard deviation; USD = United States dollars.

Table 4. Frequency of medication use according to drug class and time that had elapsed since coronary heart disease, at baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

Drug class and combination	Time since CHD (years) n = 398 (%)				Total
	≤ 4	5-9	10-14	≥ 15	
Only ASA/other antiplatelet	3 (1.8)	4 (3.5)	1 (1.5)	1 (2.2)	9 (2.3)
Only beta blocker	3 (1.8)	6 (5.3)	2 (2.9)	1 (2.2)	12 (3.0)
Only ACEI/ARB	7 (4.1)	3 (2.7)	8 (11.8)	6 (13.0)	24 (6.0)
Only statin/fibrate	7 (4.1)	5 (4.4)	1 (1.5)	2 (4.3)	15 (3.8)
ASA/other antiplatelet + beta blocker	2 (1.2)	1 (0.9)	3 (4.4)	1 (2.2)	7 (1.8)
ASA/other antiplatelet + ACEI/ARB	6 (3.5)	2 (1.8)	3 (4.4)	1 (2.2)	12 (3.0)
ASA/other antiplatelet + statin/fibrate	10 (5.8)	9 (8.0)	6 (8.8)	1 (2.2)	26 (6.5)
Beta blocker + ACEI/ARB	7 (4.1)	3 (2.7)	2 (2.9)	1 (2.2)	13 (3.3)
Beta blocker + statin/fibrate	4 (2.3)	2 (1.8)	2 (2.9)	1 (2.2)	9 (2.3)
ACEI/ARB + statin/fibrate	7 (4.1)	5 (4.4)	1 (1.5)	1 (2.2)	14 (3.5)
ASA/other antiplatelet + beta blocker + ACEI/ARB	6 (3.5)	4 (3.5)	4 (5.9)	3 (6.5)	17 (4.3)
ASA/other antiplatelet + beta blocker + statin/fibrate	20 (11.7)	16 (14.2)	8 (11.8)	5 (10.9)	49 (12.3)
ASA/other antiplatelet + ACEI/ARB + statin/fibrate	12 (7.0)	6 (5.3)	2 (2.9)	1 (2.2)	21 (5.3)
Beta blocker + ACEI/ARB + statin/fibrate	5 (2.9)	7 (6.2)	1 (1.5)	3 (6.5)	16 (4.0)
ASA/other antiplatelet + beta blocker + ACEI/ARB + statin/fibrate	42 (24.6)	26 (23.0)	14 (15.2)	10 (21.7)	92 (23.1)
None of the recommended drugs	30 (17.5)	14 (12.4)	10 (14.7)	8 (17.4)	62 (15.6)
Total	**171 (100)**	**113 (100)**	**68 (100)**	**46 (100)**	**398 (100)**

CHD = coronary heart disease; ASA = acetylsalicylic acid; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers.

for secondary prevention of CHD were included in the Popular Pharmacy Program (beta blockers and ACEI), but all of the recommended drugs were provided via SUS.

Despite these governmental efforts to provide access, not all drugs are constantly available in the public sector, in contrast with the situation in private establishments.[27] This could partially explain our findings of lower medication use among participants with lower income than among those with higher income. Even in the ELSA-Brasil sample, which had greater access to healthcare services and higher income than the general Brazilian population, lower mean monthly family income was still a significant barrier against use of secondary prevention.

Access to private healthcare, mainly through private health insurance, was related to lower use of standard treatment, since these people were more frequently using second-line therapies such as ARB and other antiplatelet drugs. Adverse reactions to ASA and ACEI (e.g. bleeding and coughing, respectively) are common, and could cause an increase in the use of alternative drugs (other antiplatelet medications and ARB). However, the use of these alternative drugs is considerably higher among participants with private health insurance, especially ARB use. Therefore, adverse reactions may not be the only explanation for this higher use of ARB instead of ACEI. Healthcare professionals in private institutions may be prescribing more ARB and other antiplatelet medications not only because of their possible therapeutic advantages for some CHD patients, but also because they are newer, with consequently greater pressure from the pharmaceutical industry for their prescription. Nevertheless, ASA and ACEI have been on the market for longer periods of time. They are better known and cheaper than the newer drugs, and they are still the most cost-effective option for CHD therapy.[28,29]

Frequency of medication use also differed between the sexes, such that women were less likely to use medication than men were. The women with CHD reported having lower income and education than the men in our sample. This could partially explain our findings, since these socioeconomic factors had a negative impact on medication use for secondary prevention. However, sex was associated with the use of medication independently of income and education.

Previous studies in other countries have also reported lower use of drugs among women, and have shown that they were receiving less prescription of secondary prevention for CHD than were men.[9,10] Previous studies on ELSA-Brasil data showed that women were more aware of having hypertension and had higher frequency of medication use and blood pressure control, compared with men.[30] They also had greater awareness about high LDL-cholesterol levels (or dyslipidemia), but had lower frequency of use of lipid-lowering medication.[31] Thus, these studies pointed out that women may be more conscious about their health than men are, but may be receiving less prescription of medication for secondary prevention of CHD, from healthcare professionals. Atypical symptoms and underestimation of the severity of CHD among women may lead to lower or inadequate prescription of secondary prevention drugs.[9,10] In a community-based study in Brazil, female sex presented an association with poorer one-year prognosis, and this could be explained by the lower use of secondary prevention among women.[2] Our data allowed us to conclude that there is a group of women with low socioeconomic status that forms a risk group for CHD and for lower use of secondary prevention.

Among the risk factors for CHD, the quality of diet was better among participants who reported having previously had CHD. These individuals also reported having lower use of tobacco and alcohol, but they were less active during their leisure time, thus suggesting that it may have been easier for them to change their smoking, drinking and eating habits than to increase their frequency of physical activity practices. These individuals may feel uncomfortable or unable to practice any activity, which raises another important issue: they may not be attending cardiac rehabilitation. The frequency of attendance at cardiac rehabilitation clinics among these individuals has already been reported to be suboptimal in other studies worldwide and in Brazil.[32-34]

Lastly, the rates of treatment discontinuation seem to rise with increasing time elapsed since the coronary event.[3] Our study found that participants with recent CHD had the same frequency of not using any of the recommended drugs as did those with more than 15 years since the event, but that participants with longer times since the event reported higher frequency of using only one drug. It is interesting to note that among the subjects who were using the combination recommended in the guidelines (antiplatelet plus beta blocker plus lipid-lowering drugs, with or without ACEI/ARB), the proportion of usage remained stable from the time of up to 4 years until 15 or more years since the CHD event. This suggests that this target is reachable, even if more than 15 years have elapsed since the CHD event. It is possible that the quality of medical services after a CHD event, with clear explanation about the benefits of secondary prevention, could help improve its long-term use.

This study has some strengths. ELSA-Brasil includes a large sample of men and women that enables comparisons according to sex. The sample also presents a socioeconomic gradient that enables evaluation of differences in socioeconomic levels among the participants. Moreover, this study includes detailed information about use of medications, and all the participants were instructed to bring all their medications to the study center.

Nonetheless, it also has some limitations. The previous diagnosis of CHD was self-reported, so some degree of misclassification is possible. However, other studies have shown that self-reported CHD based on information about myocardial infarction and revascularization presents good agreement with the medical records, which therefore make this useful in identifying this disease in prospective cohort studies.[35] It is also possible that some participants did not state their medication use, even though they were asked to bring all their medications and prescriptions

to the face-to-face interview, which was conducted by a well-trained interviewer using a standardized questionnaire at the ELSA-Brasil research center. In addition, it was not possible to clarify whether not using the recommended drugs was due to non-prescription by healthcare professionals or non-adherence among the participants. Moreover, although this study was based on a large and well-characterized sample, its characteristics differed from those of the general Brazilian population, especially in terms of its higher income and greater access to medical care.

CONCLUSIONS

The use of secondary prevention of CHD was lower in this sample of middle-aged individuals than what is recommended in the standard guidelines, especially among women. These findings might be even more accentuated in the general Brazilian population, which has lower income and less access to healthcare services, compared with the ELSA-Brasil cohort. Although many strategies have been adopted over the past decades, efforts are still needed to improve the availability of effective drugs (especially in deprived areas), improve their prescription by healthcare professionals and increase patients' awareness about the importance of adherence to secondary prevention of CHD.

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Supplemental file 1. Drugs included in categories of medication use.

Beta blockers	ACEI	ARB	Statins	Fibrates	Other antiplatelet medications
pindolol	captopril	losartan	simvastatin	bezafibrate	clopidogrel
propranolol	enalapril	valsartan	lovastatin	fenofibrate	ticlopidine
timolol	lisinopril	irbesartan	pravastatin	ciprofibrate	triflusal
sotalol	perindopril	candesartan	fluvastatin		cilostazol
nadolol	ramipril	telmisartan	atorvastatin		
metoprolol	benazepril	olmesartan	rosuvastatin		
atenolol	trandolapril				
betaxolol	delapril				
bisoprolol					
nebivolol					
carvedilol					

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Supplemental file 2. Sociodemographic variables associated with medication use for secondary prevention of coronary heart disease, assessed using logistic regression.

	Medication use*			
	Crude		Adjusted**	
	OR	95% CI	OR	95% CI
Income				
≤ USD 1,245	Reference		Reference	
USD 1,246 to 3,319	1.154	0.654 to 2.035	1.170	0.628 to 2.180
≥ USD 3,320	2.956	1.758 to 4.970	2.537	1.082 to 5.948
Sex				
Male	Reference		Reference	
Female	0.393	0.248 to 0.623	0.520	0.316 to 0.858
Education				
Less than high school	Reference		Reference	
High school or some college/university	0.939	0.527 to 1.676	0.858	0.443 to 1.661
Completed college/university or more	1.871	1.133 to 3.091	0.724	0.338 to 1.549
Race				
White	Reference		Reference	
Mixed	0.592	0.355 to 0.989	0.960	0.533 to 1.729
Black	0.391	0.208 to 0.738	0.652	0.324 to 1.313
Asian	0.705	0.172 to 2.893	0.759	0.173 to 3.330
Indigenous	0.201	0.024 to 1.665	0.225	0.026 to 1.957
Age	1.023	0.997 to 1.050	1.004	0.974 to 1.034
Private health insurance				
No	Reference		Reference	
Yes	1.455	0.930 to 2.274	1.150	0.680 to 1.947

*Use of antiplatelet medication (acetylsalicylic acid or other) + beta blocker + lipid-lowering medication (statin or fibrate), with or without angiotensin-converting enzyme inhibitors or angiotensin-receptor blocker. **Adjusted for income, sex, education, race, age and private health insurance.
OR = odds ratio; CI = confidence interval; USD = United States dollars.

Supplemental file 3. Sociodemographic factors associated with sex and income of participants with coronary heart disease at ELSA-Brasil.

	Sex			Income (USD)			
	Male N = 257	Female N = 148	P-value	≤ 1,245 N = 121	1,246-3,319 N = 127	≥ 3,320 N = 154	P-value
Age (years)*	61.5 (8.2)	59.9 (7.7)	0.051	58.45 (8.0)	59.51 (8.2)	63.76 (7.1)	< 0.0001
Age stratum (%)							
35-44	3 (1.2)	4 (2.7)		5 (4.1)	2 (1.6)	0 (0.0)	
45-54	53 (20.6)	33 (22.3)	0.420	33 (27.3)	37 (29.1)	16 (10.4)	< 0.0001
55-64	106 (41.2)	66 (44.6)		57 (27.3)	49 (38.6)	66 (42.9)	
65-74	95 (37.0)	45 (30.4)		26 (21.5)	39 (30.7)	72 (46.8)	
Female (%)	-	-	-	64 (52.9)	58 (45.7)	28 (16.2)	< 0.0001
Race (%)							
White	155 (62.0)	57 (39.0)		38 (31.7)	48 (38.4)	126 (83.4)	
Mixed	53 (21.2)	45 (30.8)	< 0.0001	44 (36.7)	44 (35.2)	10 (6.6)	< 0.0001
Black	30 (12.0)	39 (26.7)		34 (28.3)	27 (21.6)	8 (5.3)	
Asian	6 (2.4)	3 (2.1)		1 (0.8)	4 (3.2)	4 (2.6)	
Indigenous	6 (2.4)	2 (1.4)		3 (2.5)	2 (1.6)	3 (0.8)	
Educational level (%)							
Less than high-school	64 (24.9)	50 (33.8)	< 0.0001	70 (57.9)	36 (28.3)	7 (4.5)	< 0.0001
High school and some college/university	44 (17.1)	50 (33.8)		42 (34.7)	48 (37.8)	4 (4.3)	
Completed college/university or more	149 (58.0)	48 (32.4)		9 (7.4)	43 (33.9)	143 (92.9)	
Mean monthly family income (%)							
≤ USD 1,245	57 (22.4)	64 (43.5)	< 0.0001	-	-	-	-
USD 1,246–3,319	69 (27.1)	58 (39.5)		-	-	-	-
≥ USD 3,320	129 (50.6)	25 (17.0)		-	-	-	-
Private health insurance (%)	178 (69.3)	94 (63.5)	0.236	56 (46.3)	83 (65.4)	130 (84.4)	< 0.0001

*Presented as mean (standard deviation). USD = United States dollars.

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Experimentation with tobacco during adolescence as a factor influencing treatment of smoking in adulthood. A retrospective cohort

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KEY WORDS:
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Treatment outcome.

ABSTRACT

BACKGROUND: There are still few studies on predictors of smoking cessation in Brazilian samples. Experimentation with tobacco during adolescence (ETA) may be one of the important predictors.

OBJECTIVE: This study aimed, within the context of a treatment-seeking group of subjects, to test the hypothesis that ETA negatively affects the outcome of smoking cessation during adulthood.

DESIGN AND SETTING: Retrospective (historic) cohort study conducted at a psychosocial care center in São Paulo, Brazil, between 2007 and 2010.

METHODS: Data on sociodemographics, smoking and medical profiles were obtained through self-report questionnaires that were completed at the baseline and at any follow-up appointment. Logistic regression models were constructed to describe factors associated with the outcome of smoking cessation, measured according to the self-reported four-week success rate among 367 outpatient smokers.

RESULTS: ETA was found to be associated with not quitting smoking through the treatment (odds ratio = 0.57; 95% confidence interval = 0.33-0.96; $P < 0.05$), even after adjustment for dependence level, sociodemographics, nicotine patch use and number of years of smoking.

CONCLUSIONS: Early exposure to nicotine may lead to higher risk of continuing smoking after treatment, in adulthood.

INTRODUCTION

Cigarette smoking, including secondhand smoking, has been identified as the second leading risk factor regarding overall disease burden, only behind high blood pressure. Efforts have been made to control tobacco consumption since the 1970s, such that the overall estimated age-standardized prevalence of daily tobacco smoking declined by 25% for men and 42% for women between 1980 and 2012 globally. On the other hand, because of population growth, the number of smokers increased significantly worldwide, from 721 million in 1980 to 967 million in 2012.[1] A Brazilian study[2] documented a steep decline in smoking prevalence from 15.6% in 2006 to 10.8% in 2014. Despite this public health success story of reducing smoking, tobacco use continues to adversely influence global health patterns, leading to 5.7 million deaths, and 5.5% of disability-adjusted life-years (DALYs) in 2010.[3,4]

The health benefits of smoking cessation are well established and it is also known that Brazil presents a relatively high quit ratio, compared with other countries (around 47% of former daily smokers among those who were ever daily smokers).[5] Considering this tendency among Brazilian smokers for them to seek to abstain from tobacco use, there is an opportunity to improve existing prevention and treatment strategies that can be seized. It is also known that a majority of smokers would like to stop and indeed attempt to stop many times. However, even though 60%-70% of smokers may intend to stop in any given year, only 3%-5% of them remain abstinent through an unassisted attempt, 7%-16% through receiving behavioral therapy and 24% through receiving behavioral therapy combined with pharmacotherapy.[6,7]

Understanding the determinants of stopping smoking is important for better defining the profile of patients seeking treatment and individuals needing to receive targeted preventive interventions. Nonetheless, there are still few studies on predictors of smoking cessation in the

general population. A large systematic review found that only the dependence levels were consistently predictive of the success of these attempts.[8] On the other hand, many studies have tried to elucidate the impact that other factors, such as nicotine replacement therapy, neuropsychiatric comorbidities, smoking more often during the first hours of wakefulness, abstinence symptoms, duration of treatment and early initiation of smoking, have on treatment outcomes.[9-11] A pre-post field trial study tried to elucidate how an early start to tobacco use impacts treatment outcome and found that there was a positive association between the mean age at which smoking started and cessation rates. This showed that treatment was more likely to provide success when the mean age at which smoking started was greater.[12]

Adolescence is widely recognized as a time of greater risk-taking, compared with other age groups. Adolescents are more likely than other developmental age groups to start smoking cigarettes because of normative developmental processes, including heightened reactivity to novel and potentially rewarding stimuli and protracted maturation of cognitive control, along with lower heed given to guidance about the future and heightened sensitivity to peers.[13] Exposure to nicotine among adolescents has been directly associated with greater risk of later nicotine dependence,[13] although there is still discussion regarding the evidence of causal effects, as observed in animal models of adolescents, which are more sensitive to nicotine reward effects and less sensitive to their aversive effects.[13]

However, researchers have also considered the presence of shared genetic and environmental risk factors for both dependence and early age of onset. Regarding this issue, a monozygotic co-twin control study[14] (controlled for genetic and familial-environmental effects) suggested that early nicotine exposure directly increased the level of later nicotine dependence and craving for cigarettes when unable to smoke, thus supporting the causal effect hypothesis. If the causal effect is true, then reducing early exposure should reduce the risk of subsequent nicotine dependence and all the implications and other disorders to which it predisposes.

OBJECTIVE

The main objective of the present study was, in the context of a treatment-seeking group of subjects, to test the hypothesis that experimentation with tobacco during adolescence (ETA) is associated with not quitting smoking through treatment, in adulthood, by comparing the smoking cessation rates between two groups of individuals who completed a smoking treatment protocol (one group with and the other without ETA) and adjusting the results for 12 covariates, including the number of years of tobacco smoking, since this may be an important confounder.

METHODS

Design, ethics and setting

We conducted a six-week retrospective (historic) cohort study on all the patients who were being treated through a smoking cessation protocol at the Psychosocial Care Center for Alcohol and Drugs in the city of São Caetano do Sul, São Paulo, Brazil, from April 2007 to April 2010. Ethics approval was obtained from the local Institutional Review Board (April 13, 2011; no. 028/2011).

To calculate the sample size, we used the average success rate from smoking cessation treatment that was found among individuals using pharmacotherapy at week 12 in a previous important study (which was around 30%).[19] Considering an alpha of 5% and an error of 10%, we found that we would need 80.6 individuals enrolled in the exposure subgroups. Fortunately, we had more than 81 individuals in both exposure subgroups (ETA and non-ETA).

Participants

The subjects were recruited between July 2007 and December 2010 and data were collected using questionnaires applied at the baseline and using a follow-up chart (from T0 to T4; see section 2.1). Patients were recruited through banners that were displayed in the Psychosocial Care Unit (CAPS), and general healthcare professionals in the region were also asked to disseminate the anti-smoking program among smokers in the region. The mean age of the subjects was 51 years. Self-report questionnaires were completed at the baseline with the assistance of healthcare professionals, and evaluations and ratings were recorded at any follow-up appointment.

Treatment protocol

The treatment protocol included six sessions of weekly group therapy and four consultations with a psychiatrist (T1 = 0; T2 = 1 week; T3 = 3 weeks; T4 = 6 weeks).[15-18] The group therapy sessions were composed of up to 15 people and were based on the principles of cognitive-behavioral psychotherapy.[2]

Measurements

In the present study, the cutoff age for starting to use tobacco was taken to be 19 years of age, based on the cutoff used in several recent studies among adolescents[20] and following data on the age of initiation among Brazilians,[2] in order to establish the measurement for exposure to tobacco (experimentation with tobacco during adolescence, ETA).

The outcome measurement of success was considered to be four weeks of self-reported abstinence, in accordance with the criteria for "self-reported four-week quitter" that are encompassed in the Russell standard.[21] Individuals were deemed to have been unsuccessful both if they had not achieved success by the end of the protocol period and if they dropped out.

Statistical analysis

The Stata software, version 11, was used to create the database of information from the questionnaires and protocols and to analyze the data. Using the "enter" method, univariate logistic regression and multiple logistic regression were performed. Descriptive analysis comparing ETA and non-ETA groups regarding their sociodemographic and smoking profile was carried out. Then, twelve variables were included in the multiple logistic regression model based on current scientific literature on smoking cessation predictors, as follows: gender; educational level; number of years of smoking; time to first cigarette (i.e. the length of time after waking up until the first cigarette); number of cigarettes per day; occurrence of breathlessness; difficulty in being in non-smoking areas; most difficult cigarette to quit (i.e. the first cigarette in the morning or any other cigarette); tendency to smoke most of the day during sick leave; use of nicotine patch; presence of other smokers at home; and practice of physical activity. The variable "success" was chosen as the dependent variable. These criteria were included in order to analyze the role of ETA in smoking cessation treatment during adulthood, after adjustment for possible confounders.

RESULTS

Chi-square tests showed significant differences between the ETA and non-ETA groups in relation to the following variables (**Table 1**): gender ($P < 0.01$), occurrence of breathlessness ($P < 0.05$), number of years of smoking ($P < 0.01$), age at time of first cigarette ($P < 0.01$), tendency to smoke most of the day during sick leave ($P < 0.01$), presence of other smokers at home ($P < 0.05$) and practice of physical activity ($P < 0.01$). ETA was reported by 81% of the men and 67% of the women; 76% of those presenting breathlessness; 60% of those who had been smoking for less than 30 years; 77% of those who had been smokers for at least 30 years; 77% of those who had their first cigarette five minutes after waking up; 77% of those who lived with another smoker; and 78% of those who did not practice any physical activity. Success was associated with the non-ETA group ($P < 0.05$), such that 46.6% of this group were successful, versus 33.7% in the ETA group.

Table 2 presents the results from the crude and adjusted logistic regression models for treatment success. As shown, ETA was significantly associated with failure of the treatment (odds ratio = 0.57; 95% confidence interval = 0.33-0.96; $P < 0.05$). A longer time until the first cigarette and a greater number of years of smoking (duration of smoking) were associated with success. In further crude analysis, duration of smoking (both continuous and categorical) was associated with success. Male gender, low education level, hypertension and shorter time until the first cigarette were associated with the class with greater number of years of smoking, in the adjusted analysis. No multicollinearity was found, i.e. the

Table 1. Descriptive analysis on experimentation with tobacco during adolescence (ETA) and non-ETA groups among 367 smokers who were attending outpatient smoking cessation treatment at a psychosocial care unit (CAPS) in São Caetano, São Paulo, Brazil, 2007-2010

Variable	Non-ETA		ETA		χ^2	P
	n	%	n	%		
Gender						
Female	79	32.6	136	67.4	7.38	**0.007**
Male	24	19.2	101	80.8		
Educational attainment (years of schooling)						
Up to 8 years	45	33.8	88	66.2	3.44	0.064
9 or more years	58	24.8	176	75.2		
Breathlessness						
No	49	34.3	94	65.7	4.46	**0.035**
Yes	54	24.1	170	75.9		
Number of years smoking						
< 30	46	39.66	70	60.34	11.2847	**0.001**
≥ 30	57	22.71	194	77.29		
Cigarettes per day						
< 30	71	31.7	153	68.3	3.7543	**0.053**
≥ 30	32	22.38	111	77.62		
Time to first cigarette in the morning						
≤ 5 minutes	50	22.83	169	77.17	7.3699	**0.007**
> 5 minutes	53	35.81	95	64.19		
Difficulty staying in non-smoking areas						
No	51	32.,9	104	67.1	3.0139	**0.083**
Yes	52	24.64	159	75.36		
Most difficult cigarette to quit						
First cigarette in the morning	70	29.29	169	70.71	0.6738	0.412
Any other cigarette	31	25.2	92	74.8		
Tendency to smoke during a sick period						
No	50	41.32	71	58.68	15.1435	**< 0.01**
Yes	52	21.76	187	78.24		
Other smokers at home						
No	56	34.36	107	65.64	5.6111	**0.018**
Yes	47	23.15	156	76.85		
Physical activity						
No	46	22.22	161	77.78	7.3075	**0.007**
Yes	55	35.03	102	64.97		
Nicotine patch						
No	4	18.18	18	81.82	1.1483	0.284
Yes	99	28.78	245	71.22		
Bupropion						
No	55	28.35	139	71.65	0.0166	0.898
Yes	48	27.75	125	72.25		
Nortriptyline						
No	100	28.99	245	71.01	2.1152	0.146
Yes	3	14.29	18	85.71		
Nicotine gum						
No	85	29.41	204	70.59	1.0952	0.295
Yes	18	23.38	59	76.62		
Success						
No	55	23.91	175	76.09	5.622	0.022
Yes	48	35.04	89	64.96		
Total	**103**	**28.1**	**264**	**71.9**		

Table 2. Results from multiple logistic regression model regarding success in smoking cessation among 367 smokers who were attending outpatient smoking cessation treatment at a psychosocial care unit (CAPS) in São Caetano, São Paulo, Brazil, 2007-2010

Variables	n	%	OR	aOR	[95%	CI]	P	VIF
Exposure								
Non-ETA	48	46.6	1.00	1.00				
ETA	89	33.7	0.58	0.57	0.33	0.96	0.037	1.17
Covariates								
Gender								
Female	96	39.7	1.00	1.00				
Male	41	32.8	0.74	0.77	0.45	1.29	0.324	1.17
Education level								
Up to 8 years	58	43.6	1.00	1.00				
9 or more years	79	33.8	0.65	0.68	0.42	1.09	0.108	1.05
Number of years smoking								
Less than 30 years	34	29.3	1.00	1.00				
30 years or more	103	41.0	1.67	1.93	1.15	3.25	0.014	1.08
Time to first cigarette in the morning								
Up to 5 minutes	69	31.5	1.00	1.00				
More than 5 minutes	68	46.0	1.84	1.76	1.07	2.88	0.027	1.20
Cigarettes per day								
Less than 30	91	40.6	1.00	1.00				
30 or more	46	32.2	0.69	0.92	0.55	1.54	0.748	1.22
Breathlessness								
No	50	35.0	1.00	1.00				
Yes	87	38.8	1.18	1.57	0.95	2.60	0.077	1.13
Difficulty being in non-smoking areas								
No	64	41.3	1.00	1.00				
Yes	72	34.1	0.73	0.81	0.49	1.35	0.425	1.26
Most difficult cigarette to quit								
First cigarette in the morning	100	41.8	1.00	1.00				
Any other cigarette	36	29.3	0.57	0.65	0.39	1.06	0.090	1.05
Tendency to smoke most of the day during sick leave								
No	51	42.2	1.00	1.00				
Yes	84	35.2	0.74	0.83	0.48	1.42	0.497	1.31
Nicotine patch								
No	4	18.2	1.00	1.00				
Yes	133	38.7	2.83	2.42	0.72	8.08	0.152	1.10
Other smokers at home								
No	58	35.6	1.00	1.00				
Yes	79	38.9	1.15	1.16	0.72	1.86	0.535	1.08
Physical activity								
No	75	36.2	1.00	1.00				
Yes	62	39.5	1.14	1.08	0.67	1.75	0.755	1.13

Non-success was the reference category; aOR = adjusted odds ratio; CI = confidence interval; VIF = variance inflation factor; ETA = experimentation with tobacco during adolescence.

variance inflation factor (VIF) values were very low. No significant difference was found between the ETA and non-ETA groups regarding treatment drop-out rate (55.9% versus 48.5%, respectively). A further crude and adjusted logistic regression was carried out excluding those who dropped out. Success continued to be associated with the non-ETA group ($P < 0.05$), which had a success rate of 90.6%, versus 76.7% in the ETA group.

DISCUSSION

Our study shows that experimentation with tobacco during adolescence is an influential factor regarding failure of smoking cessation, independently of the level of dependence, number of years of smoking and other potential confounders. Consistent with the available literature,[14,22] our results confirmed that experimentation with tobacco during adolescence was also associated

with greater severity of smoking history, such as having been a smoker for longer and reporting occurrences of the symptom of breathlessness. Since the risk of developing tobacco-related disease increases as a function of the duration of time for which tobacco is used, adolescent users are at particularly high risk of physical consequences from tobacco use later on.

Tobacco smoking among adolescents remains a persistent threat to public health,[1] and most adolescents who use tobacco regularly (e.g. monthly or more frequently) continue their use into adulthood. For example, while only 5% of adolescent smokers see themselves as continuing to smoke five years later, 75% are actually still smoking eight years later.[23]

Defining the boundaries of this period and what it encompasses is a matter of controversy. A cross-sectional study revealed differences in brain activation between late adolescents (18-19 years old) and young adults (23-25 years old) during cognitive control, thus indicating that protracted functional development of the cortex continues into these individuals' twenties.[24] Moreover, maturational changes in active synaptic pruning, a process that is thought to enhance information processing capacity and speed and information rearrangement, and in white matter myelination, a process that aids the functional integration of widely distributed circuitry, begin to accelerate during early adolescence and reach a plateau approximately at the ages of 24-25 years.[25]

It is well known that adolescence is a crucial period for the development of cognitive and executive functions, working memory, reward processing, emotional regulation and motivated behavior. There is greater vulnerability to the effects of nicotine during this period. More specifically, the neurobiological impact of early-onset smoking may be especially deleterious because maturational changes in active synaptic pruning and rearrangement and white matter myelination begin to accelerate during early adolescence.[26] Persistent exposure to nicotine via tobacco smoking throughout adolescent neurodevelopment can damage newly maturing synaptic signaling pathways and alter the patterns of neurotransmitter release, thereby increasing sensitivity to reward-related neural activation and susceptibility towards developing nicotine dependence.[27] One recent laboratory study[28] demonstrated that cigarette craving, as assessed through the statement "Nothing would be better than smoking a cigarette right now", was greater among early-onset smokers than it was among late-onset smokers and healthy non-smokers. Through use of electroencephalography and event-related potentials, this study[28] showed elevated reactivity in the early-onset group after these individuals viewed salient smoking-related images.

Positive expectancies develop as a result of heightened sensitivity to rewards during this period and often when there is a pleasurable initial smoking experience. However, there are also particular risk factors to be addressed regarding the easy availability of cigarettes and the positive social norms regarding smoking.[13] The extent to which cigarette availability (perhaps concomitant to exposure to peers) affects reward-related processing among adolescent smokers has not been fully examined. This remains an important target for future research. Nonetheless, the findings of the present study add strength to policies that aim to restrict adolescents' access to tobacco.

The finding that greater numbers of years of smoking was associated with success in the treatment was conflictive with some opposite findings in the recent literature.[29] However, it is important to note that the evidence from the previous study came from a general population sample, which differed from the type of sample of the present study (clinical). In addition, more than 70% of the subjects included in the present study were undergoing psychiatric treatment for mental disorders other than nicotine dependence. Such populations are known to have exceptionally high smoking rates, due to biological, psychological and social factors. Moreover, adding to previous studies that demonstrated how starting to smoke early on acts as a negative predictor for cessation success,[9,12] the present study also reaffirmed the importance of this variable in the specific population of individuals with mental health and addiction disorders.

The present study had limitations, especially with regard to subjective measurement of success, given that the majority of the variables were based on the patients' self-reports. Objective data, such as quantification of salivary cotinine and carbon monoxide, could have been useful.[30] Despite the evidence that self-reported data regarding cessation of tobacco use is reliable,[29] biological data such as assessment of the quantities of salivary cotinine and carbon monoxide could have been useful. However, there is evidence showing that self-reported data on cessation of tobacco use is reliable.[31] Presentation of severe unpleasant withdrawal symptoms during the first days after quitting and the consequent higher likelihood of relapse emphasize the relevance of maintaining abstinence during this period in order to achieve long-term cessation. In middle-income countries, studies conducted on anti-smoking treatment in community settings have lacked instruments to objectively quantify nicotine abstinence and, thus, have continued to use self-report measurements.[10,32-34] Others limitations that need to be added were that the number of patients excluded was not recorded according to cause and that there was a high drop-out rate.

Our results may add clinical considerations to the neurobiological evidence available in relation to experimentation with tobacco during adolescence.[14] One particular feature of the treatment protocol that was used at this unit was that cognitive-behavioral therapy in groups was provided, conducted by a psychologist with broad experience relating to addiction.[20] This type of experience differs from the supportive counselling that is provided by general practitioners in most smoking cessation clinics.

CONCLUSIONS

Early exposure to nicotine may lead to higher risk of continuing smoking after treatment in adulthood. This finding needs to be incorporated into prevention and treatment strategies, in order to enhance health literacy regarding severe modifiable risk factors within smoking.

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Preoperative vitamin D deficiency is a risk factor for postoperative hypocalcemia in patients undergoing total thyroidectomy: retrospective cohort study

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KEY WORDS:
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ABSTRACT

BACKGROUND: The relationship between preoperative vitamin D deficiency and postoperative hypocalcemia in cases of total thyroidectomy (TT) is a matter of controversy and may vary according to geographical scenarios and populations.

OBJECTIVE: The objective here was to evaluate whether preoperative vitamin D deficiency was associated with postoperative symptomatic hypocalcemia in a population in South America.

DESIGN AND SETTING: Retrospective cohort study on data from all patients undergoing total thyroidectomy, with or without central compartment lymph node dissection, from January 2014 to December 2017, at the A. C. Camargo Cancer Center.

METHODS: Patients with benign thyroid disease (Graves' disease, multinodular goiter or hyperthyroidism) or thyroid cancer who underwent primary total thyroidectomy with or without central compartment lymph node dissection were included. The exclusion criteria were simultaneous parathyroidectomy and conditions that could affect serum calcium levels. The data collected included patient demographics, thyroid pathology, extent of the surgical procedure and complications. Information on preoperative and postoperative calcium, parathyroid hormone (PTH) and vitamin D levels were retrieved from the medical records.

RESULTS: 1,347 patients were assessed and postoperative hypocalcemia was diagnosed in 284 patients (21%). The vitamin D levels were considered deficient in 243 patients (18%). Postoperative hypocalcemia was diagnosed in 357 patients (31.5%). Multivariate analysis showed that central compartment dissection and preoperative total calcium and deficient vitamin D levels were significant risk factors for postoperative hypocalcemia.

CONCLUSION: Deficient preoperative vitamin D levels were a significant risk factor for postoperative hypocalcemia. Preoperative oral supplementation should be considered, to minimize this risk.

INTRODUCTION

Techniques for thyroidectomy have evolved remarkably over the past 150 years. This is currently considered to be a very safe operation with favorable results when performed by experienced surgeons.[1] Hypocalcemia as a result of hypoparathyroidism is the most common postoperative complication of thyroidectomy. Hypoparathyroidism is considered to be transient if recovery occurs within days, weeks or a few months; or permanent when calcium levels do not return to normal within six months after surgery.[2,3] Transient hypoparathyroidism is seen in 0.3 to 49% of the patients undergoing thyroidectomy, whereas permanent hypoparathyroidism is less likely and has been reported in up to 13% of the cases.[4-8]

The established risk factors for hypoparathyroidism after total thyroidectomy are advanced age, female sex, size of the thyroid gland, substernal goiter, Graves' disease, surgical technique (de-vascularization, excision or other inadvertent damage of the parathyroid glands), central compartment dissection, reoperation, less experienced surgeon and low 25-hydroxyvitamin D serum levels in the preoperative period.[9-18]

Most thyroid surgeons provide calcium supplementation based on postoperative calcium, parathyroid hormone (PTH) serum levels, or presence of symptoms, whereas others routinely prescribe calcium and vitamin D supplementation after thyroidectomy to prevent hypocalcemia symptoms.[12,13,19] In a randomized study involving 143 patients undergoing total thyroidectomy, it

was demonstrated that patients with PTH levels > 10 pg/ml on the first postoperative day could be safely discharged without routine calcium supplementation.[20] The active form of vitamin D, i.e. calcitriol (1,25 dihydroxyvitamin D3), is the preferred option because of its potency and rapid onset of action.[21]

In the United States, the National Health and Nutrition Survey (NHANES), conducted from 2005 to 2006, showed that 41.6% of adults had levels of 25-hydroxyvitamin D (25-OHD) below 20 ng/ml.[22] The prevalence of low vitamin D levels is also high globally.[23-25] Low vitamin D levels (< 10 ng/ml [25 nmol/l]) are more common in South Asia and the Middle East than in other regions.[26] Several risk factors, such as changes in milk intake, limited exposure to sunlight or use of sun protection, higher body mass index (BMI) and aging, compromise the absorption and metabolism of vitamin D.[24] In several Brazilian regions, despite their geographical location in the tropics, there is high prevalence of hypovitaminosis D (up to 60%).[27,28] Patients with prolonged vitamin D deficiency present reduced intestinal absorption of calcium and phosphorus.[29]

OBJECTIVE

The relationship between preoperative vitamin D deficiency and postoperative hypocalcemia in patients who have undergone total thyroidectomy is not well defined. Thus, the objective of this study was to evaluate whether preoperative vitamin D deficiency was a risk factor for postoperative symptomatic hypocalcemia in patients in South America.

METHODS

This was a retrospective study in which information collected from the databases of the Departments of Head and Neck Surgery and Otorhinolaryngology at the A.C. Camargo Cancer Center, Sao Paulo, Brazil, covering the period from January 2014 to December 2017, was analyzed. This study was approved by an Internal Review Board (Ethics Committee), under the number 2603/18, in September 2018.

The records of patients with benign thyroid disease (Graves' disease, multinodular goiter or hyperthyroidism) or thyroid cancer who underwent primary total thyroidectomy, with or without association with central compartment lymph node dissection, were included. The exclusion criteria were presentation of simultaneous parathyroidectomy or conditions that could affect serum calcium levels, such as renal impairment, Paget's disease, histiocytosis, hyperparathyroidism or use of thiazide diuretics or lithium.

The data collected included patient demographics, thyroid pathology, extent of the surgical procedure and complications. Information on preoperative and postoperative calcium, PTH and vitamin D levels were retrieved from the medical records. Data on preoperative vitamin D levels were only available for 395 (34.9%) of the patients.

Vitamin D levels were measured using the Elecsys total vitamin D electrochemiluminescence test, which was launched by Roche Diagnostic in 2012. This test is comparable to the liquid chromatography method performed in association with mass spectrometry (LC-MS/MS). This is an international reference method for measurement of vitamin D, in accordance with the Vitamin D External Quality Assessment Scheme (DEQAS), which is a worldwide reference program that has the objective of guaranteeing the reliability of vitamin D tests.[30-32] Intact PTH was assayed using immunometric tests. Blood samples were collected and then refrigerated and subjected to rapid centrifugation. In the assays on PTH levels, the reference range was from 12 to 65 pg/ml. The total calcium level was determined using an automated colorimetric method based on atomic absorption. Normality was taken to range from 8.4 to 10 mg/dl.

The surgeons tried to identify and preserve all parathyroid glands. In addition, every attempt was made to preserve the vascularization in the parathyroid glands. Ligature of the lower thyroid artery was usually performed at the level of the distal branches near the thyroid capsule. The parathyroid glands that were inadvertently resected or de-vascularized, or could not be preserved in situ, were cut into fragments and auto-transplanted into the ipsilateral sternocleidomastoid muscle using the technique described by Wells et al.[33] Only patients with postoperative calcium levels below the normal value or who presented muscle cramps or tingling were treated with calcium and calcitriol replacement. The clinical sign of Chvostek was not used as a parameter because in most of the patients, no preoperative evaluation of this sign had been made, and patients with normal levels of calcium could also present it.

Statistical analysis was performed using Stata 14.2. Continuous variables were described in terms of the mean and standard deviation. Multiple imputation (MI) was used under the assumption that observations could be missing at random. Dependent and independent variables were used as imputation parameters for MI. Multivariate imputation by means of chained equations was used for data management, with 20 replications. Restricting the analysis to complete cases was deemed to be satisfactory if missingness was less than 5% and totally aleatory. Otherwise, it would rely on stronger *a priori* assumptions than random distribution.

The t test was used to compare means between two groups, whereas analysis of variance (ANOVA) was used when more than two groups were involved. Preoperative vitamin D levels were stratified accordingly and were classified as deficient (< 20 ng/ml), insufficient (between 21 and 30 ng/ml) or sufficient (> 31 ng/ml). Multivariate analysis was performed to identify factors predictive of hypocalcemia, using all the variables that were considered clinically significant. Because total calcium, vitamin D and PTH

present interconnected metabolism, the interaction between these variables was tested.

A P-value of 0.05 was considered significant, and all tests were considered two-tailed. Variable selection and coefficient reduction were performed afterwards by means of the least absolute shrinkage and selection operator (LASSO). Using the selected variables, a nomogram was drawn to predict occurrences of postoperative hypocalcemia.

RESULTS

The inclusion criteria were met by 1,347 cases. Most patients were women (1,070) and the age range was from 7 to 85 years (mean, 45.0 years; standard deviation, SD, 13.4 years). A total of 1,183 patients (89.9%) underwent total thyroidectomy alone. Central compartment dissection was performed in 164 patients (12.8%).

The mean preoperative serum total calcium level was 9.34 mg/dl (range: 7.1 to 11.4 mg/dl), the PTH level was 36.7 pg/ml (range: 12.0 to 145.4 pg/ml) and the vitamin D level was 27.9 ng/ml (range: 5.9 to 91.1 ng/ml). The five patients who had preoperative PTH levels above the reference value were not excluded from the analysis because they did not have the diagnosis of primary hyperparathyroidism, given that their serum total calcium levels were at the lower limit of normality. The PTH level was considered deficient in 243 patients (18%). A total of 390 patients (29%) had vitamin D insufficiency, while 714 patients (53%) had sufficient vitamin D. The mean preoperative PTH level was 41.0 pg/ml (SD, 21.8) in patients with deficient vitamin D; 38.3 pg/ml (SD, 19.8) when the vitamin D level was classified as insufficient; and 31.9 pg/ml (SD, 12.8) in cases of sufficient vitamin D (**Table 1**). Comparing preoperative PTH levels according to categorical vitamin D level, the ANOVA test showed that there were lower PTH levels in patients with sufficient levels of vitamin D than in patients with deficient or insufficient levels (P < 0.001).

Table 1. Demographic characteristics of patients in relation to presence or absence of acute hypocalcemia

Variable		Acute hypocalcemia	No acute hypocalcemia	P-value
Age	Years	43.9 (12.71)	45.3 (13.62)	0.1219
Gender	Female	231 (17.15)	839 (62.29)	0.3051
	Male	52 (3.86)	225 (16.70)	
Malignancy	No	69 (5.12)	312 (23.16)	0.0695
	Yes	214 (15.89)	712 (52.86)	
CCD	No	217 (16.11)	966 (71.71)	< 0.001
	Yes	68 (5.05)	96 (7.13)	
Preoperative PTH		37.6 (20.14)	36.6 (17.49)	0.4540
Preoperative total Ca		9.3 (0.49)	9.3 (0.46)	0.9650
Preoperative vitamin D		26.1 (9.56)	28.5 (10.33)	0.0005

CCD = central compartment dissection; PTH = parathyroid hormone; Ca = calcium.

For the multiple imputation procedure, we initially tabulated our variables of interest, which showed 463 missing values for preoperative ionic calcium, 252 missing values for preoperative total calcium, 365 missing values for preoperative PTH, 48 missing values for postoperative PTH, 16 missing values for postoperative ionic calcium, 15 missing values for postoperative total calcium and 952 missing values for postoperative vitamin D. We then examined the pattern of missingness. A correlation matrix of potential auxiliary variables was created and, as no variable showed a correlation (r > 0.4), we created an imputation model using preoperative total calcium, preoperative PTH, age and postoperative hypocalcemia as the auxiliary variables.

Postoperative hypocalcemia was diagnosed in 357 patients (31.5%). Multivariate analysis showed that central compartment dissection and preoperative total calcium and deficient vitamin D levels were significant risk factors for postoperative hypocalcemia (**Table 2**). This model had an area under the curve (AUC) of 0.7226. The difference between preoperative and postoperative PTH was associated with preoperative vitamin D status: -22.7 (SD, 17.7) in cases of deficiency, -24.5 (SD, 19.9) in cases of insufficiency and -19.3 (SD, 13.1) in cases of sufficiency (P < 0.001).

Lastly, multivariate analysis with interaction terms alone showed that central compartment dissection and interaction between preoperative PTH and vitamin D were statistically significant (**Table 3**).

Table 2. Multivariate analysis without interaction

Variable	Coefficient	95% CI	P-value
Neck dissection	1.195	0.751-1.639	< 0.001
Malignancy	0.223	0.0233-0.570	0.041
Gender	0.197	-0.220-0.614	0.354
Age	-0.004	-0.017-0.009	0.503
Preoperative total Ca	0.130	0.040-0.243	0.045
Preoperative PTH	0.006	-0.003-0.015	0.193
Preoperative vitamin D	-0.022	-0.040 - -0.004	0.015

CI = confidence interval; Ca = calcium; PTH = parathyroid hormone.

Table 3. Multivariate analysis with interaction terms

Variable	Coefficient	95% CI	P-value
CCD	1.207	0.710-1.703	< 0.001
Malignancy	0.111	-0.337-0.559	0.628
Gender	0.166	-0.296-0.629	0.481
Age	-0.003	-0.018-0.011	0.659
Preoperative total Ca	-0.393	-1.084-0.298	0.265
Preoperative PTH	0.037	-0.091-0.165	0.567
Preoperative vitamin D	-0.197	-0.430-0.036	0.098
PTH versus vitamin D	0.017	0.005-0.040	0.039
Total Ca versus vitamin D	0.001	-0.001-0.002	0.446
PTH versus total Ca	-0.005	-0.019-0.009	0.492

CI = confidence interval; CCD = central compartment dissection; Ca = calcium; PTH = parathyroid hormone.

This model had an AUC of 0.7430. After LASSO, the interaction terms of preoperative vitamin D and PTH, preoperative PTH, preoperative vitamin D, preoperative ionic calcium and neck dissection were selected. This model had an AUC of 0.6911. Based on these variables, a nomogram was designed (**Figure 1**). The objective of the nomogram was to provide an easy visual manner for estimating the preoperative risk of hypocalcemia in candidates for total thyroidectomy.

DISCUSSION

The present study demonstrated high incidence of vitamin D insufficiency (< 30 ng/ml) and deficiency (< 20 ng/ml) in a population from tropical areas and suggested that there was an association between vitamin D deficiency and the risk of postoperative hypocalcemia. The retrospective nature of the analysis and the fact that data on preoperative vitamin D values were available for only 34.9% of the patients were limitations of the study. However, when we compared the groups with and without vitamin D assays, we did not observe any differences, and our sample of more than 1,000 patients allowed adequate statistical analysis.

Activated vitamin D plays a central role in the regulation of calcium and PTH levels. Vitamin D increases serum calcium by directly increasing intestinal absorption and bone resorption while regulating PTH secretion through its effects on calcemia and through vitamin D receptors in the parathyroid glands.[34,35] Because of these actions, the preoperative vitamin D level may have a profound impact on the perioperative kinetics of calcium and PTH after total thyroidectomy.[17,22] Some clinical studies have found that low preoperative 25-hydroxyvitamin D (25-OHD) levels are a risk factor for postoperative hypocalcemia, whereas others have not found this association.[17,35-37]

Vitamin D deficiency is a cause of secondary hyperparathyroidism, and therefore the capacity of PTH levels in the postoperative period to act as a predictor of hypocalcemia probably depends on the preoperative vitamin D level. In Brazil, it was found that 62.1% of adolescents had vitamin D levels ranging from 11 to 30 ng/ml[28] and that 85.6% of elderly patients had

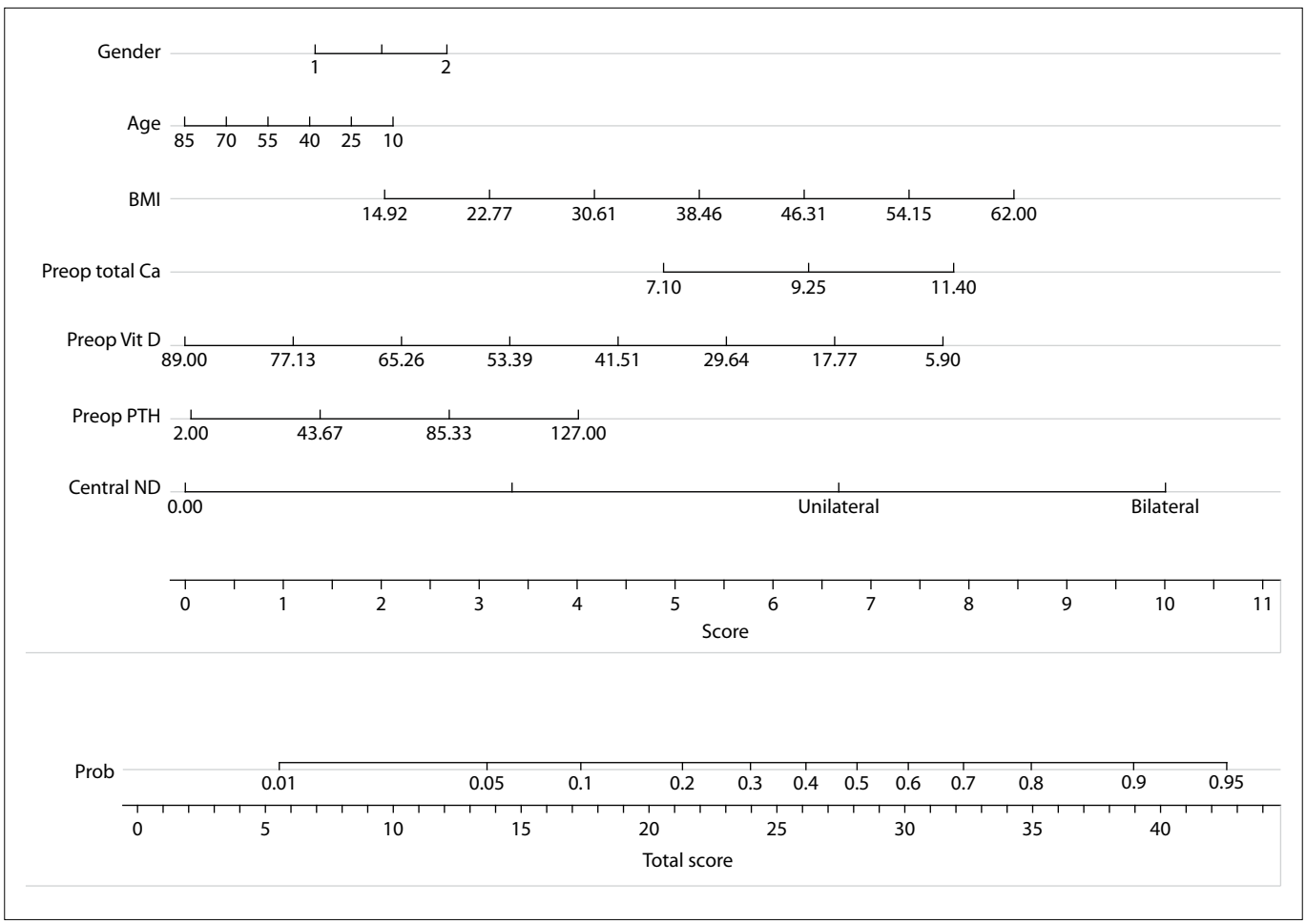

Figure 1. Nomogram with predictive factors for postoperative hypocalcemia in cases of total thyroidectomy.

vitamin D levels below 20 ng/ml.[43] In the present study, the prevalence of vitamin D deficiency was also high: 243 patients (18%) had vitamin D levels < 20 ng/ml and 390 patients (29%) between 20 and 30 ng/ml. On the other hand, the vitamin D levels that are deemed to be normal have varied over time and, moreover, the place where the study was conducted and the profile of the patients studied have also impacted the prevalence of vitamin D deficiency.[28,37,43]

Preoperative PTH levels are unreliable for predicting postoperative hypocalcemia because low levels of vitamin D lead to higher preoperative PTH levels due to secondary hyperparathyroidism.[17,41] However, postoperative serum PTH levels in patients with vitamin D deficiency may be even higher than in those without vitamin D deficiency, despite the higher risk of hypocalcemia in the first group of patients.[17] In patients with vitamin D deficiency, even minimal damage to the parathyroid glands caused by surgical manipulation may temporarily reduce PTH secretion and cause hypocalcemia, because these patients' calcium regulation presents greater sensitivity to circulating serum PTH levels than that of individuals with normal levels of vitamin D. The role of vitamin D deficiency in causing parathyroid enlargement[42] supports the idea that increased parathyroid gland activity compensates for low vitamin levels, thus making these patients more susceptible to hypocalcemia after thyroidectomy.

Total thyroidectomy is currently the standard surgical procedure for various thyroid diseases. It has the aim of reducing the incidence of recurrent disease and thus avoiding re-operations. Although it is considered to be a safe surgical procedure, postoperative hypoparathyroidism still affects a substantial number of patients. In addition, it has become a burden for the healthcare system because patients with hypocalcemia may require longer hospitalization, more biochemical studies, pharmacological treatments and more medical resources.[5] Because of this, some authors have recommended routine supplementation of calcium and vitamin D to decrease the risk of biochemical and symptomatic hypocalcemia.[13,19,38-40]

Based on this study, we recommend that preoperative vitamin D correction should be undertaken. However, postoperative calcium and calcitriol replacement should be performed only when the patient develops symptoms of hypocalcemia or when calcium or PTH levels are below normal.

CONCLUSIONS

Deficient preoperative vitamin D levels are a significant risk factor for postoperative hypocalcemia, as are also central compartment neck dissection and total preoperative calcium level. Therefore, preoperative oral supplementation of vitamin D should be considered, to minimize this risk.

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The CHA_2DS_2-VASc score for predicting atrial fibrillation in patients presenting with ST elevation myocardial infarction: prospective observational study

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KEY WORDS:
Risk factors.
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ABSTRACT

BACKGROUND: Atrial fibrillation (AF) is the most common form of supraventricular arrhythmia following ST-elevation myocardial infarction (STEMI). The CHA_2DS_2-VASc and $CHADS_2$ scores are used to estimate thromboembolic risk in cases of AF. Their usefulness in predicting the development of AF in patients presenting STEMI is unknown.

OBJECTIVE: To evaluate the predictive value of the $CHADS_2$ and CHA_2DS_2-VASc scores in patients with AF following STEMI.

DESIGN AND SETTING: This prospective cohort study on 696 patients with STEMI was conducted at a tertiary-level cardiology clinic in a public university hospital.

METHODS: Models including clinical and laboratory parameters were constructed to test the predictive value of $CHADS_2$ and CHA_2DS_2-VASc scores. Patients were divided into two groups: with and without AF. Predictors of AF were determined using multivariate regression analysis.

RESULTS: In the patients with AF, $CHADS_2$ and CHA_2DS_2-VASc scores were significantly higher than in those without AF (for both $P < 0.001$). Factors associated with AF in multivariate analyses included CHA_2DS_2-VASc score (odds ratio, OR: 1.48; 95% confidence interval, CI: 1.25-1.75; $P < 0.001$), peak creatine kinase-myocardial binding (OR: 1.002; 95% CI: 1.00-1.003; $P = 0.0024$), duration of the coronary intensive care unit stay (OR: 1.69; 95% CI: 1.24-12.30; $P = 0.001$) and no use of renin-angiotensin system blockers (OR: 2.16; 95% CI: 1.14-4.10; $P = 0.0017$). Receiver operating characteristic curve analyses showed that CHA_2DS_2-VASc scores were significant predictors for new-onset AF (C-statistic: 0.698; 95% CI: 0.631-0.765; $P < 0.001$).

CONCLUSION: $CHADS_2$ and CHA_2DS_2-VASc scores predicted new AF in patients presenting STEMI.

INTRODUCTION

Atrial fibrillation (AF) presents increasing prevalence with increasing age and is the most common type of arrhythmia in clinical practice, affecting 1%-2% of the general population.[1,2] Thromboembolic events, which can cause death, disability and impaired quality of life, are important complications of AF.[3] AF is the most common type of supraventricular arrhythmia following ST-segment elevation myocardial infarction (STEMI), and its prevalence is even higher among elderly patients with heart failure and severe left ventricular impairment.[3] Patients who develop AF following STEMI are at higher risk of stroke and death than are those who do not develop AF. Older age, female gender, low blood pressure, higher heart rate, higher Killip class, history of hypertension, prior myocardial infarction, diabetes mellitus and low ejection fraction can be predisposing factors for the development of AF following STEMI.[3]

The CHA_2DS_2-VASc risk score is a cheap and easy-to-use scoring system that is calculated by assigning one point for each of the following: congestive heart failure (ejection fraction < 40%), hypertension, age between 65 and 74 years, diabetes mellitus, vascular disease (myocardial infarction or peripheral arterial disease) and female sex; and two points for a history of stroke or transient ischemic attack (TIA) and age > 75 years. Additionally, the CHA_2DS_2-VASc risk score is used to predict the risk of thromboembolism among non-valvular AF patients.[3]

OBJECTIVE

In this study, we aimed to evaluate the association between the $CHADS_2$ and CHA_2DS_2-VASc risk scores and the development of AF in patients presenting with STEMI.

METHODS

In this prospective study, 724 consecutive patients with STEMI who were admitted to the cardiology clinic of Süleyman Demirel University Hospital (a tertiary-level cardiology clinic in Isparta, Turkey) were screened between January 2014 and December 2015. The inclusion criteria included age greater than 18 years and presence of acute STEMI. The exclusion criteria included unstable angina pectoris, non-ST-elevation myocardial infarction, hyperthyroidism, history of AF (paroxysmal, persistent or permanent), moderate to severe heart valve disease, advanced chronic obstructive pulmonary disease, infection, sepsis, rheumatic or inflammatory disease, history of malignancy and use of antiarrhythmic drugs.

Out of 724 consecutive patients with acute STEMI, the following were excluded: four patients with hyperthyroidism, five patients with severe heart valve disease, five patients with advanced chronic obstructive pulmonary disease, one patient with sepsis, three patients with a history of malignancy, two patients using antiarrhythmic therapy and eight patients with a history of AF. Therefore, the study cohort consisted of 696 patients with STEMI (**Figure 1**).

Our institutional ethics committee approved the study (date: July 29, 2011; session number: 25; decision no: 18) and all participants provided written informed consent.

Diagnoses were recorded by the participating physicians based on clinical, electrocardiographic and biochemical (elevated troponin level) criteria. The type of myocardial infarction (ST-elevation versus non-ST-elevation) and situation of unstable angina were homogeneously defined and based on current guidelines.[4] The $CHADS_2$ and CHA_2DS_2-VASc risk scores were calculated according to current guidelines.[3]

Each patient was questioned about major cardiovascular risk factors, including family history of coronary artery disease, current smoking status, hyperlipidemia, hypertension, diabetes mellitus and obesity. A family history of coronary artery disease was defined as manifestation of the disease in first-degree male relatives younger than 55 years of age or in first-degree female relatives younger than 65 years. Hyperlipidemia was defined as fasting total cholesterol level > 200 mg/dl or pharmacotherapy with lipid-lowering agents. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, measured before hospitalization or pharmacotherapy with antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl or pharmacotherapy with insulin or oral antidiabetic agents. Obesity was defined as body mass index > 30 kg/m^2. Patients who were smoking prior to hospitalization were deemed to be smokers.

Clinical data on the patients, their previous medication histories and medications started after hospitalization were recorded. The patients were divided into two groups: those with AF and those without AF. A 12-lead electrocardiogram was recorded upon admission to the hospital. AF was defined as an irregular rhythm with the absence of discrete P waves in the 12-lead electrocardiogram.[3] Patients were followed up through continuous electrocardiography (ECG) monitoring during their stay at the coronary intensive care (CICU), to detect any occurrence of AF, which was defined as an irregular narrow complex rhythm (in the absence of bundle branch block) with absence of discrete P waves. The patients did not undergo continuous ECG monitoring during their stay in the wards, and therefore rhythm follow-up was not evaluated in the wards. An AF episode lasting > 30 seconds during hospitalization at the CICU was taken to be an endpoint.

All patients were treated in accordance with the currently available guidelines.[5] Primary percutaneous coronary intervention (PCI) was performed on all patients. The patients underwent transthoracic echocardiography, and the left ventricular ejection fraction was calculated by means of Simpson's method.[6]

Blood sampling

Blood samples were drawn from the antecubital vein by means of careful venipuncture, using a 21 G sterile syringe without stasis. This was done between 08.00 and 10.00 AM after a fasting period of 12 hours. Glucose, creatinine and lipid profiles were determined using standard methods. Hemogram parameters were measured in blood samples collected in dipotassium EDTA

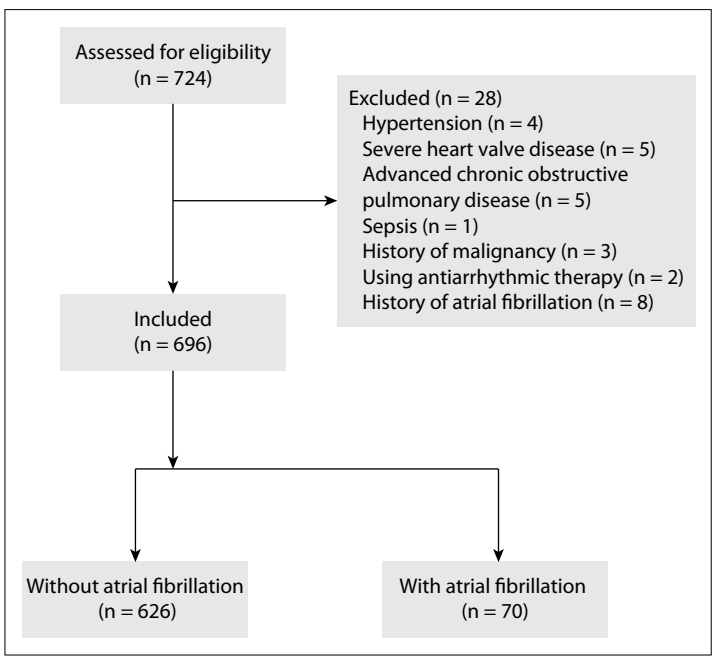

Figure 1. Flow diagram for patient selection.

tubes (Vacuette). An automatic blood counter (Beckman-Coulter Co, Miami, FL, USA) was used for whole blood counts.

Statistical analysis

The Statistical Package for the Social Sciences software, version 16.0, was used in the statistical analyses of this study.

Categorical variables were expressed as frequencies (%) and were compared using the χ^2 test. A Kolmogorov-Smirnov test was used to test the distribution of numerical variables. Those with normal distribution were expressed as the mean ± standard deviation and were compared using Student's t test. Data without normal distribution were expressed as the median with the inter-quartile range (IQR) from the 25th to the 75th percentile, and were compared using the Mann-Whitney U test. In all statistical analyses, P-values < 0.05 were considered to be statistically significant.

Correlations between CHA_2DS_2-VASc risk score, presence of AF and other clinical, laboratory and echocardiographic parameters were performed using Pearson and Spearman correlation analyses, when appropriate. Univariate analysis on binary logistic regression was performed to identify which factors were associated with incident AF. After including each of these potential confounding factors, backward conditional binary logistic regression analysis was performed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for incident AF.

We carried out multivariate analysis on two models. Firstly, risk factors involved in the CHA_2DS_2-VASc score were excluded from this analysis to avoid multicollinearity. Secondly, risk factors and other factors except the CHA_2DS_2-VASc score were subjected to multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to analyze the prognostic value of the CHA_2DS_2-VASc score for new-onset AF, following STEMI. The C-statistic (area under the curve) was presented as a unified estimate of sensitivity and specificity. The area under the curve for AF was computed to identify the Youden index (best cutoff).[7] The Youden index was defined for all points of a ROC curve, and the maximum value of the index was used as a criterion for selecting the optimum cutoff point for detecting new-onset AF. According to the cutoff value that was obtained through ROC curve analysis, the study population was divided into two groups, named the low-risk and high-risk groups.

RESULTS

A total of 696 patients (mean age: 62 ± 12 years; range: 23-92 years) with STEMI were included in this study. During the follow-up period, 70 patients (10.1%) developed AF. The demographic and clinical characteristics of the patients with and without AF are listed in **Table 1**. The patients with AF were older, and more of them were female, compared with the patients without AF (P < 0.001 and P = 0.011, respectively). While hypertension was more

Table 1. Demographic and clinical characteristics of the patients with and without AF

	Without AF (n = 626)	With AF (n = 70)	P-value
Age (years)	61.8 ± 13	69.4 ±11	< 0.001
Body mass index	26.7 ± 4.3	27.5 ± 5.1	0.154
Heart rate at admission	77.4 ± 16.3	79.8 ± 18.3	0.256
Female gender (n, %)	117 (18.7)	22 (31.4)	0.011
Diabetes mellitus (n, %)	155 (24.8)	20 (28.6)	0.28
Hypertension (n, %)	275 (43.9)	44 (62.9)	0.002
Hyperlipidemia (n, %)	136 (21.7)	15 (21.4)	0.547
Smoking (n, %)	361 (57.7)	29 (41.4)	0.007
Ejection fraction (%)	45 ± 9.6	40 ± 9.8	< 0.001
Left atrial diameter (mm)	38 ± 4.1	39.7 ± 4.9	0.002
Location of MI			0.207
Anterior (n, %)	306 (49.4)	29 (43.3)	
Non-anterior (n, %)	314 (50.6)	38 (56.7)	
History of stroke (n, %)	7 (1.1)	3 (0.4)	0.07
Pre-hospital treatment			
Statins (n, %)	75 (12)	7 (10)	0.400
Beta-blockers (n, %)	104 (16.6)	14 (20)	0.285
RAS blockers (n, %)	108 (17.3)	5 (7.1)	0.016
Acetyl salicylic acid (n, %)	144 (23)	18 (25)	0.353
Clopidogrel	24 (3.8)	4 (0.6)	0.308
Hospital treatment			
Statins (n, %)	603 (96.3)	69 (98.6)	0.284
Beta-blockers (n, %)	590 (94.2)	61 (87.1)	0.02
RAS blockers (n, %)	554 (88.5)	52 (74.3)	0.002
Acetyl salicylic acid (n, %)	619 (98.9)	70 (100)	0.475
Clopidogrel (n, %)	576 (92.0)	62 (88.6)	0.217
Ticagrelor (n, %)	49 (7.8)	7 (10)	0.328
Amiodarone (n, %)	3 (0.5)	21 (30)	< 0.001
Total cholesterol (mmol/l)	173.2 ± 41.3	168.9 ± 39.4	0.41
HDL cholesterol (mmol/l)	40.3 ± 9	41.4 ± 8.4	0.46
LDL cholesterol (mmol/l)	107.2 ± 32.5	105.9 ± 29.3	0.71
Triglycerides (mmol/l)	128.8 ± 88.5	107.7 ± 32.5	0.002
BUN (mmol/l)	19.5 ± 6.8	21.5 ± 5.7	0.008
Creatinine (lmol/l)	1.0 ± 0.2	1.1 ± 0.2	0.56
CK-MB at peak (median)	170.9 ± 120	232.6 ± 209	0.002
Troponin T at peak (lg/l) (median)	4.6 ± 2.6	5.5 ± 5.1	< 0.001
Duration of hospitalization in the coronary intensive care unit (days)	2 ± 0.5	2.5 ± 1.3	< 0.001
Glucose (mg/dl)	169.6 ± 78.8	182.1 ± 82.3	0.212
CHA_2DS_2-VASc score	1.5 ± 1.4	2.7 ± 1.3	< 0.001
CHADS score	1.0 ± 0.9	1.5 ± 1.0	< 0.001

Data are presented as mean ± standard deviation or number (%) of the patients.

AF = atrial fibrillation; MI = myocardial infarction; RAS = renin-angiotensin system; HDL = high-density lipoprotein; BUN = blood urea nitrogen; CK-MB = creatinine kinase-myocardial binding; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke, vascular disease, age 65 to 74 years, female gender.

common (P = 0.002), smoking was less common among the patients with AF than among those without AF (P = 0.007). The diabetes mellitus, obesity and hyperlipidemia rates were similar between the patients with and without AF (for all parameters P > 0.05).

The triglyceride levels were lower among the patients with AF than among those without AF (128.8 ± 88.5 versus 107.7 ± 32.5; P = 0.002), but there were no statistically significant differences between the patients with and without AF regarding other cholesterol parameters (for all parameters P > 0.05). The left ventricle ejection fraction was lower (P < 0.001) and the left atrial diameter was higher in the patients with AF than in the patients without AF (P = 0.002).

There were no statistically significant differences between the patients with and without AF regarding previous use of renin-angiotensin system (RAS) blockers, beta-blockers, acetyl salicylic acid, clopidogrel or statins. Use of in-hospital treatments, beta-blockers and renin-angiotensin system blockers was lower among patients with AF (P = 0.02 and P = 0.002, respectively), but use of other medications was similar between the patients with and without AF (P > 0.05). The patients with AF had a longer period of CICU follow-up than did the patients without AF (2.5 ± 1.3 versus 2.0 ± 0.5; P < 0.001).

The mean CHA_2DS_2-VASc and $CHADS_2$ scores were significantly higher in the group with AF than in the group without AF (2.7 ± 1.3 versus 1.5 ± 1.4; P < 0.001; and 1.5 ± 1.0 versus 1.0 ± 0.9; P < 0.001, respectively).

Binary logistic regression regarding incident AF

Univariate analysis showed that high CHA_2DS_2-VASc score, enlarged left atrium, high peak creatine kinase-myocardial binding (CK-MB) level, low left ventricle ejection fraction, long duration of hospitalization in the CICU, advanced age, female gender and history of hypertension were significantly associated with higher risk of incident AF (**Table 2**). On the other hand, use of renin-angiotensin system (RAS) blockers and beta-blockers in hospital was inversely associated with the risk of incident AF (**Table 2**).

Multivariate binary logistic regression analysis was firstly conducted including the characteristics associated with new-onset AF in univariate analysis except for CHA_2DS_2-VASc score. This showed that no use of RAS blockers in hospital (OR: 2.40; 95% CI: 1.25-4.53; P = 0.006), age (OR: 1.03; 95% CI: 1.017-1.062; P = 0.001), left ventricle ejection fraction (OR: 0.972; 95% CI: 0.94-0.99; P = 0.039) and duration of hospitalization in the CICU (OR: 1.63; 95% CI: 1.19-2.23; P = 0.002) remained independent factors related to incident AF (**Table 3**).

Following this, multivariate binary logistic regression analysis was then conducted including the characteristics associated with new-onset AF in univariate analysis except for hypertension, age and left ventricle ejection fraction. This showed that no use of RAS blockers in hospital (OR: 2.16; 95% CI: 1.14-4.10; P = 0.017), duration of hospitalization in the CICU (OR: 1.69; 95% CI: 1.24-2.30; P = 0.001), peak CK-MB level (OR: 1.002; 95% CI: 1.00-1.003; P = 0.024) and CHA_2DS_2-VASc score (OR: 1.48; 95% CI: 1.25-1.75; P < 0.001) were significant predictors for new-onset AF. Furthermore, individuals with high CHA_2DS_2-VASc scores exhibited higher risk of incident AF than did those with low scores (**Table 3**).

Prediction of incident AF

ROC curve analysis showed that both the $CHADS_2$ score (C-statistic: 0.663; 95% CI: 0.595-0.758; P < 0.001) and the CHA_2DS_2-VASc score (C-statistic: 0.698; 95% CI: 0.631-0.765; P < 0.001) were significant predictors of AF following STEMI (**Figure 2**). We calculated cutoff points of 1.5 for the $CHADS_2$ and CHA_2DS_2-VASc scores, to estimate the presence of AF, with sensitivities of 56% and 75% and specificities of 71% and 54%, respectively.

According to the cutoff point of 1.5 that was obtained through ROC analysis, the patients were divided into two groups, with high and low risk. Both for higher $CHADS_2$ score and for higher CHA_2DS_2-VASc score, the predicted risk of incident AF was higher: OR: 3.14; 95% CI: 1.89-5.22; P < 0.001; and OR: 3.72; 95% CI: 2.10-6.57; P < 0.001, respectively.

According to the CHA_2DS_2-VASc score, the duration of hospitalization in the CICU was longer among the patients with higher risk than among the patients with lower risk (2.18 days ± 0.7 versus 2.04 days ± 0.4; P < 0.001). The time when AF started was earlier in the low-risk group than in the high-risk group (median of 5 hours versus 20 hours; P = 0.02). The time at which AF started and the duration of hospitalization in the CICU presented a correlation with each other (r: 0.698; P < 0.001).

Table 2. Univariate regression analysis of study variables

	Odds ratio	Confidence interval	P-value
CHA_2DS_2-VASc score	1.5	1.33-1.82	< 0.001
HT	2.1	1.29-3.59	< 0.001
Non-use of ACE blocker in hospital	2.6	1.47-4.80	0.001
Left atrial diameter	1.0	1.003-1.16	0.002
Peak CK-MB level	1.0	1.001-1.003	0.005
Duration of hospitalization in the coronary care unit	1.99	1.54-2.64	< 0.001
Female gender	1.99	1.15-3.43	0.013
Age	1.02	1.0-1.073	< 0.001
Left ventricle ejection fraction	0.952	0.92-0.97	< 0.001

CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke, vascular disease, age 65 to 74 years, female gender. HT = hypertension; ACE = angiotensin converting enzyme; CK-MB = creatinine kinase-myocardial binding.

DISCUSSION

The main findings of this study indicated that CHA_2DS_2-VASc and $CHADS_2$ scores were independently associated with the development of AF in patients presenting with STEMI. Consequently, both of these scores may be helpful and appropriate scoring systems for predicting AF following STEMI.

Atrial fibrillation following acute coronary syndromes

Atrial fibrillation is the most common type of supraventricular arrhythmia following STEMI.[3] Although AF that is developed following acute coronary syndrome is rare, it is associated with worse clinical signs and prognosis. Rapid management of arrhythmia is required in order to reduce the risk of complications.[8]

Left and right ventricular dysfunction, atrial ischemia, pericarditis, drugs, acute hypoxia and hypokalemia have been correlated with development of AF in the course of STEMI.[7]

In the GUSTO I trial,[9] which included patients with acute coronary syndrome (AMI) who were eligible for thrombolysis, an incidence of AF of 10.4% was reported. Similarly, in the present study, the incidence of AF was 10.1%.

Among acute coronary syndromes that were logged in the Global Registry of Acute Coronary Events (GRACE),[10] development of new-onset AF was predicted by older age, female gender, history of hypertension, presence of STEMI or non-STEMI, higher Killip class, higher heart rate, lower blood pressure, cardiac arrest on presentation and high initial serum creatinine levels.

In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial,[11] AF was found more often in elderly patients with comorbidities like heart failure, hypertension and diabetes, and in those who were taking treatment with aspirin, oral anticoagulants, digoxin or antiarrhythmics before hospitalization. Patients with AF had higher heart rate at presentation, higher rates of ST depression, higher CK-MB levels and pulmonary edema. Similarly, in two studies, the predictors of AF in following up STEMI were found to be old age, female sex, higher Killip class, chronic kidney disease, large left atrium and low left ventricular ejection fraction.[11]

In our study, older age, large left atrium, female gender, low left ventricular ejection fraction, history of hypertension, higher peak CK-MB levels and long hospitalization in the CICU were determined to be predictors of AF.

According to the CHA_2DS_2-VASc score, the time taken for AF to start was longer among patients who presented high risk than among those presenting low risk. However, also according to this

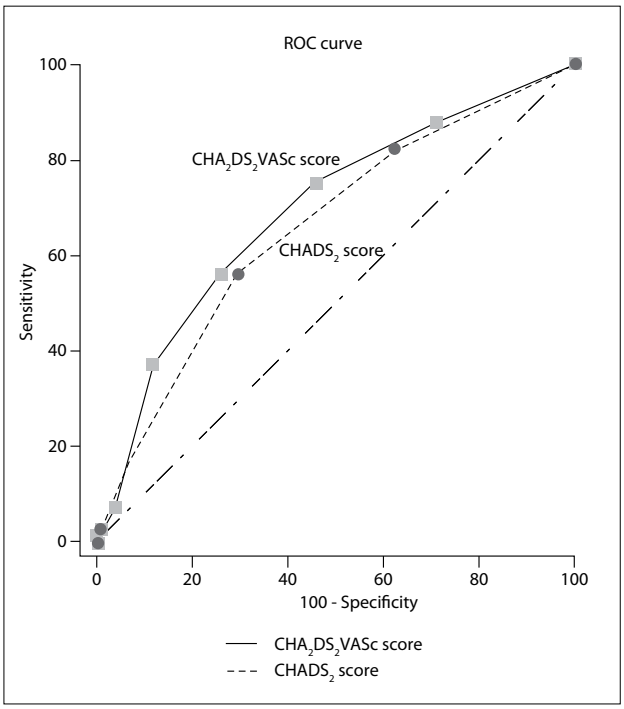

Figure 2. Receiver operating characteristic (ROC) curve with calculated area under the curve and optimal cutoff point for the CHA_2DS_2-VASc score and $CHADS_2$ score, for identifying the presence of AF. C-statistic (area under the curve) and 95% confidence interval (95% CI) for $CHADS_2$: 0.663 (0.595-0.731); P < 0.001; and for CHA_2DS_2-VASc: 0.698 (0.631-0.765); P < 0.001. We calculated a cutoff point of 1.5 with the Youden index for $CHADS_2$ and CHA_2DS_2-VASc scores, to estimate the presence of atrial fibrillation, with sensitivities of 56% and 75% and specificities of 71% and 54%, respectively.

Table 3. Multivariate regression analysis on study variables

	Model 1			Model 2		
	Odds ratio	Confidence interval	P-value	Odds ratio	Confidence interval	P- value
Non-use of ACE in hospital	2.40	1.28-4.53	0.006	2.16	1.14-4.10	0.017
Age	1.03	1.017-1.062	0.001			
Duration of hospitalization in the coronary care unit	1.63	1.196-2.230	0.0039	1.69	1.24-2.30	0.001
Left ventricle ejection fraction	0.972	0.94-0.99	0.002			
Peak CK-MB level				1.002	1.00-1.003	0.0024
CHA_2DS_2-VASc score				1.48	1.25-1.75	< 0.001

Model 1: risk factors and other factors except CHA_2DS_2-VASc score; Model 2: Variables except risk factors involved in CHA_2DS_2-VASc score.
CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke, vascular disease, age 65 to 74 years, female gender; ACE = angiotensin-converting enzyme; CK-MB = creatinine kinase-myocardial binding.

score, the patients who presented high risk spent longer times in the CICU than did the low-risk patients. Additionally, the length of time spent in the CICU and the time taken for AF to start showed a correlation with each other. Multiple risk factors may have contributed towards long times spent in the CICU. It is possible that new-onset AF continued to be diagnosed for as long as the stay in the CICU lasted.

Although it has been reported that pre-hospital treatment with RAS blockers and beta-blockers protects against AF following acute coronary syndrome,[13] this was not the case in our study. Nonetheless, we found that in-hospital treatment with RAS blockers and beta-blockers had a protective effect against AF.

CHA_2DS_2-VASc and $CHADS_2$ scores and atrial fibrillation

The most relevant finding of our study was that $CHADS_2$ and CHA_2DS_2-VASc scores are relatively strongly predictive of new-onset AF following STEMI. Previous studies had shown that both of these scores were associated with the risk of incident or recurrent AF. Yin et al.[14] reported that $CHADS_2$ and CHA_2DS_2-VASc scores were directly associated with the incidence of postoperative AF following valve surgery, and that higher scores were strongly predictive of postoperative AF. Barkas et al.[15] reported that both scores were predictive of new AF in dyslipidemic patients. These findings were not surprising, since CHA_2DS_2-VASc and $CHADS_2$ scores contain causal risk factors for AF.

Diabetes mellitus, hypertension, older age, congestive heart failure and cerebrovascular disease, which are components of CHA_2DS_2-VASc and $CHADS_2$ scores, are associated with higher inflammatory status among patients.[16] An association between inflammation and AF has been indicated in the literature.[17,18] We previously reported that oxidative stress and inflammation parameters were associated with development of AF in patients presenting with STEMI.[19] Inflammation may have provided a strong relationship between development of AF and both scores.

Increased left atrium size is the best-known predictive factor for AF.[20] Studies evaluating patients with myocardial infarction have reported that these patients present greater incidence of AF, in relation to left atrial enlargement.[21,22] The present study found a similar association between left atrial diameter and development of AF. Additionally, left atrial diameter was found to be an independent predictor for the development of AF. Hypertension causes structural changes, including left ventricular hypertrophy, impaired diastolic dysfunction and increased left atrial pressure and volume.[23] Similarly, in the present study, hypertension was more often seen in patients with AF. Furthermore, left atrial diameter was greater in patients with AF than in patients without AF.

Although it has been suggested that better management of myocardial infarction will lead to improved outcomes for patients with AF,[24,25] development of AF during STEMI still significantly influences short and long-term mortality rates, including occurrences of sudden cardiac death.[26] In the light of this evidence, our study may give rise to suggestions regarding screening for AF, especially among high-risk groups. Physicians should carefully screen for AF among patients with high CHA_2DS_2-VASc and $CHADS_2$ scores and/or long hospitalization in the CICU. They should also screen for high peak CK-MB levels, especially among patients with symptoms of cardiac arrhythmia or with a diagnosis of thromboembolic cardiovascular events. Prompt management of arrhythmia is required, to reduce the risk of complications.

There are several limitations to our study. First, this study was observational and was conducted in a single center. Therefore, further studies are needed in order to reach definite conclusions. Lastly, our analysis involved a simple baseline determination at a single time point, but this may not reflect the patients' status over long periods.

CONCLUSION

$CHADS_2$ and CHA_2DS_2-VASc scores predicted new-onset AF following STEMI. These data may inform AF screening strategies.

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Methylation status of the *PPP1R13L* promoter region among lung cancer patients and healthy controls. Analytical cross-sectional study

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Promoter region, genetic.
CpG islands.
Methylation.
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ABSTRACT

BACKGROUND: There is evidence that genetic predisposition and epigenetic alteration (e.g. DNA methylation) play major roles in lung cancer. In our genetic epidemiological studies, rs1970764 in oncogene *PPP1R13L* was most consistently associated with lung cancer risk. Here, we explored the role of *PPP1R13L* methylation in lung cancer development.

DESIGN AND SETTING: Analytical cross-sectional study (45 lung cancer cases and 45 controls), conducted in China.

METHODS: We investigated the DNA methylation status of 2,160 cytosine-phosphate-guanine (CpG) sites in the *PPP1R13L* promoter region using the EpiTYPER assay of the Sequenom MassARRAY platform.

RESULTS: In the whole study group, the methylation levels of CpG-6, CpG-9, CpG-20 and CpG-21 were significantly lower and those of CpG-16 were significantly higher in cases than in controls. Among smokers, the methylation levels at five CpG sites (CpG-6, CpG-11, CpG-15, CpG-20 and CpG-21) were statistically significantly lower among cases. Among men, the methylation levels at four CpG sites (CpG-11, CpG-15, CpG-20 and CpG-21) were significantly lower among cases. Regarding smokers, the methylation levels at CpG-7.8 and CpG-21 among cases and at CpG-22 among controls were significantly lower, compared with nonsmokers. The frequency of positivity for methylation was not significantly different between lung cancer cases and controls (68.22% for cases and 71.87% for controls; P = 0.119).

CONCLUSION: Our study on a Chinese population suggests that lung cancer patients have aberrant methylation status (hypomethylation tended to be more frequent) in peripheral blood leukocytes at several CpG sites in the *PPP1R13L* promoter region and that exposure to smoking may influence methylation status.

INTRODUCTION

Lung cancer is considered to be one of the deadliest types of cancer worldwide. Lung cancer will continue to be a major health problem well through the first half of this century. It is a multifactorial disease with complex pathogenesis in which lifestyle, individual genetic background and environmental risk factors are involved. Tobacco use is an important environmental risk factor for lung cancer development. However, genetic predisposition and epigenetic alteration also play major roles in the genesis of lung cancer.[1-3]

The chromosomal subregion 19q13.3 harbors four genes that are involved in deoxyribonucleic acid (DNA) repair, apoptosis, ribosomal ribonucleic acid (rRNA) transcription and cell proliferation. From 3'→5', these are: *ERCC2/XPD* [excision repair cross-complementing rodent repair deficiency, complementation group 2/xeroderma pigmentosum complementary group D]; *PPP1R13L/IASPP/RAI* [protein phosphatase 1, regulatory (inhibitor) subunit 13-like/inhibitory member of the apoptosis stimulating proteins of p53 (ASPP) family/RelA-associated inhibitor]; *CD3EAP/ASE-1* [CD3e molecule, epsilon-associated protein/antisense to ERCC1)]; and *ERCC1* [excision repair cross-complementing rodent repair deficiency, complementation group 1].[4]

DNA methylation is an epigenetic DNA modification catalyzed by DNA methyltransferase 1 (DNMT1). Gene expression can be epigenetically regulated via changes in DNA methylation. In particular, site-specific DNA methylation alterations in cytosine-phosphate-guanine (CpG) islands around the 5'-untranslated regions (5'-UTRs) of genes, including hypomethylation of

oncogenes and hypermethylation of tumor suppressor genes, may be crucial promoters of cancer progression.[5]

Accumulating evidence indicates that differential DNA methylation patterns of genes are involved in lung carcinogenesis.[5-11] In our genetic epidemiological fine-mapping studies, the polymorphism rs1970764 in the oncogene *PPP1R13L* has been most consistently associated with lung cancer risk.[4] Currently, the role of *PPP1R13L* methylation in lung cancer development remains unclear.

OBJECTIVE

To compare the DNA methylation status of the *PPP1R13L* promoter region between lung cancer patients and healthy controls, we conducted this Chinese analytical cross-sectional study.

METHODS

Ethical considerations

The Chinese Administration Office of Human Genetic Resources approved this protocol (no. [2001]015; approval date: May 10, 2001). All study participants granted written or oral informed consent.

Study design and sample

No data on methylation levels in the promoter region of *PPP1R13L* have been reported in any population. We designed this cross-sectional study such that its sample consisted of 45 lung cancer cases and 45 controls. In total, 2,160 CpG sites (24 CpG sites/subject; 1,080 CpG sites for cases and 1,080 CpG sites for controls) were analyzed.

Newly diagnosed primary lung cancer cases were recruited between March 2010 and August 2012 at Liaoning Cancer Hospital, China. The diagnosis of lung cancer was based on standard clinical and histological criteria. Eligible cases had not previously undergone any treatment by means of either chemotherapy or radiotherapy. Cancer-free controls were primarily recruited from the orthopedics wards of the Affiliated Second Hospital of Shenyang Medical College, China. The controls were matched to the cases in terms of age (± 3 years), gender and ethnicity. All subjects were unrelated, and from the Han Chinese ethnic group. At enrollment, each participant was personally interviewed by doctors in order to acquire and record information on demographic characteristics, family history of cancer and lifetime history of tobacco use. Stratification was determined according to age, gender, family history of cancer, smoking history and pathological type. Family history and smoking status were assessed, because both of these variables are expected to be associated with *PPP1R13L* methylation.

Determination of target region

We searched for potential CpG islands in the *PPP1R13L* promoter region in three sources: the website http://www.ncbi.nlm.nih.gov/ (GRCh38.p2 primary assembly), with the aim of intercepting sequences of 2,000 base pairs (bp) upstream and 1,000 bp downstream from the transcription start site; the website http://www.ebi.ac.uk/Tools/seqstats/emboss_cpgplot/, with the aim of predicting potential CpG islands; and the Sequenom EpiDesigner software, with the aim of designing primers for this genetic sequence.

We obtained this sequence and identified three CpG islands in the *PPP1R13L* promoter region of chr19: 45405350~45408349. Two primer schemes (#9 and #11) were recommended. We performed methylation analyses on #11 scheme region (-360 bp to +131 bp upstream and downstream from the transcription start site, chr19: 45406219-45406709) in the current study. This sequence covered a product size of 491 bp (relative sequence range: 1641-2131), from which 24 CpG sites were assessed (**Figure 1**).

DNA extraction

Genomic DNA was extracted from peripheral blood samples of 1.5 ml, using the FlexiGene DNA kit 250 (Qiagen, Germany).

DNA methylation analysis

The EpiTYPER assay on the Sequenom MassARRAY platform was used to perform the quantitative gene-specific methylation

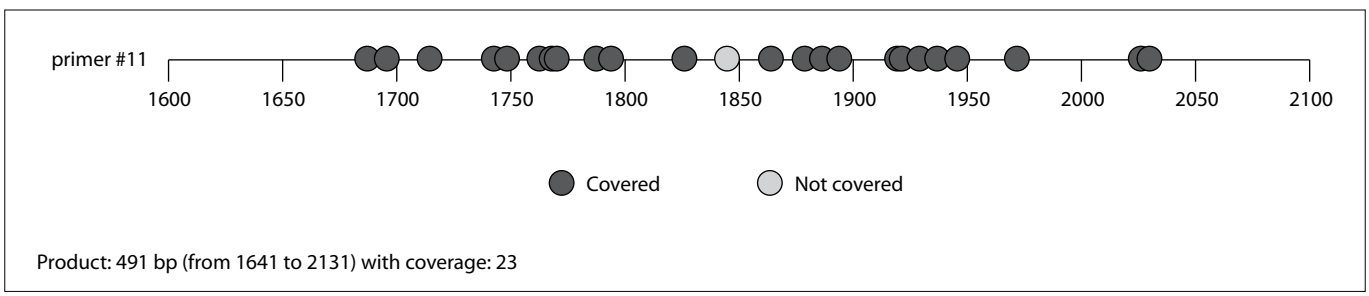

Figure 1. Schematic diagram of cytosine-phosphate-guanine (CpG) sites in #11 scheme of the *PPP1R13L* promoter region from CpG-1 to CpG-24 (from left to right). The sequence is from 5′ to 3′. The dots represent the CpG sites. Blue dots indicate CpG sites that could be detected. The red dot indicates a CpG site that could not be detected because of a sequencing problem.

analysis. This is a tool for detection and quantitative analysis of DNA methylation using base-specific cleavage and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

In short, the steps include the following: primer design, bisulfite treatment of DNA, amplification of DNA, shrimp alkaline phosphatase (SAP) reaction, RNA transcription, base-specific cleavage using RNase A, MALDI-TOF MS analysis[12,13] and DNA methylation standards (negative control of 0% and positive control of 100%). These were used for quality control regarding the bias of PCR amplification. The sequences of Primer-Plus-Tag (lowercase: Tag; capital: primer) were:

- LeftPrimer-PlusTag-aggaagagagGGGGTTTTTTTATTTTGGGATTTAT;
- RightPrimer-PlusTag-cagtaatacgactcactatagggagaaggctCTTATAAAACATCTAAACCTCCCCA.

Statistical analysis

The methylation levels of CpG sites were compared between cases and controls or between stratified subgroups using Student's t test for analyses with equal variances assumed, or the t' test for analyses with equal variances not assumed. Differences in methylation levels of CpG according to pathological subgroup were analyzed using one-way ANOVA test or non-parametric test. The methylation frequency was compared between cases and controls using the chi-square test.

Evaluations were performed using the Statistical Package for the Social Sciences 11.0 software (SPSS Inc., Chicago, IL, USA). For all statistical analyses, differences were considered to be statistically significant if the P-value was less than 0.05.

The power of the test was calculated using online statistical software (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html). "Inference for means: comparing two independent samples" was selected. From the mean values and standard deviations that were observed for the whole study group, the chances of detecting differences in methylation levels between cases and controls at the significance level of 0.05 for CpG-6, CpG-9, CpG-16, CpG-20 and CpG-21 were 64%, 76%, 57%, 82% and 68%, respectively. Thus, larger sample sizes would be required to achieve 80% power for all these CpG sites.

RESULTS

The study population included a total of 2,160 methylation status calls for 24 CpG sites among 90 subjects (45 lung cancer cases and 45 cancer-free controls). The basic description of the cases and controls is shown in **Table 1**. There were no statistically significant differences in mean age, gender or smoking history between the cases and controls. However, the cases had significantly higher frequency of family history of cancer than the controls. The distribution of pathological subtypes of the cancer cases is shown in **Table 1**.

The target sequence included 24 different CpG sites, denoted CpG-1.2, CpG-3, CpG-4, CpG-5, CpG-6, CpG-7.8, CpG-9, CpG-10, CpG-11, CpG-12, CpG-13, CpG-14, CpG-15, CpG-16, CpG-17.18.19, CpG-20, CpG-21, CpG-22 and CpG-23.24 (**Figure 1**). The methylation status of the CpG sites in the *PPP1R13L* promoter region for the cases and controls is shown in **Table 2**. Some of the CpG sites were analyzed together, which resulted in reporting of mean methylation levels for CpG-1.2, CpG-7.8, CpG-17.18.19 and CpG-23.24, respectively. Equal variation was assumed for all methylation levels except for CpG-3, CpG-4, CpG-9 and CpG-16 in the whole group and for CpG-9 among nonsmokers and among women. The mean methylation levels of all CpG sites were below 10%, except for CpG-10, CpG-14, CpG-16 and CpG-22. The standard deviations were close to the mean values, thus indicating the existence of substantial inter-individual variation in the methylation levels of these CpG sites (**Table 2, Table 3** and **Figure 2**).

In the whole study group, the methylation levels of CpG-6, CpG-9, CpG-20 and CpG-21 were statistically significantly lower among cases than among controls. The methylation level of CpG-16 was statistically significantly higher among cases than among controls. There were no statistically significant differences between cases and controls regarding methylation levels at all CpG sites taken together, or at the remaining CpG sites (**Table 2**).

Stratified analyses were made for subgroups based on smoking history, gender and pathological type. Among smokers, five CpG sites had statistically significantly lower methylation levels among cases than among controls. These were CpG-6, CpG-11, CpG-15, CpG-20 and CpG-21 (**Table 3** and **Figure 2**). Among nonsmokers, there was statistically significantly lower methylation levels for CpG-9 and higher methylation levels for CpG-3 among cases

Table 1. Basic description of lung cancer cases and controls

	Cases n (%) (n = 45)	Controls n (%) (n = 45)	P-value
Age (years)			
Mean (± SD)	58 (± 11)	60 (± 9)	0.63[a]
Gender			
Male	32 (71.1)	32 (71.1)	
Female	13 (28.9)	13 (28.9)	1.0[b]
Family history of cancer			
No	40(88.9)	45 (100.0)	
Yes	5(11.1)	0 (0.0)	**0.02**[b]
Smoking history			
Never	18 (40.0)	25 (55.6)	
Yes	27 (60.0)	20 (44.4)	0.14[b]
Pathological type			
Squamous carcinoma	20 (44.4)		
Adenocarcinoma	14 (31.1)		
Other	11 (24.4)		

SD = standard deviation; [a]for t test; [b]for χ^2 test (two-sided).

than among controls (**Table 3**). Among men, lower methylation levels at four CpG sites (CpG-11, CpG-15, CpG-20 and CpG-21) were found among cases than among controls. Higher methylation levels at the CpG-16 site were found among male cases than among male controls (**Table 3**). Among women, only CpG-9 had significantly lower methylation levels among cases than among controls (**Table 3**). In addition, smokers had statistically significantly lower methylation levels at CpG-7.8 (0.0570 ± 0.0458 versus 0.1028 ± 0.0926; P = 0.033) and CpG-21 (0.0167 ± 0.0166 versus

Table 2. Methylation status of selected cytosine-phosphate-guanine (CpG) sites in the *PPP1R13L* promoter region, compared between cases and controls in the whole group

CpG site	Group[a]	N	Mean	Standard deviation	P-value[b]
CpG-1.2[c]	1	43	0.0586	0.05809	0.74
	2	45	0.0547	0.05392	
CpG-3	1	33	0.0752	0.11046	0.07[d]
	2	42	0.0357	0.05662	
CpG-4	1	43	0.0007	0.00258	0.13[d]
	2	43	0.0116	0.04649	
CpG-5	1	33	0.0012	0.00696	0.45
	2	35	0.0003	0.00169	
CpG-6	1	43	0.0186	0.01684	**0.04**
	2	44	0.0339	0.04596	
CpG-7.8[c]	1	43	0.0788	0.07089	0.70
	2	45	0.0844	0.06525	
CpG-9	1	33	0.0176	0.01838	**0.036[d]**
	2	32	0.0331	0.03658	
CpG-10	1	44	0.2232	0.14323	0.09
	2	45	0.1760	0.11659	
CpG-11	1	44	0.0443	0.03624	0.052
	2	45	0.0600	0.03885	
CpG-12[e]	1	0	-	-	-
	2	0	-	-	
CpG-13	1	43	0.0005	0.00305	0.72
	2	42	0.0007	0.00342	
CpG-14	1	44	0.2232	0.14323	0.09
	2	45	0.1760	0.11659	
CpG-15	1	44	0.0443	0.03624	0.052
	2	45	0.0600	0.03885	
CpG-16	1	44	0.2491	0.19263	**0.036**
	2	45	0.1607	0.19949	
CpG-17.18.19[c]	1	44	0.0266	0.02342	0.80
	2	45	0.0280	0.02897	
CpG-20	1	44	0.0198	0.02205	**0.007**
	2	45	0.0380	0.03788	
CpG-21	1	43	0.0242	0.02363	**0.019**
	2	44	0.0364	0.02402	
CpG-22	1	44	0.1236	0.06627	0.86
	2	45	0.1267	0.08710	
CpG-23.24[c]	1	43	0.0186	0.06760	0.69
	2	43	0.0137	0.04220	

[a]1: cases, with 1,080 CpG sites tested; 2: controls, with 1,080 CpG sites tested; [b]for t test; [c]mean values of these sites; [d]for t' test; [e]testing failed.

Table 3. Methylation status of selected cytosine-phosphate-guanine (CpG) sites in the *PPP1R13L* promoter region, compared between cases and controls in different subgroups[a]

Subgroup/ CpG site	Group[b]	N	Mean	Standard deviation	P-value[c]
Smokers					
CpG-6	1	26	0.02	0.016	**0.047**
	2	20	0.03	0.019	
CpG-11	1	27	0.0356	0.03030	**0.024**
	2	20	0.0590	0.03865	
CpG-15	1	27	0.0356	0.03030	**0.024**
	2	20	0.0590	0.03865	
CpG-20	1	27	0.02	0.022	**0.005**
	2	20	0.04	0.025	
CpG-21	1	26	0.02	0.017	**< 0.0001**
	2	19	0.04	0.017	
Nonsmokers					
CpG-9	1	14	0.0207	0.01940	**0.039[d]**
	2	17	0.10435	0.03757	
CpG-3	1	13	0.0946	0.10047	**0.045**
	2	13	0.0365	0.06733	
Men					
CpG-11	1	31	0.0403	0.03027	**0.047**
	2	32	0.0569	0.03421	
CpG-15	1	31	0.0403	0.03027	**0.047**
	2	32	0.0569	0.03421	
CpG-20	1	31	0.0197	0.02359	**0.005**
	2	32	0.0375	0.02476	
CpG-21	1	30	0.0230	0.02246	**0.028**
	2	31	0.0358	0.02187	
CpG-16	1	31	0.2619	0.20988	**0.044**
	2	32	0.1572	0.19525	
Women					
CpG-9	1	11	0 .0164	0.01433	**0.007[d]**
	2	9	0.0533	0.03041	

[a]Only statistically significant results are listed; [b]1: cases, with 1,080 CpG sites tested; 2: controls, with 1,080 CpG sites tested; [c]for t test; [d]for t' test.

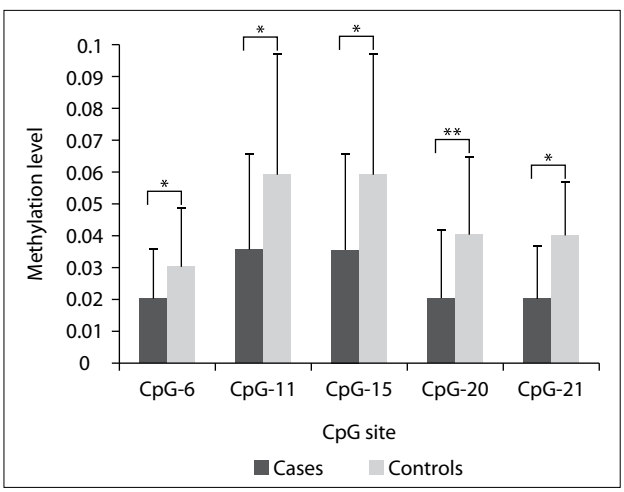

Figure 2. Significantly lower methylation level of the cytosine-phosphate-guanine (CpG) sites (CpG-6, CpG-11, CpG-15, CpG-20 and CpG-21) in cases than in controls, among smokers. Error bars represent standard deviation (SD). P-values were calculated using Student's t test. *P < 0.05; **P < 0.01.

0.0328 ± 0.0293; P for t' test = 0.045) among cases and at CpG-22 (0.0915 ± 0.0809 versus 0.1548 ± 0.0829; P = 0.014) among controls, compared with nonsmokers. The methylation level of all CpG sites taken together, or for the remaining CpG sites, did not differ significantly between cases and controls based on smoking status or gender (data not shown). Methylation levels were unaffected by pathological subgroup (data not shown).

The frequency of methylation-positive CpG sites in the *PPP1R13L* promoter region was not statistically significantly different between lung cancer cases and controls [68.22% for cases (positive versus negative = 513:239) and 71.87% for controls (positive versus negative = 557:218); $\chi^2 = 2.483$; P = 0.119]. Hypomethylation was most frequently observed, and was present at 81% of the aberrantly methylated CpG sites.

DISCUSSION

Main findings of the study

To the best of our knowledge, this is the first study investigating the association between DNA methylation in the promoter region of the oncogene *PPP1R13L* and lung cancer. We report that in the *PPP1R13L* promoter region, the methylation levels of some CpG sites in peripheral blood leukocytes differed between lung cancer cases and controls and that hypomethylation was observed more often in lung cancer cases than in controls. Lowered methylation levels were also more prominent among smokers and among men.

Studies addressing methylation in lung cancer

The association between the methylation status of specific genes in peripheral blood and lung cancer has previously been addressed.[5-11,14]

In a study on the EPIC-Italy cohort and the MCCS cohort, hypomethylation of six CpG sites was associated with smoking and lung cancer risk: cg05575921 in the AHRR (aryl-hydrocarbon receptor repressor) gene; cg03636183 in the F2RL3 (F2R-like thrombin/trypsin receptor 3) gene; cg21566642 and cg05951221 in 2q37.1; cg06126421 in 6p21.33; and cg23387569 in 12q14.1. This provided evidence that smoking and possibly other factors may lead to DNA methylation changes that can be detected in peripheral blood and that are predictive of lung cancer risk.[6]

In a Chinese case-control study, it was reported that subjects with hypermethylation of the promoter region of hOGG1 (human 8-oxoguanine DNA glycosylase) had a 2.25-fold increased risk of developing non-small cell lung cancer (NSCLC), compared with methylation-free subjects.[5] In another Chinese case-control study, it was reported that there were statistically significant differences in the promoter methylation levels of p16 (*CDKN2A*, cyclin dependent kinase inhibitor 2A), RASSF1A (Ras association domain family member 1A), and FHIT (fragile histidine triad) between lung cancer cases and controls. Moreover, it was reported that high methylation levels of the p16, RASSF1A and FHIT genes were associated with significantly increased risk of lung cancer. It was concluded that further investigation of the potential usefulness of methylation status of these three genes in clinical practice was warranted.[7]

In an American prospective nested case-control study, it was reported that hypomethylation of the p53 (tumor protein p53) gene in exons 5-8, the hypermutable region, was associated with a 2-fold increased risk of lung cancer [OR (95% CI) = 2.20 (1.04-4.65)]. It was suggested that hypomethylation status within exons 5-8 of p53 from peripheral lymphocyte DNA might be a relevant predictor of lung cancer among male smokers.[8]

A Thai case-control study found that the methylation percentage of LINE-1 (interspersed DNA repetitive sequences) loci ((u)C(u)C) was significantly higher in lung cancer patients than in healthy controls and suggested that changes in the levels and patterns of genome-wide methylation of peripheral blood mononuclear cells (PBMCs) were associated with lung cancer risk.[9] The study confirmed that methylation of the SHOX2 (short stature homeobox gene 2) gene may be a reliable marker for lung malignancies and suggested that SHOX2 methylation in blood plasma may represent an alternative diagnostic test for patients who are unable to undergo bronchoscopy.[10] SHOX2 encodes a homeo-domain transcription factor which has been identified as a close homologue of the SHOX gene, and both genes are involved in skeletogenesis and heart development.[10]

In a Polish case-control study, it was reported that the methylation levels of DNA from peripheral blood plasma were slightly higher in patients with small-cell lung cancer (SCLC) (75% of SCLC patients), compared with healthy individuals. The median overall survival of patients with *DCLK1* (doublecortin-like kinase 1) promoter methylation was lower than that of patients without *DCLK1* gene methylation (hazard ratio, HR = 4.235).[11]

A meta-analysis on genome-wide DNA methylation showed that smoking left a long-term signature in relation to DNA methylation and that this was a potential mechanism through which tobacco exposure would predispose towards adverse health outcomes, such as cancer, osteoporosis and lung and cardiovascular disorders.[15] Cigarette smoking has a broad impact on genome-wide methylation that, at many loci, persists many years after smoking cessation.[15]

A multicenter case-control study that used data from six countries in Central and Eastern Europe suggested that global blood DNA methylation in peripheral blood was not associated with the risk of lung cancer among nonsmoking women.[14]

Implications, strengths and limitations

The finding from the present study is consistent with previous observations that hypomethylation of the oncogene promoter may be an early and frequent molecular event in occurrences

of cancer.[5] However, we were unable to determine whether the changes in methylation levels were a cause or a consequence of lung cancer. The difference in methylation levels between smokers and nonsmokers among both cases and controls suggested that smoking might lead to lower methylation levels at CpG sites of the *PPP1R13L* promoter region in peripheral blood leukocytes from lung cancer patients. This would thus also provide evidence that DNA methylation may be an intermediate step between smoking and lung cancer.[15] Altered levels of DNA methylation in the *PPP1R13L* promoter therefore might be useful in detection of lung cancer.

Case-control studies, in which methylation levels in DNA isolated from peripheral blood cells from cancer patients are compared with methylation levels in healthy controls, cannot be used to establish causal relationships and, thus, establish whether the changes in promoter methylation levels are part of the carcinogenesis or are caused by disease. Nor can cross-sectional studies be used to infer the causal relationships between exposures and outcomes. However, changes in methylation levels may be used as diagnostic or prognostic biomarkers. Prospective studies in which the biological samples are collected prior to making a diagnosis of cancer may provide evidence of causality.

PPP1R13L (*iASPP*) is one of three members of the ASPP (apoptosis-stimulating proteins of *p53*) family. *p53*, the guardian of the genome, plays a critical role in the induction of apoptosis, typically in response to DNA damage. The ASPP family is involved in regulation of *p53*. The ASPP family includes *ASPP1*, *ASPP2* and *ASPP* (*iASPP*). *ASPP1* and *ASPP2* are tumor suppressors, whereas the inhibitor of ASPP (*iASPP*) functions as an oncogene. *ASPP1* and *ASPP2* promote apoptosis, while overexpression of *iASPP* inhibits apoptotic cell death typically after DNA damage. In cancer cells, increased expression of *iASPP* is associated with worse prognosis.[16] Mechanistically, changes to DNA methylation status are thought to alter the transcriptional regulation of gene expression.[13] On the other hand, *iASPP* mRNA levels were not found to be associated with lung cancer risk in a prospective study.[17]

The current study has some limitations. Its statistical power was limited due to the relatively low number of participants. The retrospective or cross-sectional design does not allow us to determine whether the observed associations between changes in methylation status and lung cancer are causal. The matching between cases and controls regarding age, gender and ethnicity in this study was insufficient to exclude potential confounding factors such as smoking.

CONCLUSION

Our study suggests that lung cancer patients have aberrant methylation status (hypomethylation tended to be more frequent) in peripheral blood leukocytes, for several CpG sites in the *PPP1R13L* promoter region, and that exposure to smoking may influence methylation status in this Chinese population. Further research using larger sample sizes and a prospective study design is necessary in order to assess the potentially causal roles of these changes to methylation levels at CpG sites in the *PPP1R13L* promoter region, relating to lung cancer.

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The Brazilian version of the Bournemouth questionnaire for low back pain: translation and cultural adaptation

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Back pain

ABSTRACT

BACKGROUND: The Bournemouth questionnaire is a multidimensional instrument for evaluating health domains among patients with low back pain.

OBJECTIVE: The objective of this study was to translate and cross-culturally adapt the Bournemouth questionnaire for individuals with low back pain, to Brazilian Portuguese.

DESIGN AND SETTINGS: This was a cross-sectional study conducted at the Federal University of São Carlos.

METHODS: The Brazilian version of the Bournemouth questionnaire was developed following the processes of translation, back-translation, committee review and pre-testing. The translation phase involved two independent bilingual translators whose mother language was Brazilian Portuguese. The back-translation phase involved two independent translators whose mother language was English. In order to verify comprehension of the questionnaire, 44 individuals (43.1% men) with low back pain, and with mean age of 45.4 ± 13.8 years, participated in the pre-testing phase.

RESULTS: During the translation phase, some terms and expressions were changed to obtain cultural equivalence to the original Bournemouth questionnaire. In the pre-testing phase, each item of the questionnaire showed a comprehension level of over 90%.

CONCLUSION: The Bournemouth questionnaire was translated and culturally adapted to the Portuguese language, to be used among individuals with low back pain.

INTRODUCTION

Low back pain is one of the most common health conditions worldwide. The Global Burden of Disease study showed that low back pain was the leading cause of the overall number of years lived with diseases in 188 countries from 1990 to 2013.[1] The results relating to the burden of disease in Brazil from 1990 to 2016 showed that low back pain was a main cause of disease.[2] In 2015, the overall point-prevalence of activity-limiting low back pain was 7.3%, thus implying that 540 million people were affected at any one time.[3]

The one-year incidence of low back pain has been found to range from 6.3% to 15.4% for the first episode, and from 1.5% to 36% for any episode of low back pain. The prevalence is higher among females and people aged 40 to 80 years.[4,5] Low back pain is associated with high costs, and the estimated indirect costs in United States have been found to be 19 billion dollars per year.[6]

Analysis on any disease or injury requires standardized tools that measure patient conditions with precision and quality, in order to follow the clinical course and progression of rehabilitation and to verify treatment efficacy in relation to self-perceived health. Questionnaires and functional scales are important for clinical practice and scientific research, since they can measure subjective information in an efficient, trustworthy and low-cost manner.[7-9] Questionnaires created in other languages have to be adapted to the environment in which they will be used, considering the language and culture. Therefore, the process of translation and cross-cultural adaptation of a questionnaire needs to be standardized to reach equivalence between the original and the translated versions. Subsequently, the psychometric properties of the questionnaire need to be evaluated to ensure that the tool possesses characteristics, validity and reliability that are similar to those of the original version.[9-11]

Low back pain is a condition of complex and subjective nature. It is more than just a response to a nociceptive stimulus to a tissue lesion: it is also a multidimensional experience described by

the biopsychosocial model, which includes pain-related, disability-related, cognitive and affective domains.[5,8,12]

The Bournemouth questionnaire was created by Bolton and Breen in 1999,[8] to fill the need for a tool that was able to measure multidimensional health domains, such as pain, function, incapacity and psychological and social factors among patients with low back pain. This questionnaire can be easily applied and is reproducible and responsive to clinical alterations, which makes it appropriate for use in scientific research and clinical practice, for monitoring the progression of symptoms and for assisting in planning treatments for patients with low back pain.[8,12,13] Furthermore, the Bournemouth questionnaire has been linked to many important core sets contained within the International Classification of Functioning (ICF), Disability and Health, such as body function, activities and participation.[12]

The original version of this questionnaire was written in English, but it has already been translated and culturally adapted to different languages such as German,[14] Danish[15] and Turkish[16] and has been widely used as an evaluation tool in several studies.[17-19] The neck pain version of the Bournemouth questionnaire has already been translated into Brazilian Portuguese.[20] However, the low back pain version has not been translated to Brazilian Portuguese yet. For this to be used in Brazil, it needs to be translated and culturally adapted.

OBJECTIVES

The purpose of this study was to translate and culturally adapt the Bournemouth questionnaire for low back pain, to Brazilian Portuguese.

METHODS

Translation and adaptation procedures

The author of the original Bournemouth questionnaire confirmed the originality of this study. The translation and cultural adaptation procedures were based on previous studies[20–23] and followed the proper guidelines.[10,11,24] The procedures were divided into the following stages: translation, back-translation, expert committee review and pre-testing (**Figure 1**).

The original version was translated from English to Portuguese by two independent bilingual translators whose mother language was Brazilian Portuguese. One of them was aware of the constructs of the questionnaire, while the other one was a layman regarding this subject. In the next phase, the translated versions that had been elaborated independently (T1 and T2) were compared and discussed by the committee, which was composed of three specialized physical therapists and both of the bilingual translators who had participated in the previous phase. In the event of any disagreement, alterations were made to the consensual Portuguese version (T12), while maintaining the main characteristics of the original questionnaire.

T12 was translated back to English by two independent translators whose mother language was English. These translators did not have access to the original questionnaire. They generated two new versions: BT1 and BT2. Subsequently, the same members of the previous committee participated in a second meeting to verify the differences among the translated versions (T1, T2, T12, BT1 and BT2), in relation to the original questionnaire. They verified semantics and idiomatic and cultural equivalence, and they modified or eliminated any irrelevant, inadequate or ambiguous topics. The second meeting resulted in a pre-final version (V1), which was then applied in the pre-testing stage (**Figure 2**).

After the translation procedures had been completed, 44 subjects older than 18 years, who were recruited through verbal and digital invitation, took part in the cultural adaptation part of the study. Participants were considered eligible for the study if they had low back pain and were physically and mentally able to give responses to the questionnaires.

The pre-testing stage was performed to verify the comprehension and acceptability of the questions and answers among patients with low back pain. These subjects were asked to read and answer the questionnaire. Then, the researcher asked whether they comprehended the questions, what they understood and whether they had any suggestion for modifying the questions, in the event that any topic remained unanswered.[20-23]

This study was approved by the Human Research Ethics Committee (approved on September 9, 2014, under protocol no. 31477314.0.0000.5512). All participants received verbal and written explanations about the aims and methodology of the study, and those who agreed to participate signed an informed consent agreement.

Score calculation

The original Bournemouth questionnaire comprises seven questions, and each of them represents a different dimension of low back pain: pain intensity (question 1), functional status in daily living (question 2), functional status in social activities (question 3), affective dimensions of anxiety (question 4), affective dimensions of depression (question 5), cognitive aspects of fear-avoidance behavior (question 6) and pain locus of control (question 7).[8,15] Each topic of the Bournemouth questionnaire is scored using an 11-point numerical rating scale. The final total score ranges from 0 to 70 and is obtained by summing the scores of the seven topics. Higher scores reflect greater pain and disability.[8,15]

RESULTS

The results from the translation stage (T1, T2 and T12) are described in **Table 1**. The results from the back-translation phase

(BT1 and BT2) are described in **Table 2** and the V1 version of the questionnaire is shown in **Figure 2**.

In the pre-testing phase, 44 individuals (43.1% men) answered the pre-testing version of the Bournemouth questionnaire, in Brazilian Portuguese (V1). The participants were native speakers of Portuguese with mean age of 45.4 ± 13.8 years, who had presented low back pain for 70.8 ± 143.6 months. Ten individuals (22.7%) had not completed elementary school and 10 (22.7%)

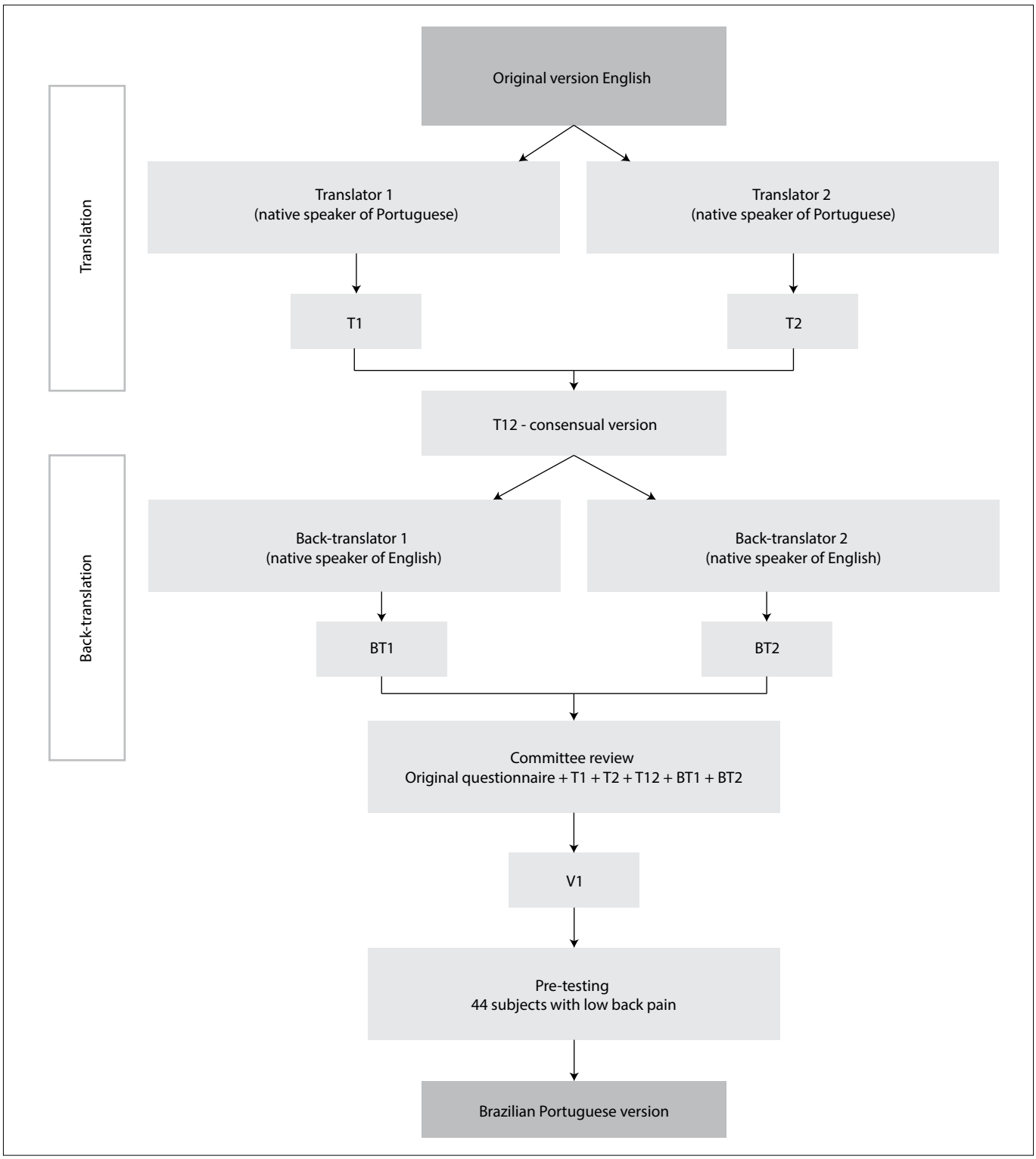

Figure 1. Study flowchart.

had completed it; 14 (31.81%) had completed high school and 10 (22.7%) had a bachelor's degree. In this phase, the subjects did not have any suggestions for improving the comprehension of the topics. According to these individuals, there was no difficulty in filling out the questionnaire. All questions showed comprehension level higher than 90%, and therefore it was not necessary to modify V1 after the pre-testing phase.

DISCUSSION

The purpose of this study was to translate and culturally adapt the Bournemouth questionnaire for low back pain, to Brazilian Portuguese. Translation and cultural adaptation studies make it possible to provide common measurements for investigations within different cultural contexts, a standard measurement for application in international studies and a means for comparisons between national/cultural groups. Moreover, they have the advantage of being less costly and less time-consuming than it would be to generate a new measurement.[10,11,24]

To ensure equivalence between the original questionnaire and the new adapted version, and to maintain the characteristics of the original instrument at a conceptual level across different cultures, the methods used in cross-culturally adapting a questionnaire should follow the guidelines proposed by Beaton in 2000.[10] The translation and cross-cultural adaptation methods used in the present study have become well established in the literature and have been applied in several studies.[20-23] Versions of the Bournemouth questionnaire translated to other languages have been provided through previous studies[14-16] using the same methodology. The cross-cultural adaptation process was successfully completed in all cases.

In the translation phase for producing the Portuguese version of the Bournemouth questionnaire, the T12 consensual version was elaborated in order to avoid ambiguous or

Dimensões Globais do Questionário de Bournemouth

As escalas abaixo foram desenvolvidas para sabermos sobre a sua dor nas costas e como ela está te afetando. Por favor, responda TODAS as perguntas, circulando apenas UM número em CADA escala que melhor represente como você se sente.

1. Durante a última semana, em média, como você classificaria sua dor nas costas?

Sem dor										Pior dor possível
0	1	2	3	4	5	6	7	8	9	10

2. Ao longo da última semana, quanto sua dor nas costas interferiu nas atividades diárias (tarefas domésticas, tomar banho, colocar roupa, caminhar, subir/descer escadas, levantar-se/deitar-se da cama, levantar-se/ sentar-se na cadeira)?

Não interferiu										Impossibilitou a realização de atividades
0	1	2	3	4	5	6	7	8	9	10

3. Ao longo da última semana, quanto sua dor nas costas interferiu nas suas atividades recreativas, sociais e/ou familiares?

Não interferiu										Impossibilitou a realização de atividades
0	1	2	3	4	5	6	7	8	9	10

4. Ao longo da última semana, quão ansioso(a) você se sentiu (tenso(a), nervoso (a), irritado(a), com dificuldade para se concentrar/relaxar)?

Nada ansioso										Extremamente ansioso
0	1	2	3	4	5	6	7	8	9	10

5. Ao longo da última semana, quão deprimido(a) você se sentiu (desanimado(a), triste, pessimista, infeliz)?

Nada depressivo										Extremamente depressivo
0	1	2	3	4	5	6	7	8	9	10

6. Ao longo da última semana, quanto você acha que seu trabalho (dentro ou fora de casa) afetou/afetaria na sua dor nas costas?

Não piorou										Piorou muito
0	1	2	3	4	5	6	7	8	9	10

7. Ao longo da última semana, quanto você conseguiu controlar (reduzir/aliviar) sua dor nas costas por conta própria?

Controle total										Nenhum controle
0	1	2	3	4	5	6	7	8	9	10

Figure 2. Brazilian Portuguese version of the Bournemouth questionnaire for low back pain.

hard-to-comprehend words such as *cotidianas, sequer, aptidão* and *irritadiço*, which were present in at least one of the translations. In the back-translation phase, there was no difference in meanings between the translation and the original version, thus indicating that the adaptations that were made in the initial phase did not alter the meanings of the topics. In the pre-testing phase, the level of comprehension of all the topics was higher than 90%, which indicates that the new version of this questionnaire was easily understood.

Although the guidelines (2000)[10] highly recommend that, after the translation and adaptation process, the reliability and construct validity of the product should be verified, several studies have reported the translation and cross-cultural adaptation phases without analysis on the psychometric properties.[22,23,25-27]

Table 1. Translation and modification of the consensual version

Bournemouth questionnaire	T1 and T2 versions	T12 consensual version
1. Over the past week, on average how would you rate your back pain? No pain/Worst pain possible	**T1**. Ao longo da última semana, como você classificaria, em média, sua dor nas costas? Não senti dor/Senti a pior dor possível. **T2**. Durante a última semana, em média, como você classificaria sua dor nas costas? Sem dor/Pior dor possível.	Durante a última semana, em média, como você classificaria sua dor nas costas? Sem dor/Pior dor possível.
2. Over the past week, how much has your back pain interfered with your daily activities (housework, washing, dressing, walking, climbing stairs, getting in/out of bed/chair)? No interference/Unable to carry out activities	**T1**. Ao longo da última semana, quanto sua dor nas costas interferiu nas atividades cotidianas (trabalhos do lar, banhar-se, vestir-se, caminhar, subir/descer escadas, levantar-se/deitar-se na cama, levantar-se/sentar-se na cadeira)? Não houve interferência/Sequer consegui executar essas atividades. **T2**. Durante a última semana, quanto sua dor nas costas interferiu suas atividades diárias (tarefas domésticas, limpeza, vestir-se, andar, subir escadas, deitar-se ou levantar-se da cama/de cadeiras)? Não interferiu/Impossibilitou a realização de atividades.	Ao longo da última semana, quanto sua dor nas costas interferiu nas atividades diárias (tarefas domésticas, tomar banho, colocar roupa, caminhar, subir/descer escadas, levantar-se/deitar-se na cama, levantar-se/sentar-se na cadeira)? Não houve interferência/Impossibilitou a realização de atividades.
3. Over the past week, how much has your back pain interfered with your ability to take part in recreational, social, and family activities? No interference/Unable to carry out activities	**T1**. Ao longo da última semana, quanto sua dor nas costas interferiu na sua aptidão para participar de atividades recreativas, sociais e/ou familiares? Não houve interferência/Sequer consegui executar essas atividades. **T2**. Durante a última semana, quanto sua dor nas costas interferiu na sua habilidade em participar em atividades recreativas, sociais e familiares? Não interferiu/Impossibilitou a realização de atividades.	Ao longo da última semana, quanto sua dor nas costas interferiu nas suas atividades recreativas, sociais e/ou familiares? Não interferiu/Impossibilitou a realização de atividades.
4. Over the past week, how anxious (tense, uptight, irritable, difficulty in concentrating/relaxing) have you been feeling? Not at all anxious/Extremely anxious	**T1**. Ao longo da última semana, quão ansioso(a) você se sentiu? (tenso(a), irritadiço(a), com dificuldade para se concentrar/relaxar). Não me senti ansioso(a)/Me senti extremamente ansioso(a). **T2**. Durante a última semana, quão ansioso (tenso, nervoso, irritado, com dificuldade em se concentrar/relaxar) você tem se sentido? Nada ansioso/Extremamente ansioso.	Ao longo da última semana, quão ansioso(a) você se sentiu (tenso(a), irritado(a), com dificuldade para se concentrar/relaxar)? Nada ansioso/Extremamente ansioso.
5. Over the past week, how depressed (down-in-the-dumps, sad, in low spirits, pessimistic, unhappy) have you been feeling? Not at all depressed/Extremely depressed	**T1**. Ao longo da última semana, quão deprimido(a) você se sentiu? (desanimado(a), triste, pessimista, infeliz). Não me senti deprimido(a)/Me senti extremamente deprimido(a). **T2**. Durante a última semana, quão depressivo (pra baixo, triste, desanimado, pessimista, infeliz) você tem se sentido? Nada depressivo/Extremamente depressivo.	Ao longo da última semana, quão deprimido(a) você se sentiu (desanimado(a), triste, pessimista, infeliz)? Nada depressivo/Extremamente depressivo.
6. Over the past week, how have you felt your work (both inside and outside the home) has affected (or would affect) your back pain? Have made it no worse/Have made it much worse	**T1**. Ao longo da última semana, quanto você acha que seu trabalho (dentro ou fora de casa) interferiu na sua dor nas costas? Não interferiu nada/Piorou muito a dor nas costas. **T2**. Durante a última semana, quanto você sentiu que seu trabalho (tanto dentro quanto fora de casa) afetou (ou afetaria) sua dor nas costas? Não piorou/Piorou bastante.	Ao longo da última semana, quanto você acha que seu trabalho (dentro ou fora de casa) afetou na sua dor nas costas? Não piorou/Piorou muito.
7. Over the past week, how much have you been able to control (reduce/help) your back pain on your own? Completely control it/No control whatsoever	**T1**. Ao longo da última semana, quanto você conseguiu controlar (reduzir/aliviar) sua dor nas costas por conta própria? Consegui controlar completamente/Não consegui controlar nem um pouco. Consegui controlar completamente/Não consegui controlar nem um pouco. **T2**. Durante a última semana, quanto você tem sido capaz de controlar (reduzir/ajudar) sozinho sua dor nas costas? Controle total/Nenhum controle.	Ao longo da última semana, quanto você conseguiu controlar (reduzir/aliviar) sua dor nas costas por conta própria? Controle total/Não consegui controlar.

Table 2. Back-translation phase. Differences between BT1 and BT2 and the original version

Bournemouth questionnaire	Differences between BT1 and BT2 versions
1. Over the past week, on average how would you rate your back pain? No pain/Worst pain possible	**BT1.** During the last week, on average, how would you classify your back pain? Without pain/Worst pain possible. **BT2.** During the past week, on average, how would you rate your back pain? No pain/Worst pain possible.
2. Over the past week, how much has your back pain interfered with your daily activities (housework, washing, dressing, walking, climbing stairs, getting in/out of bed/chair)? No interference/Unable to carry out activities	**BT1.** Over the last week, how much did your back pain interfere in daily activities (housework, bathing, dressing, walking, going up/down stairs, getting up from/sitting down on a chair)? Did not interfere/Made performance of activities impossible. **BT2.** Over the past week, to what extent did your back pain interfere in your daily activities (household chores, washing, dressing, walking, going up/downstairs, getting into/out of bed, getting up from/sitting down on a chair)? It did not interfere/Unable to carry out activities.
3. Over the past week, how much has your back pain interfered with your ability to take part in recreational, social, and family activities? No interference/Unable to carry out activities	**BT1.** Over the last week, how much did your back pain interfere with your recreational, social and/or family activities? Did not interfere/Made performance of activities impossible. **BT2.** Over the past week, to what extent did your back pain interfere in your recreational, social and/or family activities? It did not interfere/Unable to carry out activities.
4. Over the past week, how anxious (tense, uptight, irritable, difficulty in concentrating/relaxing) have you been feeling? Not at all anxious/Extremely anxious	**BT1.** Over the last week, how anxious have you felt (tense, irritated, with difficulty concentrating/relaxing)? Not anxious at all/Extremely anxious. **BT2.** Over the past week, how anxious have you felt (tense, irritated, unable to concentrate/relax)? Not at all anxious/Extremely anxious.
5. Over the past week, how depressed (down-in-the-dumps, sad, in low spirits, pessimistic, unhappy) have you been feeling? Not at all depressed/Extremely depressed	**BT1.** Over the last week, how depressed have you felt (gloomy, sad, pessimistic, unhappy)? Not depressed at all/Extremely depressed. **BT2.** Over the past week, how depressed have you felt (down, sad, pessimistic, unhappy)? Not at all depressed/Extremely depressed.
6. Over the past week, how have you felt your work (both inside and outside the home) has affected (or would affect) your back pain? Have made it no worse/Have made it much worse	**BT1.** Over the last week, to what extent do you think your work (inside or outside the home) affected/would affect your back pain? Did not get worse/Got much worse. **BT2.** Over the past week, to what extent do you think that your work (inside or outside of your home) affected/could affect your back pain? It did not make it worse/It made it a lot worse.
7. Over the past week, how much have you been able to control (reduce/help) your back pain on your own? Completely control it/No control whatsoever	**BT1.** Over the last week, to what extent have you been able to control (reduce/relieve) your back pain on your own? Total control/No control. **BT2.** Over the last week, to what extent were you able to reduce/alleviate your back pain by yourself? Completely/Not at all.

BT1 = back-translation 1; BT2 = back-translation 2.

It is valuable to report a detailed description of the translation and cultural adaptation process before the validation, in order to prevent occurrences of multiple translations of the same tool and to avoid the extensive amount of work that would be entailed in translating and/or validating the same tool more than once.

The test-retest reliability of other versions of the Bournemouth questionnaire has been analyzed, and this analysis showed that the questionnaire had excellent reliability.[8,14-16] This questionnaire has also been shown to have good internal consistency, with the capacity to demonstrate clinically significant improvement in patients' conditions.[8,14-17,28] The psychometric properties of the Brazilian Portuguese version are currently under evaluation and the results from this assessment will soon be available in the literature. This process will allow its use in an appropriate manner in Brazil.

CONCLUSION

The Bournemouth questionnaire was translated and culturally adapted to Brazilian Portuguese, in a comprehensive version for evaluating low back pain among Brazilians.

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Translation and cross-cultural adaptation of the International Trauma Questionnaire for use in Brazilian Portuguese

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KEY WORDS:
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ABSTRACT

BACKGROUND: The most recent editions of diagnostic manuals have proposed important modifications in posttraumatic stress disorder (PTSD) criteria. The International Trauma Questionnaire (ITQ) is the gold-standard measurement for assessing PTSD and complex PTSD in accordance with the model of the 11th International Classification of Diseases (ICD-11).

OBJECTIVE: The aim of this study was to adapt the ITQ for the Brazilian context.

DESIGN AND SETTING: The translation and cross-cultural adaptation of the ITQ for use in Brazilian Portuguese was performed in trauma research facilities in Porto Alegre, Rio de Janeiro and Belo Horizonte, Brazil.

METHODS: The adaptation followed five steps: (1) translation; (2) committee synthesis; (3) experts' evaluation through the content validity index (CVI) and assessment of interrater agreement though kappa statistics; (4) comprehension test with clinical and community samples (n = 35); and (5) final back-translation and authors' evaluation.

RESULTS: Two independent translations were conducted. While working on a synthesis of these translations, the committee proposed changes in six items to adapt idiomatic expressions or to achieve a more accurate technical fit. Both the expert judges' evaluation (CVI > 0.7; k > 0.55) and the pretest in the target population (mean comprehension > 3) indicated that the adapted items were adequate and comprehensible. The final back-translation was approved by the authors of the original instrument.

CONCLUSION: ITQ in its Brazilian Portuguese version achieved satisfactory content validity, thus providing a tool for Brazilian research based on PTSD models of the ICD-11.

INTRODUCTION

Posttraumatic stress disorder (PTSD) has high prevalence worldwide,[1] and it is frequently diagnosed by mental health professionals.[2,3] However, controversies surround this diagnosis. The high number of symptoms, among which some are present in other mental disorders (e.g. detachment from others, sleep disturbance, concentration problems and reckless behavior), leads to high rates of comorbidities.[4-6] Furthermore, there are studies investigating a certain type of PTSD that is different from what is described in diagnostic manuals. When repeated exposure to trauma is associated with symptoms such as emotional dysregulation, dissociation and negative self-concept, the reaction is often described as "disorder of extreme stress not otherwise specified" or complex PTSD.[7,8] In the literature on trauma, PTSD criteria are often discussed, particularly with regard to which general symptoms of psychological distress should be understood as frequent comorbidities and not as part of the disorder; and which responses are directly related to trauma and therefore should be added to the diagnosis.[8-10]

The most recent version of the International Classification of Diseases (ICD-11) sought to encompass current scientific knowledge and proposed a new model for PTSD, in which the basic and complex forms of PTSD were distinguished and many symptoms that were considered to relate to general distress were eliminated. PTSD is described as a reaction to trauma that includes (1) re-experience of the traumatic event (i.e. vivid intrusive memories, flashbacks or nightmares accompanied by overwhelming emotions); (2) avoidance of thoughts, memories, situations, people or activities reminiscent of the event; and (3) a state of perceived current threat in the form of hypervigilance or enhanced startle reactions to stimuli such as unexpected noises. Complex PTSD

is described as a disorder that typically arises after an extreme or prolonged stressor from which escape is difficult or impossible (e.g. childhood sexual abuse, torture or prolonged domestic violence) and would comprise the sum of PTSD and more persistent symptoms of disturbances in self-organization (DSO), in three clusters: (1) affective dysregulation (e.g. self-destructive behavior, emotional anesthesia or dissociative states); (2) persistent beliefs about oneself as diminished, defeated or worthless, accompanied by feelings of shame, guilt or failure; and (3) persistent difficulties in maintaining relationships and feeling close to others. Both diagnoses require that symptoms cause significant impairment in important areas of functioning, such as social, educational or occupational.[11,12]

Another important diagnostic guide, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), provides a broader approach towards defining this phenomenon. Instead of separating posttraumatic reactions into two conditions and reducing the overall number of symptoms (as in ICD-11), this approach does not eliminate any previous criteria and adds symptoms that are often associated with repeated exposure to trauma, to make a unique diagnosis through a new cluster of negative alterations in cognition and mood (e.g. overly negative thoughts and assumptions about oneself or the world, or difficulty in experiencing positive affect) and a new dissociative subtype.[13]

Differences in the definition of posttraumatic symptoms may impact the work of clinicians and researchers in an important way. Current diagnostic differences should be investigated through empirical work, with the aim of evaluating the validity of both models in different cultures and populations, in order to achieve overall comprehension of posttraumatic reactions and to define approaches for future editions of diagnostic manuals.[14,15] Thus, it is necessary that instruments representing these new models are available in as many languages as possible. In Brazil, an adaptation of the PTSD model of the DSM-5 has already been produced,[16] but this has not yet been done for the model of the ICD-11.

The International Trauma Questionnaire (ITQ) is the gold-standard tool for evaluating the ICD-11 model of PTSD and complex PTSD. The ITQ is a 12-item questionnaire, with evidence of factorial, discriminant and concurrent validity in its original version.[17] This instrument has already been used to investigate the ICD-11 model of PTSD and complex PTSD in different countries such as Australia,[18] Germany, Lithuania, United States, United Kingdom,[19] West Papua,[20] Lebanon[21] and Uganda.[22] To our knowledge, no similar studies have yet been conducted in Latin America. It is especially relevant to have measurements for investigating posttraumatic reactions in Brazil, since this country presents high rates of exposure to traumatic events such as urban violence and traffic accidents.[23,24] Many instruments used in Brazilian settings were originally designed in other languages. Adaptation of instruments is an important step in ensuring the quality of these measurements, with the aim of maintaining content validity (i.e. the extent to which a measurement represents the construct) while still addressing important cultural and linguistic factors of relevance to the target population.[25,26]

OBJECTIVE

The aim of this study was to translate and culturally adapt the ITQ for use in Brazilian Portuguese, which will enable adequate investigation of the PTSD and complex PTSD models of the ICD-11 in Brazil.

METHOD

The ITQ is a gold-standard open-access tool for investigating PTSD and complex PTSD as defined by the ICD-11. In the present study, the ITQ in its final 12-item version, which was recently finalized after extensive empirical work, was used.[17] The instrument comprises two diagnostic questionnaires: one for PTSD and the other for DSO. The responses in both of these questionnaires are measured on five-point Likert scales ranging from 0 (not at all) to 4 (extremely) with six items divided into three clusters (for PTSD, re-experience, avoidance and state of perceived current threat; for DSO, affective dysregulation, negative self-concept and disturbances in relationships); plus three items for identifying functional impairment. For the diagnosis of PTSD, it is necessary to score at least one symptom in each cluster > 2 (on the Likert scale) with a functional impairment score also > 2 in at least one item, in the PTSD questionnaire. For complex PTSD, it is necessary to score at least one symptom > 2 in each cluster in both the PTSD and the DSO questionnaire, also with a functional impairment score > 2 in at least one item in both questionnaires.

The cross-cultural adaptation was based on the guidelines of the International Test Commission,[25] on data in the specialized literature[26-30] and on adaptations of posttraumatic measurements in previous studies.[16,31,32] It followed five steps: (1) translation; (2) committee synthesis; (3) expert judges' evaluation through the content validity index (CVI) and assessment of interrater agreement though kappa coefficients; (4) comprehension test with clinical and community samples (n = 35); and (5) final back-translation and authors' evaluation.

1. **Translation** - The original version of ITQ was translated into Brazilian Portuguese by two bilingual Brazilian psychologists (both with MSc degrees) with expertise in trauma-related disorders. Independently, each translator created one translated version of the instrument.
2. **Committee synthesis** - A committee of academics compared the two translated versions with the original ITQ to certify that all items expressed the same ideas, in order to achieve semantic, idiomatic and conceptual equivalences. The committee was composed of undergraduate, master's and doctoral

students. Items were chosen from either of the translated versions and, whenever necessary, were changed and refined by the committee. This step generated a unified version of the ITQ in Brazilian Portuguese.

3. **Expert judges' evaluation** - The unified version was evaluated through the content validity index (CVI), which is used to quantify the adequacy of items within a certain context. The quality of the items should be judged by a group of experts within the construct that the instrument is supposed to measure. The CVI indicates the clarity, coherence and semantic correspondence of the scale, in relation to the original version. In our study, CVI responses were given independently by three judges in different Brazilian cities, in order to minimize the impact of regional speech patterns: one psychologist (MSc) who was an expert in trauma-related disorders, in Porto Alegre; one psychiatrist (PhD) who was an expert in trauma-related disorders, in Rio de Janeiro; and one psychologist (PhD) who was an expert in cross-cultural adaptation of instruments, in Belo Horizonte. The judges had to evaluate the relevance of each item through a five-point Likert scale, ranging from 0 ("not at all") to 4 ("totally"), in three dimensions: (1) language clarity, which measures how comprehensible the items are; (2) practical relevance, which measures how adequate each item is to the target population; and (3) theoretical relevance, which measures how much the item agrees with the construct theory. Following this, CVI scores were calculated in accordance with the specific CVI formula, based on division of the mean values given by the experts (for further details, see Cassepp-Borges, Balbinotti & Teodoro, 2010[27]). Items with CVI lower than 0.7 would be rephrased and repeatedly resubmitted to the three judges until a satisfactory value was reached.[25] Also, the judges were asked to indicate to which questionnaire (i.e. PTSD or DSO) each item belonged. The degree of agreement between the judges would be assessed through Cohen's weighted kappa. In accordance with the guidelines,[33] kappa scores > 0.41 would indicate moderate agreement, > 0.61 substantial agreement and > 0.81 almost perfect agreement.
4. **Comprehension test** - Thirty-five individuals in three Brazilian state capitals (Belo Horizonte, Rio de Janeiro and Porto Alegre) were independently asked about the ease of comprehension of all items of the pre-final version, with responses on a five-point Likert scale ranging from 1 ("I didn't understand anything") to 5 ("I completely understood"). The indicators of understanding were the central trend scores (mean) and dispersion (standard deviation) for each item. Sample size and satisfactory understanding (mean score > 3) were defined based on previous studies.[16,29,30] A convenience sample was recruited from research facilities in all three cities. Almost half of the sample (45.7%; n = 16) was composed of trauma victims seeking treatment at psychological or psychiatric centers at the universities that collaborated in this study; and the remaining sample was composed of individuals within the general population (54.3%; n = 19) who were mostly friends and family of the clinical population that participated in the study. The goal was to recruit a sample of participants with different sociodemographic characteristics and backgrounds, to increase the validity of the instrument. The sample was heterogeneous in terms of gender distribution (37.1% men [n = 13] and 62.9% women [n = 22]); educational level (17.1% with primary education [n = 6], 31.4% with secondary education [n = 11] and 51.5% with higher education [n = 18]); and state of residence (28.6% in Rio Grande do Sul [n = 10], 31.4% in Minas Gerais [n = 11] and 40% in Rio de Janeiro [n = 14]).
5. **Backtranslation** - Lastly, the final Brazilian Portuguese version was back-translated by a bilingual translator, with a major in Languages, with no expertise in mental health and blinded to the original instrument. The backtranslation result was sent to the authors of the original study for their final approval.

This study was approved by the Ethics Committee of the Pontifícia Universidade Católica do Rio Grande do Sul (approval number 2.558.869; March 2018). All participants were informed about the objectives of this study and regarding its voluntary nature, with confidentiality assured, and they signed an informed consent form before filling out the questionnaires. This study was conducted between March and August 2018.

RESULTS

In making the synthesis from the two translated versions, the committee proposed minor changes regarding the use of idiomatic expressions or with the aim of achieving a more accurate technical fit in four items of the PTSD questionnaire (items 2, 3, 4 and 5) and in two items of the DSO questionnaire (items 1 and 5).

1. In item 2 of the PTSD questionnaire, the term "intensas" (= intense) was chosen over "poderosas" (the literal translation of "powerful", which had been chosen by both translators) to describe trauma memories, because the term "poderosas" has a positive connotation in Brazilian Portuguese.
2. The best translation for the word "reminders", present in items 3 and 4 of the PTSD questionnaire, was extensively discussed. Both translators suggested terms that could be related to memories ("lembranças" and "lembretes"). This was considered by the committee to be inadequate because of item 4, which refers to external reminders of the trauma. The term "pistas" (= triggers or cues) was chosen.
3. Item 5 of the PTSD questionnaire contained the term "super-alert" to describe hyperarousal symptoms. Both translators chose the literal term "super-alertas", but the committee decided that "hiperalertas" (= hyper-alert) would be a better technical fit for this expression in Brazilian Portuguese.

4. In item 1 of the DSO questionnaire, the term "upset" was translated as "triste" (= sad) or "abalado" (= shaken). Neither of these was considered appropriate by the committee, who defined the word "chateado" (another possible translation of "upset") as more adequate.
5. In item 2 of the DSO questionnaire, the expression "cut off" was translated as "afastado" (= away) or "isolado" (= isolated), but was rewritten as "desconectado" (= detached) by the committee.

The unified version created through the committee's synthesis was evaluated by the three judges in different Brazilian districts using the CVI. The results from the expert judges' evaluation showed that all items were considered adequate (> 0.7), as seen in **Table 1**. One change was made in response to the experts' comments and suggestions, in order to achieve a more appropriate expression. In item 1 of the DSO questionnaire, the term "demoro bastante tempo" replaced "levo bastante tempo" to translate "takes me a long time". Cohen's weighted kappa coefficient indicated overall agreement of 77.8% between the judges, with PTSD items showing k = 0.56 [95% confidence interval, CI, 0.18-0.93] and DSO items showing k = 0.55 [95% CI, 0.22-0.88], thus indicating moderate agreement between the judges with regard to deciding which questionnaire each item belonged to.

Table 1 also shows the results from the comprehension test on the target population. All items were considered comprehensible (> 3) in the first round of evaluations. The backtranslation result was compared with the original version and was approved by the authors of the original study. **Appendix 1** presents the final version of the Brazilian version of the ITQ.

Table 1. Expert judges' evaluation, pretesting in the target population and backtranslation of the Brazilian Portuguese Version of the International Trauma Questionnaire (ITQ)

	Original version	Brazilian version	CVI- LC	CVI- PR	CVI-TR	Population evaluation (mean [SD])	Backtranslation
	PTSD questionnaire						
1	Having upsetting dreams that replay part of the experience or are clearly related to the experience?	Ter sonhos desagradáveis que reproduzem parte da experiência ou são claramente relacionados à experiência?	0.82	0.96	0.96	4.26 [1.20]	Having unpleasant dreams that reproduce part of the experience or are clearly related to it?
2	Having powerful images or memories that sometimes come into your mind in which you feel the experience is happening again in the here and now?	Ter imagens ou memórias intensas que, às vezes, vêm a sua mente, fazendo com que você sinta que a experiência está acontecendo novamente no aqui e agora?	0.96	0.96	0.96	4.38 [1.02]	Having intense images or memories that sometimes come to your mind, making you feel that the experience is happening again, here and now?
3	Avoiding internal reminders of the experience (for example, thoughts, feelings, or physical sensations)?	Evitar pistas internas da experiência (por exemplo, pensamentos, sentimentos ou sensações físicas)?	0.76	0.96	0.96	3.71 [1.43]	Avoiding internal cues of the experience (for instance, thoughts, feelings or physical sensations)?
4	Avoiding external reminders of the experience (for example, people, places, conversations, objects, activities, or situations)?	Evitar pistas externas da experiência (por exemplo, pessoas, lugares, conversas, objetos, atividades ou situações)?	0.96	0.96	0.96	4.29 [1.27]	Avoiding external cues of the experience (for instance, people, places, conversations, objects, activities or situations)?
5	Being "super-alert", watchful, or on guard?	Estar "hiper-alerta", vigilante ou em guarda?	0.89	0.96	0.96	4.74 [0.56]	Being hyper-alert, vigilant or on guard?
6	Feeling jumpy or easily startled?	Sentir-se sobressaltado(a) ou facilmente assustado(a)?	0.82	0.96	0.89	4.54 [0.89]	Feeling startled or easily scared?
	DSO questionnaire						
1	When I am upset, it takes me a long time to calm down	Quando estou chateado(a), demoro bastante tempo para me acalmar	0.89	0.96	0.96	4.86 [0.35]	When I'm upset, it takes quite a long time to calm me down again
2	I feel numb or emotionally shut down.	Eu me sinto anestesiado(a) ou emocionalmente desligado(a)	0.76	0.96	0.96	4.57 [0.85]	I feel insensitive and emotionally disconnected
3	I feel like a failure	Eu me sinto um fracasso	0.96	0.89	0.96	4.83 [0.38]	I feel like a failure
4	I feel worthless	Eu me sinto sem valor	0.96	0.96	0.96	4.74 [0.74]	I feel worthless
5	I feel distant or cut off from people.	Eu me sinto distante ou desconectado(a) de outras pessoas	0.96	0.96	0.96	4.74 [0.74]	I feel distant or disconnected from other people
6	I find it hard to stay emotionally close to people.	Acho difícil ficar emocionalmente próximo(a) de outras pessoas	0.89	0.96	0.96	4.71 [0.62]	It's difficult for me to be emotionally attached to other people

CVI-LC = Content Validity Index – Language Clarity; CVI-PR = Content Validity Index – Practical Relevance; CVI-TR = Content Validity Index – Theoretical Relevance; SD = standard deviation; PTSD = Posttraumatic Stress Disorder; DSO = Disturbances in Self-Organization.

DISCUSSION

This study reports on the cross-cultural adaptation of ITQ for use in Brazilian Portuguese. The literature on psychometrics indicates that the adaptation process is important because it provides more than just a literal translation. However, there is no technical agreement on how to conduct this process in a reliable and objective manner.[25,26] The steps of the present study were an attempt to cover the methodological guidelines and linguistic specificities regarding both quantitative and qualitative criteria. Items 3 and 4 of the PTSD questionnaire, which contain the terms *internal* and *external reminders of trauma*, were extensively discussed and may be considered to be an example of the importance of cultural adaptation. There is no literal translation for these expressions, and suggestions made by the committee were tested on different populations before final approval was reached, in order to ensure that these items kept the same meaning as in the original version and were fully comprehensible.

The overall results showed evidence of content validity for the ITQ in its Brazilian version, since the original construct was preserved after conceptual, idiomatic, cultural and semantic issues had been carefully handled by the researchers and subsequently approved by the independent expert judges, clinical and community samples and authors of the original scale. Although the kappa statistics were not perfect, they were considered satisfactory, given that the proposal of ICD-11 regarding posttraumatic reactions is novel in the field, especially the one for complex PTSD. This may have contributed towards making the agreement between the judges only moderate.

Most studies on the ITQ have been performed using its original version or without any report of cross-cultural adaptation steps. Only in the study that reports on data from the Arabic version of the ITQ were interviews about content validity conducted with therapists.[21] Although satisfactory qualitative evidence was found, the authors of the Arabic version suggested that the ITQ would be best administrated with the assistance of a trained professional among illiterate and poorly literate individuals. Our results did not indicate that assistance would be needed when using the ITQ in the Brazilian context, since the 35 people used to test the version did not present difficulties in comprehending any items of either questionnaire (and not even when the scores of the participants with lower education levels were evaluated separately). The aim of the ITQ is that it should be a brief self-report screening instrument for PTSD and complex PTSD, and our results indicate that this goal was achieved in the Brazilian version of the instrument.

Some important limitations of our study need to be addressed. Although we made an attempt to minimize the influence of regional speech patterns by conducting the study in three different cities, it was not possible to represent the entire Brazilian population with this sample. Also, further validation of the ITQ is needed (especially regarding construct validity) in studies with larger samples, in order to establish whether the items replicate the model of the ICD-11 properly. More robust psychometric studies are currently being conducted to achieve these goals.

These findings enable initial research using the ICD-11 model for PTSD and complex PTSD in Brazil. Future studies should focus on advancing knowledge regarding the nature, predictors, course and outcomes of these disorders in the Brazilian population. This approach is likely to contribute to the discussion of these diagnoses in an overall manner.

CONCLUSION

The Brazilian Portuguese version of the ITQ was translated and culturally adapted to its context, and it exhibited satisfactory content validity.

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Appendix 1. Questionário de Trauma Internacional (International Trauma Questionnaire, ITQ)

Questionário de sintomas de transtorno de estresse pós-traumático

Abaixo, há uma lista de problemas e queixas que as pessoas, às vezes, têm em resposta a experiências de vida traumáticas ou estressoras. Por favor, leia cada item cuidadosamente, e circule um dos números à direita para indicar o quanto esse problema tem lhe incomodado **no último mês.**

	Nem um pouco	Um pouco	Moderadamente	Bastante	Extremamente
1. Ter sonhos desagradáveis que reproduzem parte da experiência ou são claramente relacionados à experiência?	0	1	2	3	4
2. Ter imagens ou memórias intensas que, às vezes, vêm a sua mente, fazendo com que você sinta que a experiência está acontecendo novamente no aqui e agora?	0	1	2	3	4
3. Evitar pistas internas da experiência (por exemplo, pensamentos, sentimentos ou sensações físicas)?	0	1	2	3	4
4. Evitar pistas externas da experiência (por exemplo, pessoas, lugares, conversas, objetos, atividades ou situações)?	0	1	2	3	4
5. Estar "hiperalerta", vigilante ou em guarda?	0	1	2	3	4
6. Sentir-se sobressaltado ou facilmente assustado?	0	1	2	3	4
No último mês, os sintomas acima:					
7. Afetaram seus relacionamentos ou sua vida social?	0	1	2	3	4
8. Afetaram seu trabalho ou sua capacidade de trabalhar?	0	1	2	3	4
9. Afetaram qualquer outra parte importante da sua vida, como o cuidado com seus filhos, vida escolar ou acadêmica, ou outras atividades importantes?	0	1	2	3	4

Questionário de sintomas - desorganização interpessoal

Abaixo, há problemas ou sintomas que as pessoas que passaram por eventos de vida traumáticos ou estressores, às vezes, experenciam. As questões se referem a como você tipicamente se sente, como você tipicamente pensa a respeito de si mesmo, e como você tipicamente se relaciona com outras pessoas. Responda às seguintes perguntas pensando no quão verdadeira cada afirmativa é para você.

O quão verdadeiro isso é para você?	Nem um pouco	Um pouco	Moderadamente	Bastante	Extremamente
1. Quando estou chateado, demoro bastante tempo para me acalmar	0	1	2	3	4
2. Sinto-me anestesiado ou emocionalmente desligado	0	1	2	3	4
3. Sinto-me um fracasso	0	1	2	3	4
4. Sinto-me sem valor	0	1	2	3	4
5. Sinto-me distante ou desconectado de outras pessoas	0	1	2	3	4
6. Acho difícil ficar emocionalmente próximo de outras pessoas	0	1	2	3	4
No último mês, os problemas emocionais, as crenças sobre você mesmo e nos seus relacionamentos listados acima:					
7. Afetaram seus relacionamentos ou sua vida social?	0	1	2	3	4
8. Afetaram seu trabalho ou sua capacidade de trabalhar?	0	1	2	3	4
9. Afetaram qualquer outra parte importante da sua vida, como o cuidado com seus filhos, vida escolar ou acadêmica, ou outras atividades importantes?	0	1	2	3	4

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Thyroid function among women with gestational trophoblastic diseases. A cross-sectional study

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KEY WORDS:
Gestational trophoblastic disease.
Hydatidiform mole.
Thyroid gland.
Propylthiouracil.

ABSTRACT

BACKGROUND: Gestational trophoblastic diseases (GTDs) are treatable rare tumors with wide distribution. The estimated incidence of GTDs varies dramatically between different regions globally. In early pregnancy, there may be high human chorionic gonadotropin (HCG) concentrations, normal or slightly increased free T4 (fT4) and subnormal thyroid-stimulating hormone (TSH), causing hyperthyroidism ranging from subclinical to severe. Beta-HCG causes thyrotoxicosis through thyroid stimulation in patients with trophoblastic tumors.

OBJECTIVE: To assess thyroid function among patients diagnosed with complete or partial hydatidiform mole, within the GTD spectrum.

DESIGN AND SETTING: Cross-sectional study based on patients' medical records at Van University Hospital, Van, Turkey.

METHODS: 50 patients monitored due to diagnoses of hydatidiform mole were included and were examined regarding thyroid function. Thyroid gland size and volume were measured using thyroid ultrasonography. Beta-HCG, TSH, fT4, free T3 (fT3), total T4 (TT4), total T3 (TT3), anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-TG) and thyroglobulin levels were measured.

RESULTS: Among these patients, 15 (30%) were diagnosed with complete hydatidiform mole and 35 (70%) with partial hydatidiform mole, according to pathology results. Those with complete hydatidiform mole were older (P = 0.003), with higher number of pregnancies (P = 0.032), lower TSH level (P = 0.011) and higher fT4 and TT4 levels (P = 0.04; P = 0.028), compared with partial hydatidiform mole patients.

CONCLUSION: In hydatidiform mole patients, thyroid disease severity increases with age, parity, beta-HCG level and mole size. However, prospective multicenter studies on this topic are needed, with larger numbers of patients and closer monitoring.

INTRODUCTION

Gestational trophoblastic diseases (GTDs) are treatable rare tumors with wide distribution. The first thyrotoxicosis case was identified in a woman with hydatidiform mole in 1955.[1] Subsequent studies increased the numbers of cases reported.[2-4] The estimated incidence of GTDs varies dramatically between different regions globally. For example, the incidence of hydatidiform mole pregnancy is 2/1000 pregnancies in Japan, while in Europe and North America it has been reported as 0.6-1/1000 pregnancies.

Tumor cells produce human chorionic gonadotropin (HCG).[5] HCG released by hydatidiform moles has greater thyroid-stimulating activity than does HCG released from a normal placenta.[6] The amount of HCG released is very specific and is linked to the number of live tumor cells. Women with hydatidiform mole pregnancy and choriocarcinoma may present pathologically high HCG levels. In early pregnancy, there may be high HCG concentrations, normal or slightly increased free T4 (fT4) and subnormal thyroid-stimulating hormone (TSH) level, and these may cause hyperthyroidism ranging from subclinical to severe grade.

Beta-HCG causes thyrotoxicosis through thyroid stimulation in patients with trophoblastic tumors.[2] Beta-HCG comprises two subunits. The alpha subunit is the same as TSH, LH (luteinizing hormone) and FSH (follicle-stimulating hormone). The beta subunit is similar to the beta subunit of TSH, but is larger. Thyroid-stimulating activity of beta-HCG has been shown in mice, rats and humans.[6-8]

In trophoblastic diseases the spectrum of thyroid function changes varies from slight increases in fT4 and free T3 (fT3) and low TSH levels with no thyrotoxicosis symptoms, to moderate increases in fT4 and fT3 and up to increases large enough to cause clinical thyrotoxicosis or

even thyroid storms.[9] In women with hydatidiform mole pregnancy and choriocarcinoma, pathologically high HCG levels cause clear hyperthyroidism. However, thyrotoxicosis is not observed in all trophoblastic patients. Although the majority of trophoblastic tumors cause high fT4 and fT3 levels in women, some women have typical clinical findings with very few thyrotoxicosis symptoms. These include weight loss, muscle weakness, fatigue, excessive sweating, heat intolerance, tachycardia, irritability and tremors. In women with trophoblastic tumors, the thyroid gland may not grow or may display slight growth. Rarely, it may reach twice normal size. These patients do not have ophthalmopathy.[10]

Surgical removal of the hydatidiform mole rapidly ameliorates thyrotoxicosis and, if possible, surgical intervention should be performed in the early period of pregnancy. For preoperative hyperthyroidism, propylthiouracil (PTU) or methimazole may be administered.[2]

OBJECTIVE

The aim of our study was to assess thyroid function among patients with diagnoses of complete or partial hydatidiform mole, within the gestational trophoblastic disease spectrum.

METHODS

Study design, date, setting and ethical concerns

Our observational study included consecutive patients who were being monitored at the gynecology and obstetrics clinic because of a diagnosis of hydatidiform mole and who underwent consultations at the internal medicine clinic regarding their thyroid function during a 20-month period. The research protocol was approved by the Research Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine, on June 17, 2011, under number 15. The patients participating in the study were informed about it and their consent was obtained.

Participants and data collection

The patients' ages, number of pregnancies, parity, number of surviving children, number of aborti, number of cesareans, week of pregnancy, history of goiter and previous history of hydatidiform mole pregnancy were recorded. Serum samples were studied using an Abbott Architect I4000SR device using standard methods. The patients' initial TSH, fT4, fT3, total T4 (TT4), total T3 (TT3), beta-HCG, anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-TG) and thyroglobulin (TG) levels were measured. All patients with euthyroid values were operated at the gynecology and obstetrics clinic.

The patients underwent thyroid ultrasonography at the endocrine clinic using a Siemens-Acuson 7500 device. On thyroid ultrasonography images, the patients' thyroid size (right lobe, left lobe and isthmus) was measured. Thyroid volume was calculated using the formula: width $\boldsymbol{x}$ length $\boldsymbol{x}$ height $\boldsymbol{x}$ 0.523.[11]

Statistical analysis

The study results were uploaded from the prepared forms to the Statistical Package for the Social Sciences for Windows software, version 22.0 (SPSS Inc, Chicago, USA), for statistical analysis. Comparison of groups was performed using the unpaired t test, and correlations between variables were analyzed using Pearson correlation analysis. Variations before and after treatment were compared using the paired-sample t test. To compare frequencies between groups, the chi-square test was used. Results were presented as the mean ± standard deviation, and $P < 0.05$ was accepted as statistically significant.

RESULTS

During the study period, 50 women with a diagnosis of hydatidiform mole diagnosis were recruited. The descriptive characteristics of the patients included in the assessment are given in **Table 1** and **Table 2**.

The number of pregnancies among the patients ranged from 1 to 16. The mean number of pregnancies was five. Nine patients (18%) were pregnant for the first time. There were eight patients (16%) on their second pregnancy. There were seven patients on their third pregnancy (14%). There were 19 patients with six or more pregnancies (38%). There were seven patients with 10 or more pregnancies (14%).

In terms of parity (live births), our patients' parity range was from 0 to 12. Their mean parity was 3.4. Thirteen patients (26%) had parity of one. The most common parity for our patients was one. There were 10 patients (20%) with parity of zero. There was one patient each with parity of 4, 9, 10, 11 and 12.

Thirty-three patients (66%) had no history of aborti, while 17 had had at least one abortus. The highest number of aborti was four (one patient). While 48 patients did not have histories of cesareans, there were two patients with a total of three cesareans.

Table 1. Age and fertility characteristics of patients

	N	Min.	Max.	Mean	SD
Age (years)	50	17	54	31.08	11.31
Number of pregnancies	50	1	16	5.04	3.82
Parity	50	0	12	3.42	3.35
Number of surviving children	50	0	12	3.36	3.30
Number of aborti	50	0	4	0.61	0.99
Number of cesareans	50	0	2	0.06	0.31
Week of pregnancy at operation time	50	4	24	11.18	3.51

N = number; min. = minimum; max. = maximum; SD = standard deviation.

Preoperatively, 33 patients (66%) did not receive antithyroid treatment, while the other 17 patients (34%) received this treatment.

According to the pathology results from the 50 hydatidiform mole patients included in the study, 15 patients (30%) were diagnosed with complete hydatidiform mole while 35 patients (70%) were diagnosed with partial hydatidiform mole. The patients were grouped according to the pathology results as presenting partial hydatidiform mole or complete hydatidiform mole. The patient group with complete mole had higher mean age (P = 0.003), higher number of pregnancies (P = 0.032), lower TSH values (P = 0.011) and higher fT4 and TT4 (P = 0.04, P = 0.028), compared with the patient group with partial mole. The thyroid volume was larger in the complete mole patients (P = 0.032). The statistical data on the complete mole and partial mole patients are shown in **Table 3**.

In our study, there were 30 patients with HCG titers above 200,000 uIU/l, and 20 of them had titers above 400,000 uIU/l. Out of the 30 patients with HCG titers above 200,000 uIU/l, 13 had TSH values above 0.2 IU/l, while the remaining 17 patients had TSH levels below 0.2 IU/l. Additionally, out of the 20 patients with HCG titers above 400,000 uIU/l, five had TSH levels above 0.2 IU/l and 15 patients had TSH levels below 0.2 IU/l. Out of the 30 patients with HCG titers above 200,000 uIU/l, 17 (70%) began treatment due to clear presence of hyperthyroidism, while 15 (71%) of the 20 patients with HCG titers above 400,000 uIU/l began treatment for this reason.

Regarding the anti-TPO and anti-TG levels among the patients in this study, only three of the 50 patients (6%) were positive for anti-TPO (above 20 IU/ml) and only one patient (2%) was positive for anti-TG (above 20 IU/ml).

Table 2. Initial laboratory values for patients

	N	Min.	Max.	Mean	SD
TSH (uIU/ml)	50	0.01	5.32	0.72	1.08
fT4 (ng/dl)	50	0.91	4.22	1.79	0.81
fT3 (pg/ml)	50	2.22	14.71	5.38	3.32
fT3/fT4	50	0.21	0.53	0.34	0.07
TT4 (ug/dl)	50	7.62	24.01	14.53	5.51
TT3 (ng/ml)	50	0.91	7.32	2.15	1.20
Thyroglobulin (ng/ml)	50	2	262	74.18	75.59
Thyroid isthmus size (mm)	50	0	23	3.47	3.37
Total thyroid volume (mm^3)	50	5529.11	29486.49	13515.71	6180.89
Beta-HCG (mIU/ml)	50	8159	1820573	491684.70	490615.45

N = number; min. = minimum; max. = maximum; SD = standard deviation; TSH = thyroid-stimulating hormone; fT4 = free T4; fT3 = free T3; TT4 = total T4; TT3 = total T3; Beta-HCG = beta-human chorionic gonadotropin.

Among all the patients included in the study, 34 had nausea and 16 did not have nausea. Comparison between the patients with and without nausea showed that there was no significant difference between women with and without nausea regarding beta-HCG levels, thus nausea was independent of beta-HCG levels (P = 0.706). The fT4 and fT3 levels in the nausea group were identified as higher than those in the group without nausea, and this situation was significant (P = 0.042 and P = 0.023, respectively) (**Table 4**).

DISCUSSION

In our region of Eastern Anatolia, the birth rates are high in rural areas and therefore complications linked to pregnancy are commonly observed in this population. During the 20-month study period, 50 hydatidiform mole pregnancy cases were collected. It has been reported that the risk of hydatidiform mole pregnancy is 0.6-2/1000 pregnancies.[12]

Table 3. Comparison of data on patients with complete and partial mole

	Pathology results	N	Mean	SD	P-value
Age (years)	Partial	35	28.03	10.39	**0.003**
	Complete	15	38.20	10.40	
Number of pregnancies	Partial	35	4.29	3.37	**0.032**
	Complete	15	6.80	4.32	
Week of pregnancy at operation time	Partial	35	11.37	3.92	0.562
	Complete	15	10.73	2.34	
TSH (uIU/ml)	Partial	35	0.91	1.21	**0.011**
	Complete	15	0.28	0.47	
fT4 (ng/dl)	Partial	35	1.64	0.75	**0.042**
	Complete	15	2.15	0.85	
fT3 (pg/ml)	Partial	35	4.85	3.001	0.283
	Complete	15	6.58	3.787	
TT4 (ug/dl)	Partial	35	12.37	4.29	**0.028**
	Complete	15	17.04	5.87	
TT3 (ng/ml)	Partial	35	2.04	1.26	0.422
	Complete	15	2.37	1.04	
Thyroglobulin (ng/ml)	Partial	35	59.81	70.25	0.531
	Complete	15	108.46	79.56	
Beta-HCG (mIU/ml)	Partial	35	491699.37	547934.03	1.004
	Complete	15	491650.47	336642.51	
Total thyroid volume (mm^3)	Partial	35	12272.91	530.68	**0.032**
	Complete	15	16332.71	7027.52	
Thyroid isthmus size (mm)	Partial	35	3.47	3.91	0.995
	Complete	15	3.47	1.68	

N = number; SD = standard deviation; TSH = thyroid-stimulating hormone; fT4 = free T4; fT3 = free T3; TT4 = total T4; TT3 = total T3; Beta-HCG = beta-human chorionic gonadotropin.

Among women with hydatidiform mole pregnancies, the risk of repetition of this condition is 10 times greater.[5] While the risk of a second hydatidiform mole pregnancy is 1/76 for women with one previous such pregnancy, the risk of a third hydatidiform mole pregnancy is 1/7 for women with two such pregnancies.[12] In our study, there was one patient with a second hydatidiform mole pregnancy (2%).

The risk of hydatidiform mole pregnancy is higher at the end of the reproductive period. The risk is higher especially for women over the age of 40. A study investigating 2202 hydatidiform mole pregnancies showed that the risk was significantly higher for women aged 15 and younger and for those aged 40 and older.[13] In our study group, our youngest patient was 17 years of age, while there were 13 patients above the age of 40 years. Most patients were aged from 20 to 25 years (n = 15). To estimate whether the risk increases above the age of 40 years or not, it is necessary to know the age-specific birth rates, and we were unable to assess this information in this study (the age when women had their children).

It has been proposed that a low-protein diet, with nutrition poor in animal fats and poor in fat-soluble carotene, increases the risk of hydatidiform mole pregnancy.[14] This risk occurs especially among individuals of low socioeconomic level. We believe that the risk of occurrence of hydatidiform mole pregnancy in our region, which has a low socioeconomic profile, is higher because of diet-linked factors.

In the group of patients with nausea, the free T4 and free T3 levels were identified as higher. Dopamine inhibits TSH-mediated T4 secretion.[15] Thyroxine is not known to have a feedback control mechanism relating to dopamine. As with other endocrine control mechanisms, the final hormone increase suppresses secretory hormones and, if this causes an increase in inhibitory hormone, it can be expected that thyroxine will stimulate dopamine. The increase in dopamine plays a role in mechanisms relating to nausea and vomiting.[16] Although the effects of dopamine on TSH and TRH have been researched, the effects of thyroid hormones on dopamine have not been researched. This is a significant deficiency and there is therefore a need for new research on this topic.

Some studies investigating the effect of high HCG titers on TSH and fT4 levels have shown that when the HCG titer increases above 200,000 IU/l, the probability of incidence of TSH suppression (TSH < 0.2 IU/l) is 67%, while at titers above 400,000 IU/l, TSH suppression reaches 100%.[17-19] In our study, contrary to the data in the literature, there were euthyroid patients with even the highest HCG values. Among the 30 patients with HCG values above 200,000 uIU/l, 17 (70%) began treatment for clear hyperthyroidism, while among the 20 patients with HCG above 400,000 uIU/l, 15 (71%) began treatment. There are some studies with results similar to those of our research.[20] In this group of patients who were euthyroid despite high HCG levels, we believe that the stimulating effect of HCG on the thyroid gland may have led to development of resistance at receptor levels for an unknown reason. However, there is a need for more immunological research and animal experiments to support our hypothesis.

Since the patients with complete hydatidiform mole were older, with more pregnancies and larger thyroid volumes, we think that HCG stimulation may have caused synthesis and release of more hormones. There is a need for randomized prospective studies on this topic, with more patients.

Hydatidiform mole pregnancies stimulate the thyroid not only through higher HCG levels but also through increasing estrogen concentrations.[21] Thus, the thyroid volume increases with increasing numbers of pregnancies. Moreover, both the high estrogen concentrations in pregnancy and the increasing iodine requirements may have a stimulatory effect on growth of the thyroid.

Some difficulty in perioperative monitoring of gestational trophoblastic diseases exists. These diseases are frequently complicated by hyperthyroidism. Uncontrolled hyperthyroidism may transform into a thyroid crisis or cause serious arrhythmia during the perioperative period.[22-23] Gestational trophoblastic neoplasia

Table 4. Comparison of data between patients with nausea and without nausea

	Nausea status	N	Mean	SD	P-value
Age (years)	Absent	16	26.94	9.92	0.075
	Present	34	33.03	11.53	
Number of pregnancies	Absent	16	4.31	3.24	0.361
	Present	34	5.38	4.06	
Week of pregnancy at operation time	Absent	16	10.75	3.47	0.558
	Present	34	11.38	3.56	
TSH (uIU/ml)	Absent	16	1.25	1.38	0.053
	Present	34	0.48	0.81	
fT4 (ng/dl)	Absent	16	1.51	0.49	**0.042**
	Present	34	1.92	0.91	
fT3 (pg/ml)	Absent	16	4.13	1.77	**0.023**
	Present	34	5.99	3.72	
TT4 (ug/dl)	Absent	16	12.44	2.45	0.104
	Present	34	15.32	6.15	
TT3 (ng/ml)	Absent	16	1.76	0.61	0.055
	Present	34	2.34	1.37	
Thyroglobulin (ng/ml)	Absent	16	74.60	79.52	0.979
	Present	34	73.97	74.92	
Beta-HCG (mIU/ml)	Absent	16	445994.56	643480.57	0.706
	Present	34	513185.94	409520.94	

N = number; SD = standard deviation; TSH = thyroid-stimulating hormone; fT4 = free T4; fT3 = free T3; TT4 = total T4; TT3 = total T3; Beta-HCG = beta-human chorionic gonadotropin.

is one of the most rapidly metastasizing tumors. The first-choice medication for thyroid crises, which are a complication of hyperthyroidism requiring emergency treatment, is thionamides.[24] In our study, none of the patients presented any thyroid crises, and so we used monotherapy consisting of PTU. The postoperative decline in HCG levels was most commonly seen in patients receiving PTU therapy.[25]

CONCLUSION

The severity of thyroid disease in hydatidiform mole patients increases according to age, parity, beta-HCG level and mole size. Determination of thyroid volume may help in estimating the severity of thyroid disease. However, there is a need for prospective multicenter studies on this topic, with higher numbers of patients and closer patient monitoring.

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What do Cochrane systematic reviews say about ultrasound-guided vascular access?

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KEY WORDS:
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Evidence-based medicine.
Vascular access devices.

ABSTRACT

BACKGROUND: Ultrasonography is currently used in investigating many vascular diseases, especially for guiding vascular access.

OBJECTIVE: The objective here was to summarize the evidence from Cochrane systematic reviews (SRs) on the effects of ultrasound-guided vascular access as an intervention approach.

DESIGN AND SETTING: Review of SRs, conducted in the Division of Vascular and Endovascular Surgery of Universidade Federal de São Paulo.

METHODS: A broad search was conducted in the Cochrane Database of Systematic Reviews to retrieve any Cochrane SRs that assessed the effects of ultrasound guidance as a therapeutic approach towards performing any vascular access. The key characteristics and results of all the reviews included were summarized and discussed.

RESULTS: Three SRs on venous access at all ages and one review on arterial access in pediatric participants were included. There was low to moderate certainty of evidence that ultrasound increased the success rate from the first puncture and the overall success rate of the procedure; and reduced the total rate of perioperative and postoperative adverse events, number of punctures, time needed to achieve success and rate of failure to place catheters.

CONCLUSION: Evidence of low to moderate quality showed that ultrasound-guided vascular access seems to reduce the total rate of perioperative and postoperative complications/adverse effects, number of punctures, time needed to achieve success and rate of failure to perform venous catheterization in adults and arterial punctures in children. There is a lack of information regarding ultrasound-guided arterial puncture in adults. Further studies are still imperative for reaching solid conclusions, especially regarding arterial ultrasound-guided access.

INTRODUCTION

In almost all medical specialties, from pediatrics to geriatrics, at some point, doctors face the need to use vascular access in their patients. In the United States, over 15 million central vascular catheter-days occur in intensive care units per year.[1] Anatomical landmarks have been used as a guide for performing vascular access for a long time, but their use has been correlated with a number of complications (e.g. infections, hematomas, pneumothorax and death).[1-3]

Over recent decades, ultrasound has been used as a possible aid for diagnostic purposes, including in bedside examinations and for possibly avoiding complications in various procedures.[4] In addition, technological advances have made portable ultrasound viable.[4-6]

Although there are some practical guidelines that make recommendations regarding standard use of ultrasound to guide venous catheterization, up to 40% of doctors are resistant to using this evidence in their practice.[7,8] A number of guidelines are available for evaluating ultrasound-guide venous access but there is a lack of such guidelines for arterial sites.[9,10]

Despite the large amounts of money that have been invested in research on this topic, the relevance of ultrasound-guided vascular access as a therapeutic approach is still a matter of debate, especially in relation to arterial puncture. Because the use of ultrasound as an additional intervention may be a reasonable alternative for improving the results relating to many types of vascular

access, it is imperative to assess the effects of ultrasound-guided access through well-conducted randomized controlled trials.

OBJECTIVE

The aim of this study was to identify and summarize the evidence from Cochrane systematic reviews (SRs) regarding ultrasound-guided vascular access, in an overview.

METHODS

Design and setting

This was a review of Cochrane systematic reviews conducted in the Division of Vascular and Endovascular Surgery, Universidade Federal de São Paulo, Brazil.

Inclusion criteria

Types of study

Full Cochrane SRs published in the Cochrane Database of Systematic Reviews (CDSR) were included, without restrictions regarding date of publication. Withdrawn or outdated versions of SRs and protocols for SRs were considered not relevant.

Types of participants

We considered all participants who underwent a vascular access procedure, both males and females, of all ages, without any restriction regarding the site of puncture.

Types of interventions

We considered SRs that assessed any vascular access technique, such as the Seldinger technique, as an intervention, if comparison with ultrasound-guided access was made in at least one of the study arms.[11]

Types of outcomes

We considered any patient-relevant clinical or laboratory outcomes, as assessed by the authors of the SRs included.

Search for reviews

We conducted a sensitive systematic search in the Cochrane Database of Systematic Reviews (CDSR, via Wiley) on July 3, 2018. We used the following MeSH terms and all related variants in the titles, abstracts and keywords: "vascular access devices", "endovascular procedures", "ultrasonography", "ultrasonography, Doppler" and "ultrasonography, interventional". The detailed search strategy is presented in **Table 1**.

Selection of reviews

Two researchers (GAA and RLGF) independently evaluated the titles and abstracts to analyze whether the SRs fulfilled the inclusion criteria. Any disagreement was resolved by consulting other authors (CDQF, MAMS, EMB, HJGN, LCUN, JCCBS and JEA). The SRs were selected and summarized by two authors (GAA and RLGF).

Presentation of results

The results from the search and the SRs included were presented as a qualitative synthesis (descriptive approach).

RESULTS

Search results

Our search strategy retrieved 221 references and, after screening the titles and abstracts, 11 SRs were preselected. After assessing the full texts, four reviews fulfilled the inclusion criteria and were included in the qualitative synthesis.[12-15]

Table 1. Search strategy and results from the Cochrane Database of Systematic Reviews

Lines	Search terms	Number of records
#1	MeSH descriptor: [Vascular Access Devices] explode all trees	241
#2	MeSH descriptor: [Endovascular Procedures] explode all trees	8,508
#3	MeSH descriptor: [Ultrasonography] explode all trees	13,655
#4	MeSH descriptor: [Ultrasonography, Doppler] explode all trees	2,959
#5	MeSH descriptor: [Ultrasonography, Interventional] explode all trees	1,658
#6	(Device Vascular Access) or (Port Catheter*) or (Venous Reservoir*) or (Vascular Access Port*) or (Vascular Catheter*) or (Intra Arterial Line*) or (Intra-Arterial Line*) or (Arterial Line*) or (Port-A-Cath) or (Port A Cath) or (PortACath) or (Endovascular Procedure*) or (Intravascular Procedure*) or (Intravascular Technique*) or (Endovascular Technique*)	5,048
#7	(Echography) or (Ultrasound Imaging*) or (Ultrasonic Imaging) or (Sonography Medical) or (Diagnostic Ultrasound*) or (Echotomography) or (Diagnos* Ultrasonic) or (Echotomography Computer) or (Tomography Ultrasonic) or (Doppler Ultrasound*) or (Doppler Ultrasonography) or (Doppler Ultrasound Imaging*) or (Ultrasound Interventional) or (Interventional Ultrasonography) or (Ultrasonography Intravascular)	9,818
#8	#1 or #2 or #6	12,812
#9	#3 or #4 or #5 or #7	20,258
#10	#8 and #9	1,425
#11	Filter: in Cochrane Reviews	221

Reviews included

The latest versions of all the SRs included were published between 2011 and 2016. Details regarding the characteristics of the interventions, comparisons and outcomes and the certainty of evidence are presented in **Table 2**.

1. Ultrasound use for placement of hemodialysis catheters

The objective of this systematic review[12] was to compare real-time two-dimensional (2D) ultrasound venous imaging and the traditional "blind" landmark method for guidance of percutaneous central venous dialysis catheter insertion. Seven studies were identified,

Table 2. Characteristics of interventions, comparisons, participants and main findings and quality of evidence, as evaluated by means of grading of recommendations, assessment, development and evaluation (GRADE)

Interventions	Comparisons	Participants	Main findings	GRADE
Real-time 2D ultrasound guidance[12]	Anatomical landmarks	Adults and children requiring **venous hemodialysis catheter** Central venous catheter for non-dialysis indications and studies using audio Doppler ultrasound techniques were excluded	Favored ultrasound guidance: • reduction of 89% (overall) and 60% (first attempt) in the risk of catheter placement failure (7 studies, 830 catheters) • reduction of 87% in the risk of arterial puncture (6 studies, 535 catheters) and of 78% in the risk of hematomas (4 studies, 323 catheters) • reduction of time taken to achieve successful vein puncture (mean 1.4 minutes less)	N.A.
Real-time 2D and Doppler ultrasound guidance[13]	Anatomical landmarks	Adults and children requiring insertion of a central venous catheter via the **internal jugular veins**	Favored 2D ultrasound guidance: • reduction of 71% in the rate of total complications overall (14 trials, 2,406 participants) • reduction of the number of participants with an inadvertent arterial puncture by 72% (22 trials, 4,388 participants) • overall success rates increased by 12% (23 trials, 4,340 participants) • mean number of attempts until achieving success in the intervention groups was 1.19 lower (16 trials, 3,302 participants) • increase in the chance of success at the first attempt by 57% (18 trials, 2,681 participants) • reduction of the chance of hematoma formation by 73% (13 trials, 3,233 participants) • decrease in the time taken for successful cannulation by 30.52 seconds (20 trials, 3,451 participants) Results for Doppler ultrasound techniques versus anatomical landmark were uncertain: • increase in the chance of success at the first attempt by 58% (four trials, 199 participants) • evidence of no difference regarding all other outcomes	• very low • low • very low • very low • moderate • very low • very low • low • very low to moderate
Real-time 2D and Doppler ultrasound guidance[14]	Anatomical landmarks	Adults and children requiring insertion of a central venous catheter via the **subclavian veins**	Favored 2D ultrasound guidance: • decrease in arterial puncture by 79% (3 studies, 498 participants) • reduction of the chance of complications by 71% (6 trials, 1,058 participants) Evidence of no difference regarding 2D and Doppler ultrasound guidance together: • total number of complications overall ranged from 77% lower to 17% higher (RR 0.52; 6 trials, 1,478 participants) • overall success rate ranged from 3% lower to 13% higher (RR 1.05; 8 trials, 1,809 participants) Evidence of no difference regarding 2D ultrasound guidance: • number of attempts until achieving success in the intervention groups ranged from 1.26 lower to 0.5 higher (mean 0.38 lower; 2 trials, 471 participants) • time taken to achieve successful cannulation in the intervention groups ranged from 56.92 seconds lower to 77.87 seconds higher (mean 10.48 seconds higher; 2 trials, 471 participants) • success at first attempt ranged from reduction by 15% to increase by 36% (RR 1.08; 2 studies, 115 participants)	• low • very low • very low • low • very low • low • high

Continue...

Table 2. Continuation

Interventions	Comparisons	Participants	Main findings	GRADE
Real-time 2D and Doppler ultrasound guidance[14]	Anatomical landmarks	Adults and children requiring insertion of a central venous catheter via the **femoral veins**	Favored 2D ultrasound guidance: • increase in overall success rates ranged from none to 23% higher (RR 1.11, 4 studies, 311 participants) • increased success at first attempt in 73% (3 studies, 224 participants) Evidence of no difference regarding 2D ultrasound guidance: • risk of arterial puncture ranged from 86% lower to 16% higher (RR 0.4; 4 studies, 311 participants) • complications rate ranged from 89% lower to 212% higher (RR 0.49; 4 trials, 311 participants) No data available regarding Doppler ultrasound guidance	 • moderate • high • low • low N.A.
Real-time 2D ultrasound guidance[15]	Other techniques (palpation/ Doppler ultrasound)	Children (one month to 18 years of age) undergoing **arterial line placement**	Favored 2D ultrasound guidance: • increase in first-attempt catheter placement success in 96% (4 studies, 404 participants) • reduction of the chance of complications (hematoma or ischemia) by 80% (2 studies, 222 participants) • increase in successful cannulation within the first two attempts in 78% (2 studies, 134 participants)	 • moderate • moderate • moderate

N.A. = not available; 2D = two-dimensional; RR = relative risk.

enrolling 767 patients and 830 catheter insertions. In almost all the studies, there was no significant heterogeneity. The review authors did not use grading of recommendations, assessment, development and evaluation (GRADE) for classifying the certainty of evidence.

Main findings

Real-time 2D ultrasound guidance significantly decreased the overall risk of catheter placement failure (risk relative, RR: 0.11; 95% confidence interval, CI: 0.03 to 0.35) and the risk of catheter placement failure on the first attempt (RR 0.40; 95% CI: 0.30 to 0.52). Use of ultrasound guidance correlated with notably fewer attempts/catheter placements (mean difference (MD) -0.35; 95% CI -0.54 to -0.16).

A meaningful reduction in the time required for successful vein puncture, from the time when the skin was anesthetized, was found with real-time ultrasound guidance (MD -1.40 minutes; 95% CI: -2.17 to -0.63).

Complications

Real-time ultrasound guidance was found to significantly decrease the risk of carotid artery puncture (RR 0.22; 95% CI: 0.06 to 0.81) and led to a significant reduction in the risk of hematoma (RR 0.27; 95% CI: 0.08 to 0.88). There were no differences between patient groups regarding the risk of pneumothorax or hemothorax (RR 0.23; 95% CI: 0.04 to 1.38).

Conclusions of this study

There are benefits from the use of real-time 2D Doppler ultrasound guidance with regard to the number of catheters successfully inserted on the first attempt. There was lower risk of arterial puncture and hematomas and less time was taken for successful vein puncture.

2. Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization

This systematic review[13] had the primary objective of evaluating the safety and effectiveness of guided puncture by means of 2D imaging ultrasound or Doppler ultrasound, for insertion of central venous catheters via the internal jugular vein. As secondary objectives, the review authors assessed differences in disclosure using 2D ultrasound or Doppler ultrasound; the effects of ultrasound use during the puncture (real-time or direct) versus the use of ultrasound only for the identification and marking of the vein before the procedure (indirect); and whether the effects were different between distinct groups of patients or between different levels of experience among the professionals who inserted the catheter. Thirty-five studies were included, totaling 5,108 participants.

According to the review authors, almost all of the studies selected for the review had high risk of bias, and the meta-analysis had substantial heterogeneity. The results were presented as comparisons of landmark versus 2D ultrasound, and landmark versus Doppler ultrasound.

Main findings

Use of 2D ultrasound improved the overall success rate by 12% (23 trials with 4,340 participants; RR 1.12; 95% CI: 1.08 to 1.17;

P-value < 0.00001; I^2 = 85%), with no difference between use of Doppler and use of 2D ultrasound. However, the quality of this evidence was very low, due to uncertainty regarding the analysis on data from Doppler ultrasound.

The 2D ultrasound reduced the number of attempts needed to succeed (16 studies; 3,302 participants), with very low quality of evidence. Only at the first attempt was it found that Doppler ultrasound had better results (2 studies; 69 participants; RR 1.58; 95% CI: 1.02 to 2.43; P-value 0.04; I^2 = 57%), with low quality of evidence.

The time taken for successful cannulation was lower with use of 2D ultrasound (20 studies; 3,451 participants; MD -30.52 seconds; 95% CI: -55.21 to -5.82; P-value 0.02; I^2 = 97%), with very low quality of evidence. There was no evidence of difference in this outcome using Doppler ultrasound (5 studies; 214 participants; MD 62.04 seconds; 95% CI: -13.47 to 137.55; P-value 0.11; I^2 = 50%), with moderate quality of evidence.

Complications

Use of 2D ultrasound reduced the total number of perioperative and postoperative complications by 71% (14 trials with 2,406 participants; RR 0.29; 95% CI; 0.17 to 0.52; P-value < 0.0001; I^2 = 57%). However, the quality of evidence was very low. There was no difference when Doppler ultrasound was used instead of 2D ultrasound, but the quality of this evidence was also low.

Inadvertent arterial puncture was reduced by 72% through use of 2D ultrasound (22 trials with 4,388 participants; RR 0.28; 95% CI: 0.18 to 0.44; P-value < 0.00001; I^2 = 35%). Use of 2D ultrasound reduced significant hematoma formation by 73% (13 trials with 3,233 participants; RR 0.27; 95% CI: 0.13 to 0.55; P-value 0.0004; I^2 = 54%). However, the quality of the evidence was very low. For Doppler ultrasound, this outcome was described in only one trial, thus making statistical analysis impossible.

The results relating to other complications such as thrombosis, embolism, hemomediastinum and hydromediastinum, hemothorax and hydrothorax, pneumothorax, subcutaneous emphysema and nerve injury were better (decrease of 66%) through use of 2D ultrasound (11 trials with 3,042 participants; RR 0.34; 95% CI: 0.15 to 0.76; P-value 0.009; I^2 = 17%), with moderate quality of evidence. In Doppler ultrasound trials, these outcomes were not reported.

Conclusions of this study

This systematic review[13] suggested that use of 2D ultrasound in relation to venous catheter insertion into the internal jugular vein improves the results and diminishes adverse events, with very low to moderate quality of evidence. Use of Doppler ultrasound was better at the first attempt, with no difference in other outcomes. These results should be used with caution because of the quality of the present evidence and heterogeneity.

3. Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization

Similarly to the review by Brass et al.,[13] this systematic review[14] addressed central venous catheter implantation and its complications, according to the techniques of the procedure. The primary objective was to evaluate the safety and effectiveness of 2D imaging ultrasound or Doppler ultrasound to guide puncture for insertion of central venous catheters, this time via the subclavian vein, axillary vein and femoral vein. The secondary objectives were the same as those of the previous study: to ascertain differences in effects between 2D ultrasound and Doppler ultrasound; differences between real-time and indirect puncture techniques; and possible distinctions between different groups of patients or different levels of experience among the persons responsible for insertion of the catheter. Thirteen studies were selected, enrolling 2,341 participants and 2,360 procedures. Unclear risk of bias was mentioned for almost all of the studies and heterogeneity was substantial, according to the review authors.

Main findings

For subclavian/axillary vein cannulation, the quality of the evidence was low regarding the overall success rate. There was no evidence that use of 2D ultrasound or Doppler ultrasound-guided puncture techniques made any difference in this outcome (RR 1.05; 95% CI: 0.97 to 1.13; P-value 0.22; I^2 = 78%). However, for femoral vein catheterization, a small increase in the overall success rate was reported (RR 1.11; 95% CI: 1.00 to 1.23; P-value 0.06; I^2 = 50%) with moderate quality of evidence.

For subclavian/axillary vein cannulation, there was no evidence of any difference between landmark and 2D real-time puncture ultrasound regarding the number of attempts needed to succeed (MD -0.38; 95% CI: -1.26 to 0.50; P-value 0.39; I^2 = 92%). However, the quality of the evidence was very low. For femoral vein catheterization, this outcome was reported in only one trial.

There was no evidence of any difference in the time taken to achieve successful cannulation for the subclavian/axillary vein (MD 10.48 seconds; 95% CI: -56.92 to 77.87; P-value 0.76; I^2 = 81%), but the quality of the evidence was low. For femoral vein catheterization, only one trial could be analyzed.

There was no evidence of any difference in success at the first attempt (RR 1.08; 95% CI: 0.85 to 1.36; P-value 0.53; I^2 = 0%) regarding subclavian/axillary vein cannulation, with high quality of evidence. However, ultrasound used during puncture of the femoral vein increased the rate of success at the first attempt (RR 1.73; 95% CI: 1.34 to 2.22; P-value < 0.0001; I^2 = 31), and the quality of the evidence was high.

Complications

For subclavian/axillary vein cannulation, use of 2D ultrasound or Doppler ultrasound-guided puncture techniques did not show any difference in the total perioperative and postoperative complication rate (RR 0.52; 95% CI: 0.23 to 1.17; P-value 0.11; I^2 = 60%), although the quality of the evidence was very low. For femoral vein catheterization, this outcome was reported in only one trial.

For subclavian/axillary vein cannulation, real-time ultrasound significantly reduced the risk of arterial puncture (RR 0.21; 95% CI: 0.06 to 0.82; P-value 0.02; I^2 = 0%), but the quality of the evidence was low. No evidence of any difference was found in relation to femoral vein catheterization (RR 0.40; 95% CI: 0.14 to 1.16; P-value 0.09; I^2 = 39%). However, the quality of the evidence was low.

Real-time ultrasound significantly reduced the risk of hematoma in subclavian/axillary vein cannulation (RR 0.26; 95% CI: 0.09 to 0.76; P-value 0.01; I^2 = 0%), with moderate quality of evidence. None of the trial authors reported this outcome for femoral vein catheterization.

Regarding use of 2D ultrasound or Doppler ultrasound-guided puncture techniques for subclavian/axillary vein cannulation, the study did not find evidence of any difference in this outcome (RR 0.29; 95% CI: 0.07 to 1.21; P-value 0.09; I^2 = 60%). However, the quality of the evidence was very low. Likewise, for femoral vein catheterization, no evidence of any difference was found (RR 0.49; 95% CI: 0.11 to 2.12; P-value 0.34; I^2 = 0%), and the quality of the evidence was low.

Conclusions of this study

2D ultrasound improves the safety and quality, compared with an anatomical landmark technique for the subclavian or femoral vein, but the results are uncertain.

4. Ultrasound-guided arterial cannulation for pediatrics

Ultrasound guidance may be useful not only for central venous access, but also in arterial and peripheral cannulation.[15] Thus, this systematic review[15] differed from the others included in this overview, since it addressed arterial cannulation (not venous) and involved only pediatric patients. Before catheterization, the artery could be located using palpation or Doppler auditory assistance; this was considered to be the control group. Participants subjected to 2D ultrasound-guided puncture for arterial puncture formed the intervention group. The study aimed to evaluate success rates and complication rates between these methods at potential sites for arterial cannulation (right or left radial, ulnar, brachial, femoral or dorsalis pedis artery). Five studies were included, reporting 444 arterial cannulations in accordance with the selection criteria. The results were presented as comparisons of 2D ultrasound guidance versus palpation or Doppler auditory assistance.

Main findings

Ultrasound guidance was found to significantly increase the success rate of cannulation at the first attempt (RR 1.96; 95% CI: 1.34 to 2.85) and increased successful radial artery cannulation within the first two attempts (RR 1.78; 95% CI: 1.25 to 2.51; P = 0.002). The quality of the evidence was moderate for both outcomes. However, ultrasound guidance did not significantly improve the rate of successful cannulation in comparison with palpation (RR 1.15; 95% CI: 0.95 to 1.40; P = 0.16).

The review authors were unable to perform a meta-analysis on the time taken for successful cannulation and the number of cannulas used. The number of attempts required for successful cannulation was presented in two studies, but no meta-analysis was possible.

The review authors did not conduct a sensitivity analysis. However, results regarding the need for assistance from another operator (i.e. the primary operator failed when attempting to insert the cannula and asked for help) were presented in one of the studies. A rate of 30.6% was reported in the ultrasound group, versus 33.7% in the palpation group (P = 0.73; 152 catheters).

Complications

The rate of complications such as hematoma was significantly reduced when using 2D ultrasound guidance during radial artery cannulation (RR 0.20; 95% CI: 0.07 to 0.60). The quality of the evidence was moderate. No studies reported any data on ischemic damage.

Conclusions of this study

There is evidence of moderate quality to support the use of ultrasound guidance for radial artery cannulation. Improved success rates at the first and second attempts were identified, along with lower complication rates, compared with the other techniques. Improved success rates at the first try may be more pronounced among infants and young children.

DISCUSSION

The overall analysis on the reviews included suggested that use of 2D ultrasound-guided vascular access provided benefits, compared with use of anatomical landmarks and the palpation technique alone.

Reduction in the total rate of perioperative and postoperative complications/adverse effects was found in one of the reviews in relation to internal jugular vein catheterization using 2D ultrasound. Hematoma formation was reduced through application of ultrasound in all of the four SRs included. However, none of these reviews addressed the impact of use of ultrasound on patient discomfort and mortality. Nor did they evaluate the impact of different types of devices (e.g. point-of-care versus standard devices) and the skill with which these instruments are applied.

The major limitation of this overview was the small number of reviews included. Another limitation was that one of the reviews was out of date in the sense that it did not evaluate the evidence using the GRADE approach.[12] This imposed limits on comparison of the evidence with that of the other reviews. Another issue was the low certainty of the evidence regarding most of the outcomes and the lack of evidence regarding arterial puncture in adults. Over recent decades, use of endovascular procedures has increased, and use of arterial accesses in adults, frequently via the radial or femoral artery, has become a routine procedure. Use of other arterial access points, such as the radial artery, especially in intensive care units for hemodynamic evaluation or blood sample collection, has given rise to concerns regarding avoidance of adverse events, considering that puncture may be performed frequently.

Nevertheless, all of the reviews included suggested that use of ultrasound for guided vascular access provided various benefits, compared with use of anatomical landmarks (vein puncture) and palpation (artery puncture) alone.

Some of the most recent clinical practice guidelines[16-18] assessed the outcomes from ultrasound-guided vascular access only superficially or did not assess these outcomes, and they did not include any of the Cochrane SRs evaluated here.[12–18] Therefore, the results from the present review may also serve to improve the next versions of the guidelines relating to vascular access.[16-18]

CONCLUSION

Even with limitations regarding the quality of evidence, all of the four Cochrane reviews included in this overview showed that ultrasound guidance for vascular access provided some benefits. There is a lack of information regarding ultrasound-guided arterial puncture in adults. Therefore, further well-designed and well-conducted studies from which solid conclusions can be reached are still imperative, especially regarding arterial ultrasound-guided access. Additional evidence with high certainty regarding ultrasound guidance for venous and arterial puncture is needed in order to build up a robust body of evidence in this setting.

Ethics

This was not a primary study, i.e. we did not deal directly with patients. Therefore, no ethics committee approval was necessary.

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The cause of abdominal mass in a child with celiac disease: Rapunzel syndrome. A case report

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KEY WORDS:
Celiac disease.
Abdomen.
Bezoars.
Trichotillomania.
Depression.

ABSTRACT

CONTEXT: Rapunzel syndrome is a rare form of gastric trichobezoar that develops through outstretching of the bezoar from the stomach to the intestine.

CASE REPORT: A 12-year-old girl who had been diagnosed with celiac disease six years earlier was brought to the department of pediatric gastroenterology because of abdominal distension. A palpable mass was detected. A trichobezoar that stretched to the small intestine was removed surgically. The patient was diagnosed as having anxiety and depressive disorder, and treatment started. Following the treatment, her previous trichophagia completely disappeared.

CONCLUSION: Presence of trichobezoar should be kept in mind, especially when young girls who have psychiatric problems suffer from gastrointestinal symptoms.

INTRODUCTION

Bezoars are associated with pica, mental retardation and psychiatric disorders among children.[1] Hair pulling is defined as trichotillomania and eating hair is defined as trichophagia.[1] The most frequently observed type of bezoar is trichobezoar, which develops in connection with hair deposition.[1] The mass, which is generally composed of hair, accumulates among the mucosal folds of the stomach and expands over time. Because the rate of expansion is slow, symptoms only appear much later on, in most cases. Ninety percent of bezoars are found in adolescent girls.[1]

Rapunzel syndrome is a rare form of gastric trichobezoar and is formed by elongation of tail-like extensions from a bezoar, along the intestine. Trichophagia and trichotillomania may be observed together with depressive disorders, anxiety disorders and, particularly, obsessive-compulsive disorders.[2]

The case presented here involved presence of a trichobezoar with Rapunzel syndrome in a girl who was being followed up because of a diagnosis of celiac disease.

CASE REPORT

The patient was a 12-year-old girl, who had been followed up for six years because of a diagnosis of celiac disease. She complained of a condition of painless abdominal distension.

The patient's weight and height were in the normal range according to age. In the physical examination, a mass spreading from the left upper quadrant of the abdomen to the right upper quadrant, passing the middle line, was detected. Other systemic examinations were normal. The laboratory investigation of the case included the following results: white blood cells: 8,900/ul; hemoglobin: 12.4 mg/dl; hematocrit: 38.4%; thrombocytes: 337,000/ul; iron: 60 ug/dl; iron binding capacity: 250 ug/dl; folic acid: 11 ng/ml; ferritin: 15 ng/ml; and vitamin B12: 216 pg/ml. The results regarding tissue transglutaminase immunoglobulin A (Ig A) (27.58 RU/ml), anti-gliadin immunoglobulin A (IgA) and anti-endomysium antibody IgA were negative.

The patient was fully compliant with her gluten-free diet, according to her own declaration, and did not present any anemia. She showed significantly decreased tissue transglutaminase Ig A, which was > 200 RU/ml (normal level < 20 RU/ml) at the time when celiac disease was initially diagnosed. She was initially positive for anti-gliadin IgA and anti-endomysium IgA antibodies, at high titers, but she had become negative for these antibodies under her gluten-free diet recently.

There was no pathological finding from direct abdominal radiography. In the abdominal ultrasonography (USG), the radiologist could not detect any pathological condition. Through computed tomography (CT), most of the stomach could be seen and soft tissue densities that were possibly compatible with a bezoar were observed (**Figure 1a, b**). Surgical intervention was approved by the department of pediatric surgery. The trichobezoar, which had the shape of the stomach and stretched out towards the small intestine, was removed (**Figure 2**).

The patient had developed a habit of pulling out and eating her hair over the last year. She was reported to be successful at school, but she suffered from stress during examination periods and her relationships with friends was weak, which meant that she usually spent time on her own. Less hair was noticed in the frontal region of the skull. She underwent evaluation by a child psychiatrist, and this revealed that she was afraid of not being able to grow up adequately because of her celiac disease. Her communication with her peers was weak and she did not want to get involved in the social environment.

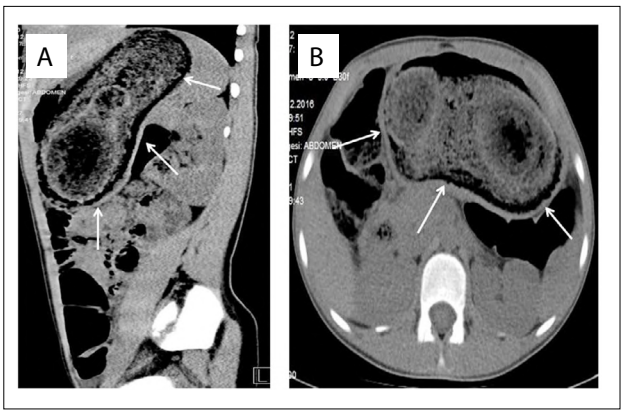

Figure 1. Computed tomography views: soft-tissue densities possibly compatible with a bezoar inside the stomach.

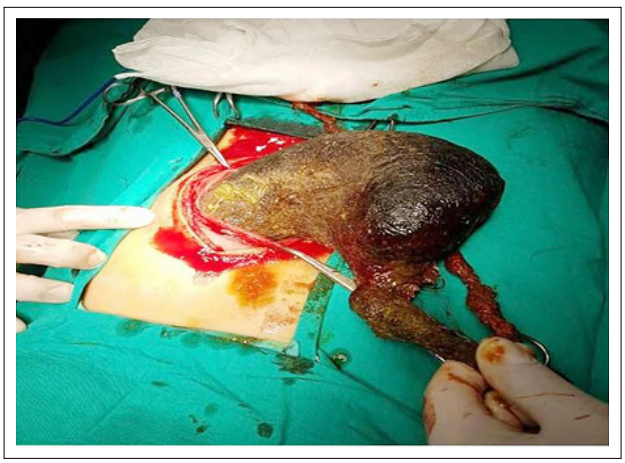

Figure 2. Surgical removal of the trichobezoar that filled the stomach and extended towards the small intestine.

She felt unable to calm herself down and she had initially started to pull out her hair and then started to eat it. The observation made at the end of her psychological assessment was that her anxiety was explicit and that she had depressive complaints. Administration of sertraline (50 mg/day) was started in connection with anxiety disorder and depressive disorder. During the follow-up at the department of child psychiatry, with cognitive and behavioral techniques therapy, the patient's trichophagia regressed completely. The patient has been followed for the last year since the operation.

DISCUSSION

Trichophagia and trichotillomania are particularly observed over the first two decades of life, and frequently in girls.[1] The most frequent findings among children are epigastric mass, epigastric pain, nausea, vomiting, weight loss, diarrhea, constipation and hematemesis.[2] The diagnosis may be delayed because of the nonspecific symptoms. When the diagnosis is delayed, presence of trichobezoars may lead to serious complications. The most frequent complication is perforation of the stomach and small intestine. Invagination, pancreatitis, intestinal obstruction and peritonitis are infrequent complications.[1,2]

Direct radiography, abdominal USG and/or CT findings can be used in diagnosing trichobezoars.[3] Upper gastrointestinal system endoscopy has the greatest sensitivity and specificity, given that it can provide information about the structure of the mass. The CT investigation can determine the existence, localization and distribution of the bezoars clearly.[3] In our case, the bezoar could not be defined by means of USG, but could be viewed using CT.

Methods such as intragastric enzyme application (cellulose, pancreatic lipase, acetylcysteine, etc.), extracorporeal or endoscopic lithotripsy, break-up by means of laser and laparoscopic or open surgery can be used to treat bezoars. Endoscopic treatment is effective for phytobezoars and lactobezoars, since they are small in size and easily breakable, but it has less effect on trichobezoars. Nonetheless, it can be used for small-sized trichobezoars.[1] Laparoscopic surgery is not advisable because of complications such as difficulty in breaking up the trichobezoar and the risk of obstruction of the intestines due to the broken pieces and deposition of hair in the abdominal cavity. The treatment advised for cases of large trichobezoars consists of the removal of the mass by means of laparotomy.[1,2]

Out of 10 papers in the literature regarding celiac disease, trichotillomania and bezoar (**Table 1**), only 6 were found to present reports on cases of these three pathological conditions occurring together[4-9] (**Table 2**). Trichotillomania and trichophagia may be associated with neuropsychiatric disorders connected with celiac disease.[4] Additionally, iron deficiency anemia and pica relating to celiac disease may be presented as the reason for presence of trichophagia and bezoars.[5] Neuropsychiatric disorders and anemia

secondary to celiac disease were ruled out in this patient's case. Trichotillomania and trichophagia may also be observed together with serious chronic psychiatric disorders such as depressive disorders, anxiety disorders and, particularly, obsessive-compulsive disorders, and together with alcohol and drug addiction.[2]

The reason for trichophagia in our case was associated primarily with the depressive disorder and the anxiety disorder that were detected. Cognitive and behavioral techniques were applied during psychiatric consultations regarding this issue and antidepressant treatment was started. The patient's trichophagia regressed completely through the treatments applied.

Table 1. Articles relating to celiac disease and bezoar that were found through searching the medical literature databases (October 10, 2017)

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	((celiac disease) OR coeliac disease) AND ((trichotillomania) OR bezoar)	1,061	10
	("celiac disease"[Mesh]) AND "bezoars"[Mesh]	818	7
LILACS (via BVS)	(celiac disease)) AND (bezoar))	8	0

Table 2. Case reports on trichotillomania and trichobezoar with celiac disease reported in the literature

Author	Publication year	Diagnosis	Treatment
Larsson et al.[4]	2004	Trichobezoar was a result of celiac disease-induced pica.	Trichobezoar was removed via surgery; gluten-free diet was started.
Marcos Alonso et al.[5]	2005	Iron deficiency anemia and pica related to celiac disease.	Trichophagia regressed through gluten-free diet.
McCallum et al.[6]	2008	Iron deficiency anemia and pica related to celiac disease.	Trichobezoar retrieved through laparotomy; gluten-free diet was started.
Irastorza et al.[7]	2014	Neuropsychiatric disorder connected with celiac disease.	Trichophagia regressed through gluten-free diet.
Lihabi et al.[8]	2016	Trichotillomania was due to behavioral disorders secondary to celiac disease.	Trichotillomania improved through gluten-free diet.
Kalyoncu et al.[9]	2017	Trichotillomania was caused by behavioral disorders secondary to celiac disease.	Trichobezoar was removed through surgery; gluten-free diet continued.

CONCLUSION

Particularly when young girls with psychiatric problems complain of gastrointestinal system symptoms like palpable mass, abdominal pain and vomiting, they should be investigated for any history of trichophagia.

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Anaphylaxis triggered by prick test with latex extract: a case report

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KEY WORDS:
Latex hypersensitivity.
Diagnostic test, routine.
Anaphylaxis.

ABSTRACT

CONTEXT: Adverse reactions associated with prick tests are rare but may be present as serious systemic reactions.

CASE REPORT: A 38-year-old female nursing technician complained of three episodes of anaphylaxis in one year, all in the workplace. To investigate latex allergy, the patient underwent the prick test with latex, and immediately developed a rash, itchy skin, hoarseness, dyspnea and dry cough. Her condition improved promptly after appropriate measures were established for controlling her anaphylaxis.

CONCLUSION: The skin test must be performed under medical supervision, since complications that can lead to life-threatening reactions, if support measures are not readily implemented, have been attributed to this test.

INTRODUCTION

Anaphylaxis is a well-recognized clinical syndrome caused by the pharmacological activity of mediators that are released after activation of mast cells and basophils through contact with an antigen. It is a serious systemic reaction with an acute onset and it is potentially fatal.[1] Specialists need to be able to recognize and treat this syndrome and to be aware of both the unpredictability of its onset and the potential for severe outcomes through its evolution.

The specific diagnostic and/or therapeutic activities of immunological allergy outpatient clinics, such as administration of allergen-specific immunotherapy, challenge tests and skin tests for immediate hypersensitivity to allergens, may lead to appearance of systemic allergic reactions that can be serious and even fatal. The incidence of systemic reactions to skin tests for immediate hypersensitivity is small, and the test is considered safe. Nonetheless, the possibility of systemic reactions should not be underestimated, especially in relation to extracts of Hymenoptera venoms and medications.[2]

In clinical practice, investigations on sensitivity are conducted initially through *in vitro* sensitization tests or skin prick tests. Both of these methods are considered safe. In *in vitro* tests, intercurrences are very rare and, when they do occur, they are due to complications during blood collection. Reactions relating to prick tests are also rare and may be due to the procedure itself (puncture wounds) or to serious reactions that might be triggered because of exposure to the allergen.[3]

Occupational anaphylaxis has become more prominent through recognition that this serious condition may occur in occupational contexts. Among the occupational agents, latex has gained prominence over recent years, especially among healthcare professionals, because of the severity of the reactions[4].

This paper aimed to describe a case of anaphylaxis triggered by a prick test with latex extract, in a patient with occupational anaphylaxis. Until now, no case of anaphylaxis during a skin test with latex extract had been reported in Brazil.

CASE REPORT

A 38-year-old female nursing technician presented a prior history of three episodes of anaphylaxis within one year, all in the workplace. She had a personal history of mild intermittent

allergic rhinitis from childhood, for which antihistamines and nasal corticosteroid had been used only during exacerbated episodes. She had a family history of atopy and presented a positive prick test for aeroallergens (*Dermatophagoides pteronyssinus* and *Blomia tropicalis*). She tested negative for serum-specific immunoglobulin E (IgE) for latex.

Because of her recurrent pattern of anaphylaxis and risk factor for latex allergy, a latex prick test using a standard commercial extract (500 mcg/ml; ALK Abelló, Spain) was performed. Five minutes after the puncturing, the patient developed a generalized rash, itchy skin, hoarseness, dyspnea, dry cough and a sensation of a foreign body in the oropharynx. Her vital signs were: blood pressure of 134 x 84 mmHg, heart rate of 130 bpm and peripheral oxygen saturation of 94%. The patient was placed in dorsal decubitus, with elevation of the lower limbs and 0.5 mg of adrenaline was applied intramuscularly in the upper third of the vastus lateralis muscle of the thigh, in addition to 200 mg of hydrocortisone and 50 mg of diphenhydramine intravenously, and inhalation of short-acting β2-agonist. The patient presented progressive improvement of the condition without presentation of the late-phase reaction.

The patient was evaluated in the context of another major study that was ongoing, and signed a free and informed consent statement for that study, which had been approved by the institution's ethics committee, under the number 0538/10 on September 22, 2010.

DISCUSSION

Immediate skin prick tests are a useful tool for assessing IgE-mediated sensitization, to make an etiological diagnosis for allergic manifestations of Gell and Coombs type I reactions. They have been performed within the clinical practice of allergist physicians for many years and are considered extremely safe.

In 1987, Lockey et al.[3] published a report on cases of fatalities during immunotherapy and skin tests for mites. These authors reviewed the mortality cases that occurred between 1973 and 1983 through medical contacts in the United States. Up until that time, only six deaths through skin tests had been reported. Of these, four cases were male and two were children under 18 years. Almost all the patients (five) had asthma and were not currently being treated.

In 1993, Reid et al.[5] reviewed the cases of mortality due to immunotherapy and skin tests for mites in the United States that occurred between 1985 and 1989. A total of 13 deaths were reported during this period, none of them related to the skin prick test. The vast majority of the patients were asthmatic patients undergoing treatment, and mortality was attributed to the severity of the underlying allergic disease as well as associations with other medications that are known to aggravate anaphylactic reactions, such as beta-blockers. At that time in the United States, 33 million doses of immunotherapeutic drugs were being used per year, and there was a proportion of 1 fatal reaction for every 2 million doses applied.

In the most recent survey, published in 2004, Bernstein et al.[6] reviewed all fatalities consequent to prick tests and immunotherapy in the United States and Canada from 1990 to 2001. In their study, aeroallergens and foods were evaluated and it was found that a total of 19 deaths occurred due to immunotherapy and a single death occurred during a skin prick test. This last death occurred in a hospital environment during application of multiple food allergens.

The initial step in diagnosing latex allergy is to obtain a thorough clinical history. However, to confirm the etiology, it is necessary to determine the presence of specific IgE *in vitro* (serological tests) or *in vivo* (skin prick tests). Serological tests have a high number of false negative results and should not be used alone for screening of latex allergy.[4] This may happen because not all latex allergens are represented in the assay, and it may explain why the serological test was negative in the case presented here. Skin prick tests have higher specificity and sensitivity than do *in vitro* tests,[4] and should be used whenever possible, although they have been associated with anaphylactic events, as presented here. In this case, because we were facing a probable occupational case with its labor-law implications, we decided to continue with the etiological investigation and carry out the prick test.

In clinical practice, the first safety measure that should be established is removal of the causal agent, which in this case meant replacement of latex with latex-free products. In addition, specific allergen immunotherapy should be implemented, but this is not available in Brazil.

We reviewed the literature in MEDLINE, PubMed and LILACS using the English-language keywords "latex hypersensitivity", "diagnostic test" and "anaphylaxis"; the Portuguese keywords "hipersensibilidade ao latex", "teste diagnóstico" and "anafilaxia"; and the Spanish keywords "hipersensibilidad al látex", "prueba de diagnóstico" and "anafilaxia". We did not find any case report describing an anaphylaxis reaction during a skin prick test with latex (**Table 1**).

Table 1. Search of the medical literature for case reports on adverse reactions associated with diagnostic test for latex allergy. The search was conducted on July 5, 2017

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	(Latex hypersensitivity AND Diagnostic test) or (Latex Hypersensitivity AND Anaphylaxis) or (Latex hypersensitivity AND Diagnostic test AND Anaphylaxis)", in ALL FIELDS	23	3
LILACS (via BIREME)	(Latex hypersensitivity AND Diagnostic test) or (Latex Hypersensitivity AND Anaphylaxis) or (Latex hypersensitivity AND Diagnostic test AND Anaphylaxis)", in ALL FIELDS	17	2

CONCLUSION

The skin prick test for allergen sensitization research is a safe test, but it must be performed in an appropriate environment, under medical supervision and with prior analysis on patients, given that complications have been attributed to this method. These complications may be serious and may lead to death if support measures are not readily available.

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Dermoid cyst with cerebellar meningoencephalocele at different locations accompanied by posterior fossa abnormalities: case report

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KEY WORDS:
Aprosencephaly and cerebellar dysgenesis [supplementary concept].
Dermoid cyst.
Encephalocele.

ABSTRACT

CONTEXT: Dermoid cysts are well-defined cysts containing sebaceous glands and dermal structures. In the literature, dermoid cysts and associated closure defects have been described in the same locations.

CASE REPORT: In this case, a dermoid cyst was found at the base of the mouth with a coexisting closure defect in the occipital calvarium. Additional abnormalities were also observed, including posterior myeloschisis, right cerebellar dysgenesis, vermian hypogenesis and posterior fusion of the second and third vertebrae. The finding of a dermoid cyst located at the base of the mouth is discussed here, with additional imaging findings.

CONCLUSION: Dermoid cysts in the head and neck region may be accompanied by posterior fossa abnormalities.

INTRODUCTION

Dermoid cysts are cystic masses that contain different structures such as sebaceous glands, hair follicles and sweat glands within squamous epithelium of ectoderm origin. About 7% of all dermoid cysts are located in the head and neck region. Approximately 11% of these dermoid cysts are found at the base of the mouth, which is the second most common location (the most common location is the lateral eyebrow). Although most of them are benign, slow growing lesions and are common in young adults, it has been reported in the literature that malignant transformation may be found in around 5% of the cases. Coalescence of sebaceous material in the cyst lumen forms a typical "sack of marbles" sign.[1]

Coexistence of dermoid cysts and spinal dysraphism has been documented in many studies. In these studies, dermoid cysts and spinal dysraphism were defined at the same locations. Three cases of a dermoid cyst and coincident encephalocele have been reported in the literature.[1,2] To the best of our knowledge, the coexistence of dermoid cyst and midline closure defects/spinal dysraphism at different locations has not previously been mentioned. In the present case report, our aim was to describe an occurrence of a dermoid cyst at the base of the mouth with accompanying occipital cephalocele.

CASE REPORT

Manuscripts structured as case reports are exempt from approval by our institution's ethics committee. We received a consent form for reporting on this case.

A 15-year-old girl who was suffering from swelling and pain in the upper neck that had started two months earlier was referred to our hospital. She was evaluated by an ear, nose and throat specialist clinician. On physical examination, there was a painful swelling in the left submandibular region, at the base of the mouth. Deep neck infection was considered as a diagnosis. No abnormality was found through blood tests.

Sonography examination of the neck was performed. Through this, an oval-shaped thick-walled cystic lesion of dimensions 58 mm x 34 mm was detected at the base of the mouth, which extended through the left submandibular region. The lesion appeared to contain dispersed solid nodules that were smaller than 15 mm in diameter, and color doppler sonography showed that there was no blood flow. Thus, a "sack of marbles" sign was revealed (**Figure 1**). Incidentally, we

found that the thyroid echo pattern was heterogeneous, secondary to parenchymal fibrous septa and hypoechoic regions, and was thus consistent with Hashimoto's thyroiditis.

The laboratory findings were as follows: thyroid-stimulating hormone (TSH) = 0.017 μU/ml (range: 0.27-4.2); free T4 = 2.81 ng/dl (range: 0.93-1.97); and anti-thyroid peroxidase (TPO) = 651 IU/ml (range: 0-40).

Contrast-enhanced magnetic resonance imaging (MRI) was performed for preoperative evaluation of the lesion. MRI showed a thick-walled mass with smooth margins located at the left side of

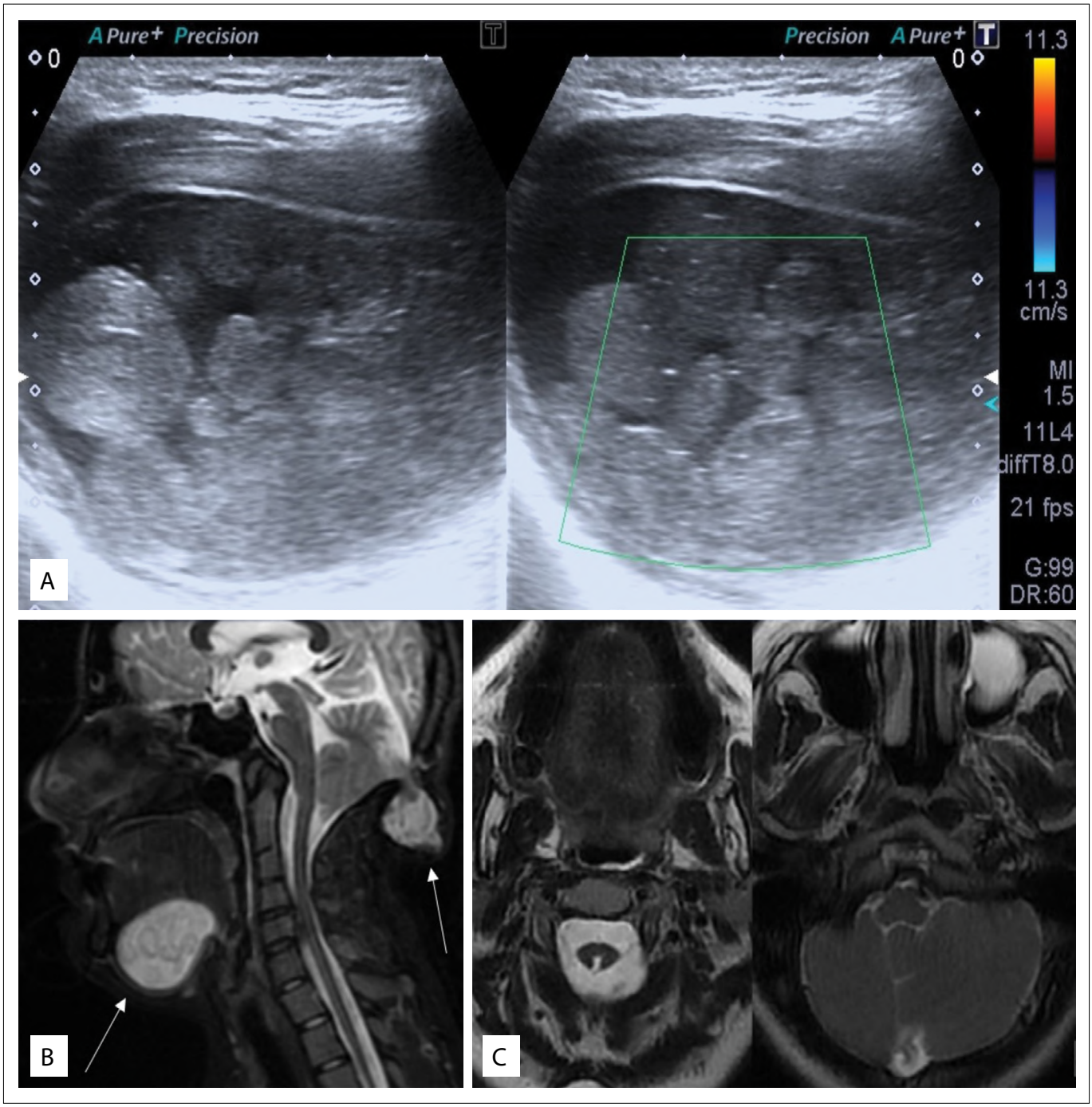

Figure 1. (A) Sonography images showing an oval-shaped, thick-walled cystic lesion. Solid nodular appearance can be seen, without blood flow on color doppler ultrasonography, thus revealing the "sack of marbles" sign. (B) Sagittal T2W Fat Sat image showing hyperintense cystic mass at the base of the mouth, cerebellar encephalomeningocele, tonsillar herniation and C2-C3 vertebral fusion. (C) Axial T2-weighted images demonstrating dysgenesis of the right cerebellum, hypogenesis of the vermis and short-segment posterior myeloschisis at the cervicomedullary junction.

the base of the mouth. The lesion was hypointense on T1-weighted images and hyperintense on T2, and it was composed of small nodules that gave a "sack of marbles" appearance. The rims of the nodules had intermediate signal intensity on T1-weighted images and low signal intensity on T2-weighted images, without signal loss on fat-saturated images. Contrast-enhanced images did not show any enhancement. MRI also showed an occipital bony defect at the midline. There was a cerebellar encephalomeningocele (**Figure 1**). In addition, partial fusion of the second and third cervical vertebrae was present. Axial brain images demonstrated dysgenesis of the right cerebellar hemisphere, hypogenesis of the vermis, tonsillar herniation and posterior myeloschisis of the cervicomedullary junction (**Figure 1**).

The medical treatment was planned as if this were a case of hyperthyroidism. Medication was administered before surgery, in order to prevent the complications relating to hyperthyroidism. At surgery, an external transcervical approach was used to enable total excision of the cyst, and there were no complications. No recurrence was detected at an evaluation three months after the surgery. The histopathological diagnosis was reported as a dermoid cyst (**Figure 1**).

DISCUSSION

Dermoid cysts may be congenital or acquired. The acquired form develops through implantation of epithelial cells into the surrounding tissue, due to trauma or iatrogenic causes. Many congenital dermoid cysts develop at 3-5 weeks of gestation as a result of embryological failure. Epithelial cells are thought to be trapped during the closure of the first and second branchial arches in the formation of dermoid cysts.[1,3] True dermoid cysts are lesions that include dermal appendages such as sweat glands, sebaceous glands, hair and hair follicles that are histologically paved with epidermis. A sudden increase in size is observed at the beginning of the puberty, due to the sebaceous glands that they contain.[4]

We used a systematic search in electronic databases (MEDLINE and LILACS) to find articles relating to dermoid cysts and posterior fossa abnormalities (**Table 1**). Dermoid cysts may be accompanied by midline closure defects, but in the cases that have been reported, cysts and the corresponding closure defects were mostly defined at the same location. Simpson et al.[5] found coexisting dermoid cysts in the herniated sac in five of their 74 cephalocele cases. They also found concurrent cleft palate (3%), microphthalmia (1%), corneal opacity (1%) and tracheo-esophageal fistula (1%). Posterior fossa anomalies and concomitant occipital encephalomeningocele have been reported in the literature.[5] In the case reported here, the dermoid cyst was situated at the base of the mouth, while the coexisting closure defect was found in the occipital calvarium, in a different location. In addition, accompanying short-segment posterior myeloschisis, right cerebellar dysgenesis, vermian hypogenesis and C2-3 vertebrae fusion were identified.

Floating fat globules in the cyst can create a characteristic "sack of marbles" appearance. The literature does not provide any knowledge regarding the frequency of the "sack of marbles" sign in dermoid cysts. However, it is known that this sign is indeed pathognomonic for head and neck dermoid cysts.[1] On sonographic examination, the globules are seen as well-defined hyperechogenic nodule-like structures without blood flow. MRI signals may alter depending on cyst content. On T1W images, these structures are isointense or mildly hyperintense, depending on the lipid content, while they are heterogeneously hyperintense on T2W images. High-lipid content cysts can be seen as dark images through fat-saturated imaging. After administration of contrast medium, mild capsular enhancement may be

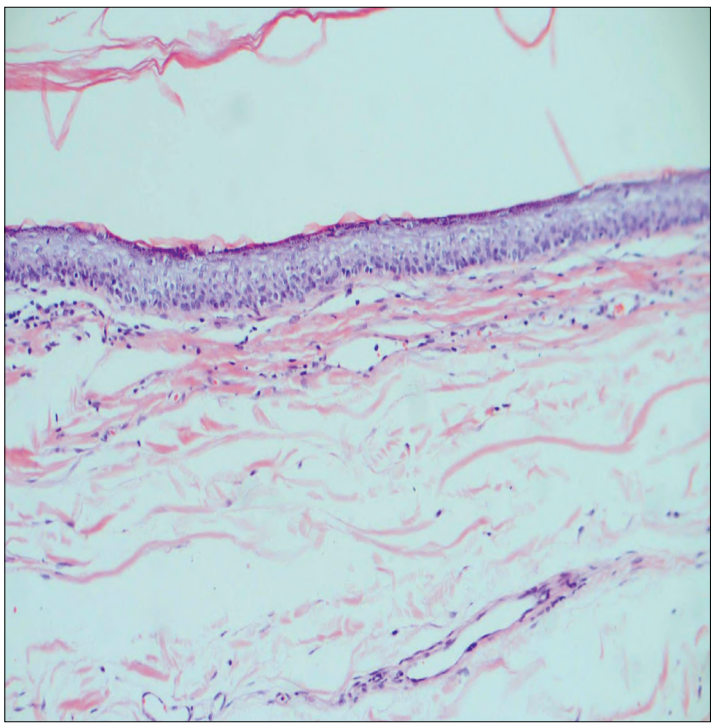

Figure 2. Hematoxylin and eosin staining of the pathological specimen, with original magnification of 40 x. The granular layer containing keratin can be seen on the squamous epithelium of the cyst wall. In addition, lymphocytes can be seen beneath the cyst wall.

Table 1. Systematic search of the literature performed in March 2018

Database	Search strategies	Found	Related
MEDLINE (via PubMed)	("Dermoid Cyst"[Mesh]) AND ("Aprosencephaly and Cerebellar Dysgenesis" [Supplementary Concept]) AND ("Encephalocele"[Mesh])	0	0
LILACS (via BVS)	("Dermoid Cyst"[Mesh]) AND ("Aprosencephaly and Cerebellar Dysgenesis" [Supplementary Concept]) AND ("Encephalocele"[Mesh])	0	0

detected on the cyst wall.[1] In our case, the dermoid cyst was isointense on T1W images and heterogeneously hyperintense on T2W images, without suppression on fat-saturated images.

In the differential diagnosis for neck dermoid cysts, the following should be considered: thyroglossal duct cyst, inclusion cyst, cystic hygroma, ranula, neoplasms of the sublingual and minor salivary glands, neurofibroma, hemangioma and lymphangioma.

CONCLUSION

The "sack of marbles" sign in cases of dermoid cysts in the neck is an important and diagnostic finding. Dermoid cysts in the head and neck region may be accompanied by posterior fossa abnormalities. Patients should also be evaluated regarding closure defects.

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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.

São Paulo Medical Journal does not charge authors any "open access fees" and submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

Articles accepted for publication become the Journal's property for copyright purposes, in accordance with Creative Commons attribution type BY.

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.

Conflicts of interest may be financial or non-financial. The Journal recommends that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest. The existence and declaration of conflicts of interest is not an impediment to publication at all.

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.

Authorship

The Journal supports the position taken by the ICMJE (http://www.icmje.org) regarding authorship. All authors should read ICMJE's recommendations to obtain clarifications regarding the criteria for authorship and to verify whether all of them have made enough contributions to be considered authors.[10]

All authors of articles published in *São Paulo Medical Journal* need to have contributed actively to the discussion of the study results and should review and approve the final version that is to be released. If one author has not contributed enough or has not approved the final version of the manuscript, he/she must be transferred to the Acknowledgement section.

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

São Paulo Medical Journal supports the ORCID initiative. All authors should create an ORCID identification (ID) record (in www.orcid.org) before submitting their article and should link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names, give credit to contributors and link authors to their professional affiliations. In addition, this may increase the ability of search engines to retrieve articles.

Redundant or duplicate publication

São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

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.

At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- 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;
4. Each author should present his/her ORCID identification number (as obtained from www.orcid.org);
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. Each author should indicate a valid, up-to-date email address for contact;
7. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
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9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
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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.
- Keywords - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh. No other keywords will be accepted.

References

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

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the "doi" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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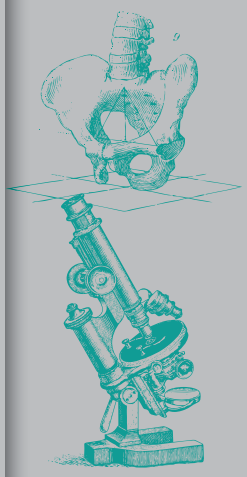

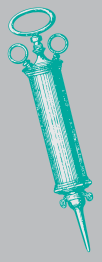

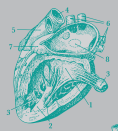

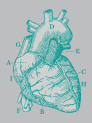

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