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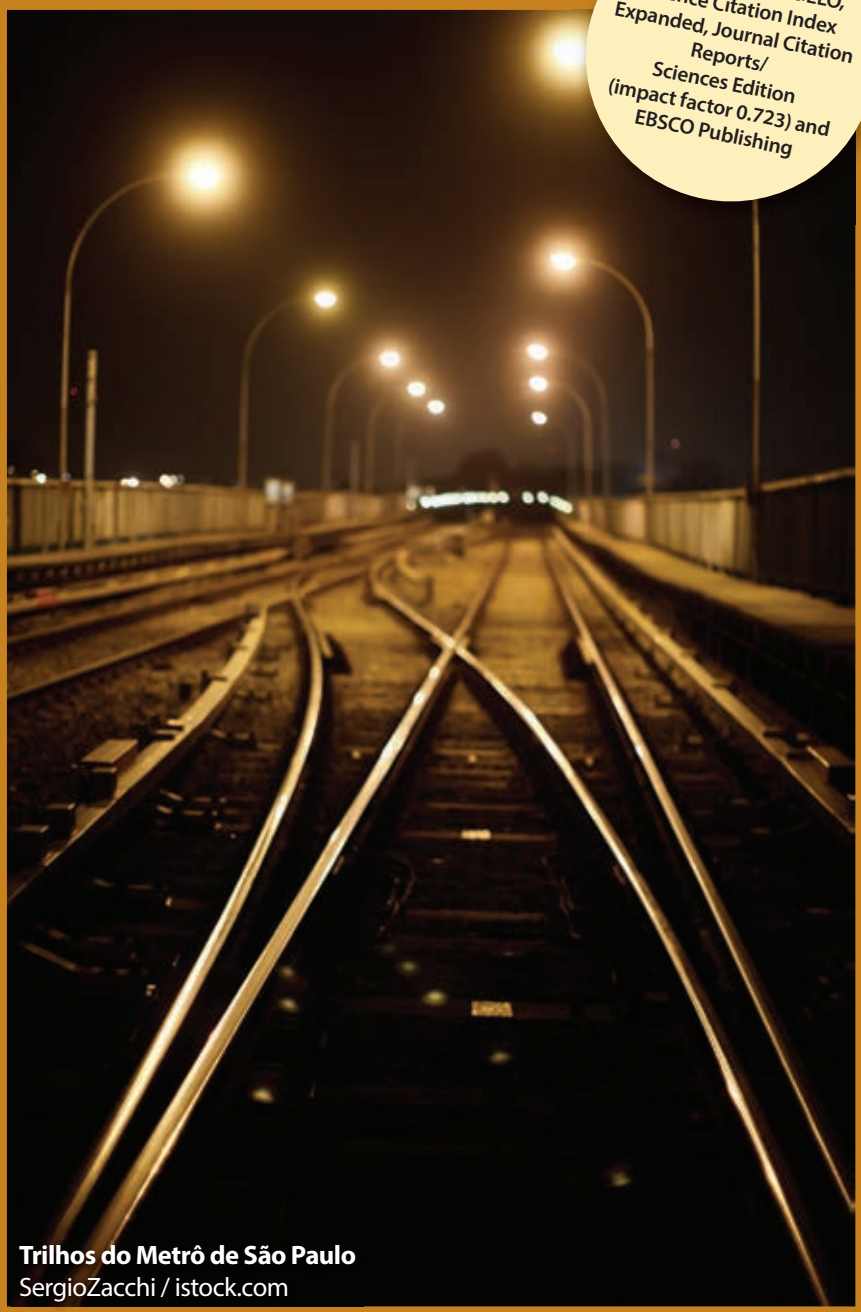

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Renal disease screening: a potential tool for reducing health inequity

Rastreamento para doença renal: uma ferramenta em potencial para reduzir a desigualdade na saúde

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The impact of chronic kidney disease on mortality, quality of life and cost of medical care is rising worldwide, such that it now affects 8-16% of the world population.[1] The Global Burden of Diseases index, which ranks the causes of deaths, has revealed that as the underlying cause of death, chronic kidney disease (CKD) jumped from 34th position in 1990 to 18th in 2013.[2] However, although the use of mortality statistics to ascertain temporal trends or make geographic comparisons has been helpful in charting other chronic diseases, this has not been the case for CKD. The reason for this is that when diabetes and CKD are mentioned together on a death certificate, the underlying cause is frequently stated as "diabetes without complications" and not "chronic kidney disease" or "diabetic kidney disease".[3] Consequently, to ascertain the situation of CKD in countries like Brazil, other types of information are needed, such as registries, reports of medical procedures and epidemiological studies.[4-7]

In Brazil, data from the National Dialysis Registry and the Ministry of Health have shown that over 10,000 people are currently undergoing kidney replacement therapy.[4] de Moura et al. analyzed data from the Brazilian National Health System on 280,667 patients with end-stage renal disease who received publicly financed kidney replacement therapy for at least three consecutive months. Men (57.2%) and people aged 45-64 years (43.4%) were predominant. The underlying causes of CKD were hypertension (20.4%), diabetes (12.0%) and glomerulonephritis (7.7%). The annual increase in the prevalence of people under dialysis from 2000 to 2012 was 3.6% (95% confidence interval, CI: +3.2% to +4.0%) and the average annual change in incidence was +1.8%/year (+1.1% to +2.5%).[5]

The prevalence of CKD among apparently healthy people was analyzed among the participants of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).[6,7] This was evaluated during baseline visits (2008-2010) to 14,636 civil servants aged 35 to 74 years. The definition of CKD based on albuminuria (albumin-to-creatinine ≥ 30 mg/g) and glomerular filtration rate < 60 ml/min/1.73 m^2). The glomerular filtration rate was obtained through an equation devised by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which was derived from pooled data from clinical studies in the United States.[8] In ELSA-Brasil, the frequency of albuminuria or low glomerular filtration rate, alone or in combination, was related to aging, lower socioeconomic status and self-reporting as black. Risk factors such as smoking, dyslipidemia, hypertension and diabetes were directly correlated with CKD. However, these risk factors did not explain the socioeconomic differences, i.e. the higher prevalence of CKD among the elderly, less affluent people and blacks.[9]

One point to emphasize is that ELSA-Brasil researchers did not correct the glomerular filtration rate for race in the manner proposed by the CKD-EPI consortium.[8] The reason for their race correction was the greater mass muscle described in the African-American population. However, in contrast with research conducted in the United States, three independent studies in different Brazilian cities did not show that correction for black race was useful for the Brazilian population.[10-12] These conclusions were the same as those relating to black people living in

Ghana and South Africa.[13,14] In the light of these results in Brazil and Africa, there is no reason for medical laboratories in Brazil to keep on presenting glomerular filtration rates corrected for race.

Although the U.S. Preventive Services Task Force concluded that the "evidence is insufficient to assess the balance of benefits and harms of routine screening for CKD in asymptomatic adults,"[15] we consider that creatinine measurements should be more widely used, so that glomerular filtration rates are not just estimated for people with hypertension or diabetes. As shown by the ELSA-Brasil results, socioeconomic status was inversely associated with CKD prevalence. Consequently, screening for CKD within primary care, especially at units located in places with poor and less educated populations, needs to evaluate this better: not only from a cost-effectiveness perspective but also from the perspective of the necessity to reduce inequity within the Brazilian population.

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Mother's lifestyle: development of a questionnaire to assess a determinant of children's health. A cross-sectional study

Estilo de vida materno: desenvolvimento de um questionário para avaliar um determinante da saúde da criança. Um estudo transversal

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KEY WORDS:
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PALAVRAS-CHAVE:
Estilo de vida.
Pré-escolar.
Relações mãe-filho.
Questionários.
Estudos de validação.

ABSTRACT

CONTEXT AND OBJECTIVE: Lifestyle includes the personal attitudes or behavioral patterns that result in risks or benefits to the individual's own health or that of others. Children's health is particularly determined by their mother's lifestyle. The objective here was to develop and evaluate the reliability of a questionnaire capable of describing the lifestyles of preschoolers' mothers in terms of their activities, interests, opinions and values.

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

METHODS: This study was conducted between January 2010 and March 2011, among 255 mothers of preschoolers living in the southeastern region of the municipality of São Paulo. A proportional stratified random probabilistic sample with two strata was selected: schools were drawn and then the children. Three instruments found in the literature were used to create the lifestyle questionnaire. The questionnaire was developed in eight stages: preliminary pretest, cultural adaptation, second pretest, pilot study, semantic correction and adaptation, third pretest, final research and final retest. Cronbach's alpha and pairwise correlation coefficients were used.

RESULTS: The Cronbach's alpha value in the final version was 0.83 and the pre and post-test pairwise correlation coefficients were greater than 0.5. Factor analysis identified five factors that explained 73.51% of the correlation variance. As a result, seven variables were eliminated from the questionnaire.

CONCLUSIONS: The questionnaire described five lifestyle domains, with good reliability, and can be used in combination with preschoolers' health and nutritional outcomes.

RESUMO

CONTEXTO E OBJETIVO: Estilo de vida compreende as atitudes pessoais ou padrões de comportamento que trazem riscos ou benefícios para a própria saúde ou de outros. A saúde das crianças é principalmente determinada pelo estilo de vida da mãe. O objetivo foi desenvolver e avaliar a confiabilidade de um questionário capaz de descrever o estilo de vida de mães de pré-escolares em termos de atividades, interesses, opiniões e valores.

TIPO DE ESTUDO E LOCAL: Estudo transversal conduzido em uma universidade pública.

MÉTODOS: Estudo realizado entre janeiro de 2010 e março de 2011 com 255 mães de pré-escolares residentes na Região Sudoeste do Município de São Paulo. Selecionou-se uma amostra probabilística aleatória estratificada proporcional com dois estratos, sendo sorteadas as escolas e depois as crianças. Três instrumentos foram encontrados na literatura e utilizados para compor o questionário de estilo de vida. O desenvolvimento do questionário cumpriu oito etapas: pré-teste preliminar, adaptação cultural, segundo pré-teste, estudo piloto, correção e adaptação semântica, terceiro pré-teste, pesquisa final e re-teste. Foram utilizados o alfa de Cronbach e coeficiente de correlação *pairwise*.

RESULTADOS: O valor do alfa de Cronbach na versão final foi de 0,83 e o coeficiente de correlação *pairwise* pré e pós-teste foram maiores que 0,5. A análise fatorial identificou cinco fatores, os quais explicaram 73,51% da variância de correlação. Como resultado, sete variáveis foram eliminadas do questionário.

CONCLUSÃO: O questionário descreveu cinco domínios de estilo de vida, com boa confiabilidade, e pode ser utilizado em associações com aspectos nutricionais e de saúde de pré-escolares.

INTRODUCTION

For all age groups, including the pediatric age group, diseases associated with behavior and lifestyle are gaining increased attention. Emerging nations are experiencing epidemiological transitions that create new challenges for the healthcare sector. One epidemiological transition is the decrease in pediatric morbidity and mortality due to infectious diseases, which is progressively diverting attention to the healthy development of children who now enjoy longer life expectancies. For adults, this transition has generated new understanding of the genesis of illnesses and has identified the fundamental role of lifestyle. Several studies have assessed the behavioral lifestyles of young adults;[1-8] however, little has been done regarding the impact of such lifestyles on children's health.

Parental lifestyle, especially the mother's, is a determinant of childhood health because parental lifestyle affects the environment in which the child grows and develops. The effects of this determinant are visible in disease epidemics among children, such as the incidence of overweight or obesity,[9,10] and the high rates of mental disorders present in school-age children.[11]

Lifestyle includes personal attitudes or behavioral patterns that result in risks or benefits to personal health or to the health of others.[8,12] However, most lifestyle studies concentrate more on behavior and less on the motivation behind these behaviors. This motivation includes attitudes, interests, opinions and values that change an individual's pattern of life.[13-20]

In addition to the activities, interests and opinions that are the basis of the mother's lifestyle, it is necessary to understand the mother's values. Values are feelings regarding what is important in relation to a person's goals in life.[21,22] Values also explain why people make decisions. Mothers' personal values need to be understood, because these values translate into particular ways of thinking and acting. Not only the behaviors but also the dimensions involved in the lifestyle of the child's mother need to be identified.

Currently, no instruments are available in Brazil for describing the mother's lifestyle, i.e. the activities, interests, opinions and values that are the expression of the person's pattern of life. Such an instrument could be used in studies relating to preschool child health and nutrition. Children's behavior, personality and health habits are shaped and values are acquired during the preschool years, and all of these characteristics are obtained primarily through the mother's influence. The greatest contribution of such an instrument would be to achieve greater capacity to change parental lifestyles through interventions.

OBJECTIVE

The objective of this project was to develop and evaluate the reliability of a questionnaire capable of describing the lifestyle of preschool-age children's mothers through their attitudes, interests, opinions and values.

METHODS

Population and sample

Between January 2010 and March 2011, a cross-sectional study was conducted among the mothers of preschool-age children (3 to 5 years of age). The target population was the mothers of children who were enrolled in preschools in the Butantã health district in the city of São Paulo (SP, Brazil), which had an estimated population of 427,757 residents in 2010.[23] The percentages of mothers belonging to each socioeconomic class followed the same distribution as shown by the whole population of the city of São Paulo in 2010. The sampling unit was the mother-child pair.

To select the mothers, a proportional stratified random sample was selected with two strata ("school" and "child"). The sampling grid included the entire list of public and private preschools indexed in the regional school directory of Butantã (59 schools; 37 private and 22 public). The directors of five private schools did not allow their children to participate in the study; in the end, the study included 11 public and 7 private schools.

The criteria for inclusion were that the child needed to be properly enrolled and regularly attending classes of the first and second stage, i.e. the first and second years of preschool. Because of the need to collect each child's anthropometric data for analysis along with other outcomes, the criterion for exclusion was a neurological deficiency in the child. The type of deficiency for exclusion was not defined. Exclusion was determined after an analysis on the child followed by the mother's confirmation that the child possessed some type of neurological disorder.

The selection took place in two stages. First, the schools were randomly selected, and the school director was contacted by phone. Then, the children were randomly selected, and an invitation addressed to the mothers was placed in the child's notebook. Next, the mothers who agreed to participate in the study were contacted by a trained field researcher, by phone. Before the study began, the mother read and signed an informed consent form, to signal agreement to participate in the project.

The sample size was calculated using an α of 0.05, a β of 0.10, and a correlation coefficient of 0.5, thus requiring 38 individuals for the questionnaire to be evaluated.[24] However, data were collected from 255 mothers in order to analyze outcomes relating to another study on child health and nutrition.

Study protocol

The interviews were conducted at the mother's house or at the child's school without the influence of a third party. For 102 mothers, a re-test was conducted within 15 days.

Data were collected from the mothers regarding age, socioeconomic class and marital status. Marital status was ascertained according to five categories: single, married, separated, divorced or widowed.

Socioeconomic class was evaluated using the Brazilian Economic Classification Criterion of 2007, developed by the Brazilian Association of Market Research Companies (Associação Brasileira de Empresas de Pesquisa; ABEP),[25] which uses schooling level and the presence of consumer goods in the home to classify individuals into five classes: A, B, C, D and E. Class A has the greatest purchasing power and education level, whereas class E possesses the lowest purchasing power and education level. ABEP's goal was to obtain a standardized scoring system to economically classify families by estimating their consumption capacity.[25]

Questionnaire construction

The questionnaire was developed in accordance with Reichenheim and Moraes.[26] A bibliographic search was conducted to identify projects that evaluated lifestyle questionnaires using the same definition utilized in that study. Three instruments[21,27,28] were found that had already been translated into Portuguese, containing 35 statements regarding values and lifestyle (i.e. personal preferences within various topics), 15 statements regarding self-image (i.e. the image that each person has of their own personality) and 47 statements regarding activities, interests and opinions based on the concept of lifestyle adopted in the present study. However, these instruments had not been validated for the Brazilian population. No Brazilian-validated instrument was found that used the same concepts as those adopted in the present study.

The instrument for the present study was constructed in eight stages: application of the questionnaire statements in a first pretest, cultural adaptation, a second pretest, pilot study, correction and adaptation of the semantics, a third pretest, final study and a re-test. All pre-tests were conducted on a convenience sample of mothers with children in public schools. In this sampling, all the mothers contacted agreed to enter the study, and the tests were conducted either at their home or at the child's school. The pilot study was conducted in two schools (one public and one private), in the same manner as the pretests. The final study was conducted in the home or in the school environment.

In the first pretest, the three instruments identified were administered to 12 mothers of preschool-age children of different social classes. The following response options were used for the questionnaire on values and lifestyle and for the questionnaire on activities, interests and opinions: "I totally disagree", "I partially disagree", "I partially agree" and "I totally agree". For the self-image questionnaire, the responses followed a Likert scale from 1 to 7.

During instrument development, the usefulness of the items and the ease of understanding by the population were taken into consideration. The need for cultural adaptation and content evaluation was noted, because all the mothers in the first pretest requested explanations for the meaning of certain items. Two of the instruments, i.e. values and lifestyle[21] and self-image,[27] for which the psychometric properties were not assessed, were eliminated because they would be difficult for mothers with fewer years of education to complete alone and because the questions were irrelevant within the Brazilian cultural context. Out of the three instruments initially proposed, only 29 selected phrases regarding attitudes, interests and opinions (AIO)[28] were used. These items were similar to those used by Kucukemiroglu in 1997.[14] However, the response options on the new form included "I completely disagree", "I disagree", "I neither agree nor disagree", "I agree", and "I agree completely". In addition, 24 statements on personal values drafted by an expert in the field were added with the following response options: "not important", "slightly important", "important", "very important", and "totally important", since these were the answers that best fitted the type of statement regarding personal values.

The second version of the questionnaire was subjected to a second pretest, which included 10 mothers. This version contained 29 items on activities, interests and opinions and 24 items on personal values. The mothers were asked to indicate whether a question was unclear or whether there was any difficulty in providing a response, as recommended by Ferreira in 2005.[29] None of the mothers reported such difficulties.

All the items tested in the second pretest were put into a pilot study to analyze outcomes relating to another study on child health and nutrition, which that included 50 mothers of preschool-age children from a public school in Vila Sonia and a private school in Butantã. During this phase, four trained field researchers (fourth-year nutrition students) administered the questionnaire. Within a mean interval of approximately 7 days (a minimum of 2 days and a maximum of 14 days), a re-test was conducted on 50 mothers. To evaluate the clarity of the questions, the mothers were asked to report any feelings of uncertainty by choosing one of the following responses at the end of the questionnaire: "I did not understand anything", "I understood little", "I understood it more or less", "I understood almost everything, but I have some uncertainties", or "I understood everything completely", as recommended by Ferreira in 2005.[29]

The need to semantically adapt the items was noted. The items used in the pilot study were semantically modified by a Portuguese teacher. Thus, a final version of the questionnaire was created, which was then subjected to a third pretest with six mothers. Among these mothers, none identified any confusing elements or difficulties in responding. A total of 28 mothers participated in the pretest, which was close to Pasquali's recommendation of 30, in 1998.[30] None of the mothers who participated in the pretests and the pilot study participated in the final study.

The final study used the version of the questionnaire that included the changes added after the second pretest and which was tested in the third pretest. The same field researchers who collected the data in the pilot study collected the data for the final study, again by means of interviews. There was no self-administration of questionnaires. The average time taken by the

researcher to fill out the questionnaire with the mother's answers was 12 minutes (range: 5 to 19 minutes).

Statistical analyses

The categorical variables were described according to their frequencies in percentages and 95% confidence intervals, to obtain the precision of the estimate. The mothers' ages were described using the mean and standard deviation.

The reliability of the instrument was evaluated using two statistical measurements: for internal consistency, Cronbach's alpha greater than 0.7 was used as the cutoff point;[31] and for temporal stability (comparing responses in the first application with those of the re-test), a pairwise inter-observer correlation coefficient greater than 0.5 was used.[18] The pairwise correlation coefficient assessed the agreement of the responses between the test and re-test.

Factor analysis was used to evaluate the data for patterns and reduce the many variables to a manageable number.[32] As a prerequisite for conducting factor analysis, two tests were performed. Bartlett's test of sphericity was used to assess the adequacy of the correlation matrix. Next, the Kaiser-Meyer-Olkin measurement of sampling adequacy was used to determine whether the correlation patterns between the variables were compact or scattered.[33] The results from this analysis were used to determine whether the factor analysis would be capable of producing different and reliable factors (positive result ≥ 0.6).

After applying these two tests, the factor analysis was performed in three steps: identifying eigenvalues > 1; constructing a scree plot;[31] and performing a parallel analysis. An eigenvalue greater than one indicates the amount of variance that each factor represents within the total variance.[31,32] The second criterion, the scree plot, uses the point where the curve begins to level off as the criterion. Finally, a parallel analysis was performed, which consisted of performing 10 repetitions of the mothers' random responses to compare the eigenvalues of the questionnaire with the eigenvalues of the parallel analysis. After the parallel analysis, oblique rotation was used to obtain the values of each item within each factor chosen (correlation of each item within each factor).[31,32] The codes of the items with negative load values were reversed during the statistical analysis. Only those items with load values greater than 0.32 or less than -0.32 from the formula $5.152/\sqrt{N-2}$ were included, as suggested by Norman and Streiner.[32] Each factor was named using its items with the greatest load and combining the meaning of all the items that it comprised. Factor 1 was named "Personal values", factor 2 "Family life", factor 3 "Bohemian", factor 4 "Socially conscious" and factor five "Modern". Version 10.0 of the STATA statistical package was used to perform these analyses.

Ethics committee

The research protocol was approved by the Research Ethics Committee of the Clinical Hospital of the School of Medicine at the University of São Paulo. The study was developed with the approval of the Butantã Regional Board of Education.

RESULTS

The median age and standard deviation of the participants were 32.9 and 6.21 years, respectively. The percentages of mothers with children in public and private schools were 80% (204) and 20% (51), respectively. **Table 1** shows the sample characteristics.

The value of Cronbach's alpha in the version applied in the pilot study was 0.81, and the value of the final version of the instrument (after semantic and cultural revision) was 0.83. The pairwise correlation coefficients for the test-retest also improved from the pilot study to the final application of the instrument (in each stage with 53 items), with all values greater than 0.50.

Bartlett's test of sphericity produced a P-value < 0.001, and the Kaiser-Meyer-Olkin (KMO) measurement of sampling adequacy was 0.815. Both results confirmed that the data matrix could be subjected to factor analysis.

Factor analysis identified 53 lifestyle factors. Using both criteria (eigenvalue > 1 and scree plot), we could maintain six factors. However, the eigenvalue of the sixth factor was similar to the eigenvalue of the parallel analysis. Beyond the sixth factor, there was still a slight slope on the curve. Five factors explained 73.5% of the variance of intercorrelations. These factors were chosen to undergo oblique rotation. **Table 2** shows the load values of each item within each factor, and the eigenvalues, percentage of variance and alpha coefficient of each factor.

Table 1. Sample characteristics according to the number, proportion and confidence interval of the economic classification, education level and marital status of the mothers of preschool-age children, southeastern region of the city of São Paulo (SP), 2011

	n	%	Confidence interval (95%)
Economic classification			
A	22	8.6	5.5 to 12.8
B	100	39.2	33.2 to 45.5
C	120	47.1	40.8 to 53.4
D	11	4.3	2.2 to 7.6
E	2	0.8	0.1 to 2.8
Educational level			
Illiterate	4	1.6	0.4 to 4.0
Grades 1-4 of elementary school completed	31	12.2	8.4 to 16.8
Elementary school completed	61	23.9	18.8 to 29.6
High school completed	114	44.7	38.5 to 51.0
University/college-level completed	45	17.6	13.2 to 22.9
Marital status			
Single	58	22.7	17.7 to 28.4
Married	169	66.3	60.1 to 72.1
Divorced	10	3.9	1.9 to 7.1
Separated	16	6.3	3.6 to 10.0
Widowed	2	0.8	0.1 to 2.8

Table 2. Description of the load values of each item, eigenvalue, % variance, number and alpha value of the items for each factor, southeastern region of the city of São Paulo (SP), 2011

Item	Load values				
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
I look for good prices.		0.39			
I am accustomed to having the most fashionable clothes.					0.44
I prefer to stay at home instead of going to a party.			-0.56		
I participate in a group of people who help in the community.				0.72	
When my children are sick, I stop doing other things to care for them.		0.33			
I think it is important that children pick up their toys.		0.52			
My friends and neighbors look for me, for advice.				0.47	
I check prices, even for small items.		0.39			
I choose fashionable clothes, even if they are uncomfortable.					0.35
I like parties where there is music and conversation.			0.50		
I do volunteer work.				0.69	
Being a mother is the most important thing in my life.		0.36			
My house is clean and organized.		0.40			
I inform myself before buying.		0.40			
In the next five years, the family income will be greater than it is now.		0.33			
I find good deals through TV advertisements.					0.41
Dressing in fashionable clothes is important.					0.56
I am a homebody.			-0.56		
It is enjoyable to work for the community.				0.63	
I clean my house for the comfort of my family.		0.65			
I like when my house is clean.		0.71			
One saves a lot of money by finding good prices.		0.45			
I experiment with fashionable hairstyles.					0.5
I teach good habits to my children.		0.61			
Having money	0.51				
Relationships with friends.			0.34		
Work/job	0.52				
Education	0.46				
Fun			0.49		
Material comfort	0.60				
Saving money	0.57				
Family relationships	0.43				
Good health	0.41				
Accomplishing goals	0.56				
Relationship with children	0.48				
Achieving recognition at work	0.62				
Living according to religious rules	0.36				
Good living conditions	0.62				
Good and long-lasting loving relationships	0.34				
A life of achieved dreams	0.74				
Respect for others	0.66				
Making the most of life	0.58				
Security in life	0.64				
Self-respect	0.54				
Feeling of having achieved goals	0.63				
Reaching God	0.48				
Eigenvalues	8.52	2.84	2.22	2.17	1.82
% variance	16.07	5.35	4.19	4.09	3.43
Number of items	20	12	5	4	5
Cronbach's alpha	0.9	0.74	0.63	0.61	0.72

The load values that were greater than 0.32 and less than -0.32 were selected, which resulted in elimination of seven variables from the lifestyle questionnaire. After eliminating these items, the value of Cronbach's alpha was 0.85.

The final questionnaire with the names of the factors and each of the items with its response options is presented in **Appendix A**.

Factor 1 related to mothers whose actions and behaviors were based on values built throughout life. Factor 2 referred to mothers for whom the link with their homes, such as organizing the household and taking care of their children, was the most important issue. High scores in factor 3 implied that this was a person for whom leisure and pleasure were very important. Seeking fun was one of its main characteristics. Factor 4 identified mothers who were interested in helping other people.

Last but not least, factor 5 identified mothers who focused on fashion-related matters.

A mother with a bohemian lifestyle could also be a mother with a socially conscious lifestyle, i.e. none of these five factors were exclusive of the others. Rather, the factors would best be used to compare mothers with higher or lower scores for each factor.

DISCUSSION

This study developed an easily administered instrument that characterized mothers into five lifestyles according to a sociological paradigm. It had a randomized design in which information was collected from mothers on their health and nutritional behaviors and risks. These data included information on nutritional state, diet, morbidity, physical activity and use of health services by their preschool-age children. Analyses on the correlations of these outcomes with the five lifestyles described in the present study will be presented in future articles.

The mothers' attitudes, interests, opinions and values determined which of the five lifestyle dimensions they possessed, which then potentially influenced the health and nutrition of their preschool-age children.

Describing lifestyle is a difficult task because of the multidimensionality of its makeup and because of the inherent difficulty of measuring a subjective phenomenon in an objective manner. Previous studies in this field have used instruments for measuring healthy lifestyle behaviors;[8] however, no studies were found that evaluated maternal lifestyle in relation to preschoolers by examining their mothers' activities, interests, opinions and values. Marketing studies have been published that establish relationships between lifestyle dimensions and eating habits among adults.[17]

The questionnaire consisted of two sections. The first section contained 29 items relating to activities, interests and opinions. The second section contained 24 items on the mothers' personal values.

In the pilot study, the value obtained for Cronbach's alpha was within the acceptable range, thus demonstrating that the questionnaire presented good reliability. However, the majority of the items in the questionnaire had a pairwise correlation coefficient in the re-test that was less than 0.5. This result may have occurred because the items used adverbs and negative words in a way that made responding difficult. In addition, the items were extensive and ambiguous, and conveyed more than one idea. Bias intrinsic to questionnaire responses made it necessary to change the items in the pilot study and, following revision, the items moved in a direction that was different to what had originally been proposed. Moreover, it had to be taken into consideration that the mothers needed to remember what type of behavior they exhibited with regard to the item in question. In evaluating the item and remembering past actions, it was also necessary for mothers to estimate or infer their own behavior. Even after addressing all of these potential problems, the mothers still could have had difficulties differentiating between the types of responses.[31]

In the final study, the internal consistency assessed by Cronbach's alpha was lower than the value of 0.92 obtained by Kucukemiroglu in 1997.[14] In that study, the questionnaire contained 56 activity, interest and opinion items that were similar to those used in the questionnaire of the present study, and 532 respondents were tested. However, when the value is less than 0.7, the questionnaire most likely addresses a construct that is different to the one that it seeks to measure, whereas when the alpha is greater than 0.9, there is an extremely high correlation due to item redundancy.[34,35] For three of the lifestyle factors, the value of Cronbach's alpha was less than 0.7 in the present study. The reason for this result was the small number of items in each factor, given that the alpha can be influenced by the number of items that compose it.

The test-retest reproducibility indicated that there was stability in the respondents' lives if the first responses were equal to or similar to those in the subsequent interview. It is important to take into consideration the time that passed between the two evaluations. In this study, the average time interval until the retest was within the recommended timeframe of 2 to 14 days.[31,32] This timeframe was chosen to reduce the possibility of large changes and the possibility that the instrument could produce false reliability.

After conducting factor analyses to determine the existence and characteristics of the lifestyle dimensions, the phrases relating to the activity, interest, opinion and value questionnaire were subjected to varimax rotation to correct certain aspects, such as those described below. The first aspect related to the generality and the high number of items belonging to factor 1. This outcome occurred because all of the measurements were conducted on the same individuals, thus favoring correlation among the items. The second aspect involved the bipolarity of the items, which made it difficult to discern which factor an item belonged to.

The third aspect was the factorial complexity of the items. In other words, without rotation, the item possessed a load value that was similar in two factors. Finally, the item might possess an average load value, whereas it would be preferable for the value to be at one of the extremes.[32]

This instrument enables measurements that can be used to compare the degree of exposure to each of the factors considered. Consequently, studies that use this instrument will be able to classify the participants into terciles of low, medium and high scores for each of the factors. This is not a questionnaire that classifies according to scores. The scoring achieved in each domain may be compared with children's nutritional characteristics, for example. In different cultures, the exposure to a specific lifestyle may imply different outcomes. Identification of the five lifestyle dimensions will, for example, make it possible to understand how the nutritional state, eating habits, morbidity and physical activity of a child correspond to the modern or economic dimension. For example, does the fact that a mother prefers to save money cause her child to have better or worse eating habits?

The limitations of this study were that we could not proceed with criterion validation because of a lack of a reference instrument for activities, interests, opinions and values; and that the questionnaire, as it was applied, was intended for use with young adult women.

The present study is part of a larger one. A future paper will demonstrate the validation of the construct. Currently, maternal lifestyle is correlated with some behavioral patterns relating to children's health. In this regard, maternal activities, interests, opinions and values are possible social and cultural determinants of children's obesity and behavior disorders.

CONCLUSIONS

The questionnaire developed here is the first instrument to describe five lifestyle domains according to the attitudes, interests, opinions and values of the mothers of preschool-age children in Brazil. The instrument content was evaluated and had good reliability as determined through Cronbach's alpha and pairwise correlation coefficients.

The present questionnaire, "Lifestyle Activities, Interests, Opinions and Values", is a tool that may be of great value in helping healthcare professionals to understand the motivations behind risky maternal behavior in relation to the health of preschoolers, thereby enabling interventions that may be more effective.

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Appendix A. Questionário de estilo de vida atividades, interesses, opiniões e valores (Questionnaire on lifestyle activities, interests, opinions and values)

Para o domínio "valores pessoais", informe o grau de importância que você atribui a alguns aspectos de sua vida. Para os demais domínios, responda às afirmações usando as seguintes categorias de resposta: discordo totalmente, discordo, não concordo e nem discordo, concordo e concordo totalmente.						
Estilo de vida	**Item**	**Opções de resposta**				
Valores pessoais	Ter saúde.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Ter estudo.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Trabalho/emprego.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Ser reconhecido no trabalho.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Ter dinheiro.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Guardar dinheiro.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Conforto material.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Uma boa condição de vida.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Realização dos sonhos.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Uma vida de sonhos realizados.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Sentimento de ter alcançado o que desejei.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Aproveitar a vida.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Relacionamento familiar.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Relacionamento com os filhos.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Relacionamentos amorosos bons e duradouros.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Ter respeito a mim mesmo.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Ter o respeito das pessoas.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Segurança para viver.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Viver de acordo com as regras religiosas.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Chegar a Deus.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
Vida familiar	Ser mãe é a coisa mais importante da minha vida.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Quando meus filhos ficam doentes, deixo de fazer algumas coisas para cuidar deles.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Ensino bons hábitos aos meus filhos.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente

Continues

Appendix A. Continuation

Para o domínio "valores pessoais", informe o grau de importância que você atribui a alguns aspectos de sua vida. Para os demais domínios, responda às afirmações usando as seguintes categorias de resposta: discordo totalmente, discordo, não concordo e nem discordo, concordo e concordo totalmente.						
Estilo de vida	**Item**	**Opções de resposta**				
Vida familiar	Acho importante as crianças arrumarem os brinquedos.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Arrumo a minha casa para o conforto da família.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Gosto quando minha casa está limpa.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Minha casa é limpa e arrumada.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Procuro por bons preços.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Me informo antes de comprar.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Eu verifico preços mesmo para itens pequenos.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Daqui a cinco anos o salário da família será maior do que agora.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Uma pessoa economiza um bom dinheiro procurando bons preços.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
Boêmio	Sou uma pessoa caseira.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Prefiro ficar em casa em vez de ir a festas.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Gosto de festas onde há música e conversa.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Divertimento.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
	Relacionamento com os amigos.	Nada importante	Pouco importante	Importante	Muito importante	Totalmente importante
Consciente socialmente	Faço trabalho voluntário.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	É gostoso trabalhar para a comunidade.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Participo de um grupo de pessoas que ajuda a comunidade.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Meus amigos e vizinhos me procuram para que eu os aconselhe.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
Moderno	Vestir roupas da moda é importante.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Costumo ter uma ou mais roupas da moda.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Escolho roupas da moda mesmo sendo desconfortáveis.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Encontro bons preços nas propagandas de TV.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente
	Experimento os cortes de cabelo da moda.	Discordo totalmente	Discordo	Não concordo e nem discordo	Concordo	Concordo totalmente

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Presence of *Mycobacterium avium* subsp. *paratuberculosis* (MAP) in Brazilian patients with inflammatory bowel diseases and in controls

Presença de *Mycobacterium avium* subsp. *paratuberculosis* (MAP) em pacientes brasileiros com doença inflamatória intestinal e em controles

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PALAVRAS-CHAVE:
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ABSTRACT

CONTEXT AND OBJECTIVE: *Mycobacterium avium* subsp. *paratuberculosis* (MAP) has attracted the interest of researchers because of similarities between paratuberculosis and Crohn's disease (CD). The aim of this study was to evaluate the frequency of MAP through cultures, histology and polymerase chain reaction (PCR) on intestinal biopsies from Brazilian CD patients. Quantitative real time PCR (qRT-PCR) was performed on positive samples.

DESIGN AND SETTING: Analytical cross-sectional study with control group at two federal universities.

METHODS: Fresh samples were collected from 25 patients; five with CD, eight with ulcerative colitis (UC) and 12 controls with non-inflammatory bowel disease (nIBD). Formalin-fixed paraffin-embedded (FFPE) samples from 143 patients were also collected: 44 CD, 49 UC and 56 nIBD.

RESULTS: None of the fresh samples was positive for MAP. Five FFPE samples (one CD, two UC and two nIBD) and three fresh samples (one in each group) were positive through IS*900*-PCR. qRT-PCR was performed on these eight samples. Among the FFPE samples, there were 192.12 copies/µl in the CD group, 72.28 copies/µl in UC and 81.43 copies/µl in nIBD. Among the fresh samples, there were 432.99 copies/µl, 167.92 copies/µl and 249.73 copies/µl in the CD, UC and nIBD groups, respectively. The highest bacterial load was in the CD group.

CONCLUSION: This study does not provide evidence for a role of MAP in the etiology of CD, although MAP DNA was detected in all three patient groups. This is the first report of MAP presence in human intestinal biopsies in Brazil.

RESUMO

CONTEXTO E OBJETIVO: *Mycobaterium avium* subsp**.** *paratuberculosis* (MAP) tem atraído o interesse de pesquisadores devido às semelhanças entre a paratuberculose e a doença de Crohn (CD). Este estudo objetivou avaliar a frequência de MAP por meio de cultura, histologia e reação da polimerase em cadeia (PCR), em biópsias intestinais de pacientes brasileiros com CD. PCR quantitativa em tempo real (qRT-PCR) foi realizada nas amostras positivas.

TIPO DE ESTUDO E LOCAL: Estudo transversal analítico com grupo controle realizado em duas universidades federais.

MÉTODOS: Amostras frescas foram coletadas de 25 pacientes; cinco com CD, oito com colite ulcerativa (UC) e 12 controles sem doença inflamatória intestinal (nIBD). Também foram coletadas 149 amostras fixadas em parafina (FFPE): 44 CD, 49 UC e 56 nIBD.

RESULTADOS: Nenhuma das amostras frescas foi positiva para MAP. Cinco amostras FFPE (uma CD, duas UC e duas nIBD) e três amostras frescas (uma de cada grupo) foram positivas por IS*900*-PCR. qRT-PCR foi realizada nessas oito amostras. Nas amostras FFPE, havia 192,12 cópias/µl no grupo CD, 72,28 cópias/µl no UC e 81,43 cópias/µl no nIBD. Nas amostras frescas, havia 432,99 cópias/µl, 167,92 cópias/µl e 249,73 cópias/µl nos grupos CD, UC e nIBD, respectivamente. A maior carga bacteriana foi encontrada no grupo CD.

CONCLUSÃO: Este estudo não fornece evidências do papel de MAP na etiologia da CD, embora DNA de MAP tenha sido detectado em pacientes dos três grupos. Este é o primeiro relato da presença de MAP em biópsias intestinais humanas no Brasil.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the human gastrointestinal tract. It has increasing incidence worldwide, and unknown etiology.[1] Paratuberculosis is a form of chronic granulomatous enteritis, caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP), which affects all species of ruminants worldwide.[2] Because of the similarities between paratuberculosis and CD, the possibility of an infectious etiology for this disease has been widely discussed and MAP has attracted the interest of many researchers.[3,4]

MAP has been detected by means of cultures and the polymerase chain reaction (PCR) in patients with CD.[3,5-8] Numerous theories about a possible cause for CD have been postulated over the years.[9] Scientific evidence supports the theory of an interaction between a persistent environmental stimulus (such as a microbial antigen) and genetic factors that regulate the immune response and/or function of intestinal mucosa.[10,11] However, it would be simplistic to conclude that one agent is solely responsible for the etiology of CD: a multifactorial cause is more likely.[4,12]

Several studies investigating these causes have been conducted, and they suggest that, although further research is required, an association between MAP and CD cannot be ruled out.[3,4,13] Some researchers believe that most CD cases are not caused by "infection with MAP" although they do not neglect the extremely strong suspicion that MAP plays a role in the pathogenesis of CD.[14]

OBJECTIVE

The aim of this study was to evaluate the frequency of MAP in fresh and formalin-fixed paraffin-embedded intestinal biopsies, through culture and molecular techniques. The samples were collected from CD patients attending a referral center for treatment of intestinal diseases in the state of Minas Gerais, Brazil.

METHODS

Patients and samples

Fresh tissues

Fresh samples were collected prospectively and randomly, using sterile biopsy forceps, from patients undergoing routine ileocolonoscopy as part of their normal clinical treatment in the Instituto Alfa de Gastroenterologia (IAG), Hospital das Clínicas (HC), Universidade Federal de Minas Gerais (UFMG), in 2011-2012. Prior to sample collection, informed consent was obtained from each individual. The confirmation of CD in each patient was based on clinical, radiological, endoscopic and histopathological findings. Patients with other inflammatory bowel diseases were included in the ulcerative colitis (UC) group. Patients diagnosed with non-inflammatory bowel disease (nIBD) were those who underwent ileocolonoscopy without a clinicopathological diagnosis of any inflammatory disease. The inclusion criteria for this study were identification of the patient's condition and informed consent received from the patient.

Samples were collected from 25 patients, comprising five patients with CD, eight with UC and 12 with nIBD. From each patient, six biopsy specimens were collected: three samples from the terminal ileum and three samples from the ascending colon. Four samples from each patient (two ileum and two colon samples) were placed in 1.5 ml microcentrifuge tubes containing Middlebrook OADC broth supplemented with 20% autoclaved glycerol, and were then stored in liquid nitrogen for subsequent microbiological culturing and DNA extraction. The remaining two samples (one ileum and one colon sample) were placed in 1.5 mL microtubes containing buffered formalin for subsequent histological analysis. For patients with CD and UC, samples were collected from inflamed and uninflamed parts of the mucosa.[6]

Formalin-fixed paraffin-embedded tissues

We obtained 149 paraffin blocks from biopsies on 143 patients who were attended at HC-UFMG between 2009 and 2011. This material was produced in the Pathology Laboratory of IAG-HC-UFMG. In the same way as with the fresh samples, the paraffin blocks were also categorized into three groups: 56 samples from patients with nIBD, 44 from patients with CD and 49 from patients with UC. From each block, two slides for histopathological analysis were prepared and three slices of 10-20 μm thickness were used for DNA extraction.

Samples were selected by convenience and their power to detect differences was estimated to be between 50% and 80%, according to Pocock's table[15] ($p1 = 0.04$; $p2 = 0.10$; $f(\alpha,\beta) = 4.17$).

Tissue processing and MAP cultures

Samples for cultivation were taken to the Bacterial Diseases Laboratory, Universidade Federal de Viçosa (LDBAC-UFV), where they were macerated and decontaminated as described by Bull et al.[6] and Sechi et al.[8] Briefly, for decontamination, 0.5 ml of 2% NaOH was added to the samples, and they were left to rest for 20 minutes at room temperature. Subsequently, the samples were centrifuged at 3000 x *g* for 30 minutes; the supernatant was discarded, and the pellet was washed with 10 ml of phosphate-buffered saline (PBS). After washing, the pellet was resuspended in 0.5 ml of TEN buffer (50 μM of Tris-HCl, 100 mM of EDTA and 150 mM of NaCl; pH 8). Aliquots of 100 μl of the suspension were inoculated into four tubes of Herrold Egg Yolk Medium (HEYM): two with mycobactin *J* and two without mycobactin *J*. The remaining 100 μl were inoculated into a tube containing Middlebrook 7H9 broth, supplemented with Middlebrook OADC and mycobactin *J*, and all the tubes were incubated at 37 °C for up to 30 weeks.

DNA extraction and PCR

For DNA extraction, the Wizard genomic DNA purification kit was used in accordance with the manufacturer's recommendations and the extracted DNA was stored at 8 °C for later use. PCR reactions were performed on all samples. Go Taq Green Master Mix was used in accordance with the manufacturer's instructions and the primers BN1 (5'-GTT ATT AAC GAC GCC CAG C-3') and BN2 (5'-ACG ATG CTG TGT TGG GCG TTA G-3'),[16] based on the insertion sequence IS*900*, which amplifies a fragment of 626 bp, were used. Each reaction had a total volume of 25 µl, comprising: 12.5 µl of mix, 1 µl of each primer at the initial concentration of 10 pmol/µl, 6.5 µl of ultrapure water and 4 µl of DNA extracted at a concentration of approximately 200 µg/µl. PCR was carried out as recommended by Sivakumar et al.,[16] i.e. initial denaturation at 94 °C for four minutes, 30 cycles of 94 °C for one minute, 60 °C for one minute, 72 °C for one minute and a final extension step at 72 °C for four minutes.

To confirm the DNA extraction process, PCR reactions were performed to target a region of the human *APC* gene, using the primers F (5'-CCC CTC CAA ATG AGT TAG CTG C-3') and R (5'-CTCTGC TTT ATT GTC ATC CAA TTC A-3').[17] Amplified fragments were viewed by means of electrophoresis, on 1% agarose gel in tris-borate-EDTA (TBE) stained with GelRed nucleic acid gel stain, using an ultraviolet transilluminator. A 100 bp ladder was used as a molecular size marker and ultrapure water was used as a negative control.

Sequencing and genetic analysis

Amplified fragments were extracted and purified from agarose gel using the Wizard SV gel and PCR clean-up system, in accordance with the manufacturer's instructions. Subsequently, both strands were sequenced in triplicate. The sequences were edited using the DNAMAN software, and then compared with the sequence of the MAP K-10 strain, which has been deposited in GenBank, using the Basic Local Alignment Search Tool (BLAST) software, which is available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov).

Histopathological analysis

The samples stored in buffered formalin were processed in accordance with the routine procedures of the Histopathology Laboratory, Veterinary Department, Universidade Federal de Viçosa (DVT/UFV). Paraffin-embedded material was used in preparing slides, which were then stained with Ziehl-Neelsen (ZN) to ascertain whether acid-fast bacilli were present.

Quantitative real time PCR (qRT-PCR)

qRT-PCR was performed on the samples that were found to be positive through PCR. Reactions with absolute quantitation were performed in duplicate on plates with 48 wells using the TaqMan Universal Master Mix II (Applied Biosystems, Foster City, CA, USA). Genomic quantitation of each sample was generated by means of the detection software through the Eco real-time PCR system, and this was compared with the standard curve of the bacterial genome (10^6 to 10^1 copies) using the values of the quantification cycle (Cq) for each reaction. The reaction used the primers MPF (5'-CCG CTA ATT GAG AGA TGC GAT T-3') and MPR (5'-CCA GAC AGG TTG TGC CAC AA-3'), which were based on the IS*900* insertion sequence and the specific probe (5'-FAM-ACC TCC GTA ACC GTC ATT GTC CAG ATC A-TAMRA-3').[18] The initial concentration of the sample for constructing the standard curve was determined by using the following formula, in accordance with the QuantiFast SYBR green PCR handbook (Qiagen, Valencia, CA, USA):

$$\text{molecules/ml} = \frac{\text{concentration of DNA (g/ml)}}{\text{size of DNA (bp)} \times 660 \times 6.022 \times 10^{-23}}$$

For each reaction (total of 20 µl), we used 10 µl of Mix II, 1 µl of each primer at the initial concentration of 10 pmol/µl, 5.5 µl of nuclease-free water, 2 µl of DNA and 0.5 µl of specific probe at the initial concentration of 10 pmol/µl. Amplifications were performed as described by Herthnek et al.,[18] and are briefly described here: incubation for two minutes at 50 °C followed by activation of polymerase for 10 minutes at 95 °C; after this pretreatment, the samples were subjected to 45 cycles of 95 °C for 15 seconds and 60 °C for one minute.

Statistical analysis

All the statistical analyses were performed using the Statistica 7.0 software (StatSoft Inc, 2007). The data were subjected to analysis of variance (ANOVA) and means were compared using the F test. In cases of significant differences Tukey's test was used at 5% probability ($P < 0.05$).

Ethical considerations

This study was approved by the Research Ethics Committee of Universidade Federal de Minas Gerais (UFMG) (ETIC no. 0471.0.203.000-10). All participants provided documented informed consent prior to taking part in this study.

RESULTS

Patients

Fresh samples were collected from 14 male and 11 female patients, whose mean age was 46.5 years, (range 23-74 years; **Table 1**). One hundred and forty-nine formalin-fixed paraffin-embedded samples were collected from 143 patients: 56 males and 87 females whose mean age was 40.5 years (range 2-83 years). Six samples were collected from patients from whom samples were taken at

two different times. The samples were divided into three groups: 44 from patients with CD, 49 from patients with UC and 56 from patients with nIBD (**Table 2**).

MAP cultures

Fresh samples from CD, UC or nIBD patients did not provide any positive result for viable MAP with any culture medium used in this study, even after 30 weeks.

PCR

DNA was extracted successfully from all samples. In five formalin-fixed paraffin-embedded samples, fragments of a size similar to what was expected were amplified by means of PCR: 1/44 (2.3%) from patients with CD, 2/49 (4%) from patients with UC and 2/56 (3.5%) from patients with nIBD. However, these differences between the groups were not statistically significant (**Table 3**). In three fresh samples, fragments of a size similar to what was expected were amplified: 1/5 (20%) from patients with CD, 1/8 (12.5%) from patients with UC and 1/12 (8.3%) from patients with nIBD. These differences between the groups were not statistically significant (**Table 3**).

Sequencing and genetic analysis

All the amplicons of size 626 bp were sequenced; genetic analysis revealed that these amplicons were 97-99% identical to the sequence of the MAP K-10 strain, which is available in the NCBI database.

Histopathological analysis

Among the formalin-fixed paraffin-embedded samples, acid-fast bacilli were identified (**Figure 1**) on 15/149 (10%) of the slides stained with ZN. These comprised 9/44 (20.4%) from patients with CD, 1/49 (2%) from patients with UC and 5/56 (8.9%) from patients with nIBD. The mean detection rate for acid-fast bacilli in the CD group was 10 times higher than in the UC group ($P < 0.01$); there were no statistically significant differences between the CD and nIBD groups, or between the UC and nIBD groups (**Table 4**). Among the fresh samples, acid-fast bacilli were detected on 1/25 (4%) of the slides, from one patient with UC. Acid-fast bacilli were not identified on slides from patients with CD or nIBD. Among the fresh samples, the differences between the groups were not statistically significant (**Table 4**).

Table 1. Characteristics of patients with Crohn's disease (CD), ulcerative colitis (UC) and non-inflammatory bowel disease (nIBD) (controls): fresh samples included in the study

	CD	UC	nIBD	Total
n	5	8	12	**25**
Age at time of biopsy, mean (range)	26 (23-29)	49.2 (31-74)	49.5 (32-70)	
Female sex	3 (60%)	4 (50%)	4 (33%)	**11**
Male sex	2 (40%)	4 (50%)	8 (67%)	**14**

Table 2. Characteristics of patients with Crohn's disease (CD), ulcerative colitis (UC) and non-inflammatory bowel disease (nIBD) (controls): formalin-fixed paraffin-embedded samples included in the study

	CD	UC	nIBD	Total
n	44	49	56	**149**
Age at time of biopsy, mean (range)	40.5 (11-77)	37 (2-77)	44.5 (13-83)	
Female sex	24 (54.5%)	32 (65.3%)	34 (60.7%)	**87**
Male sex	20 (45.5%)	17 (34.7%)	22 (39.3%)	**56**

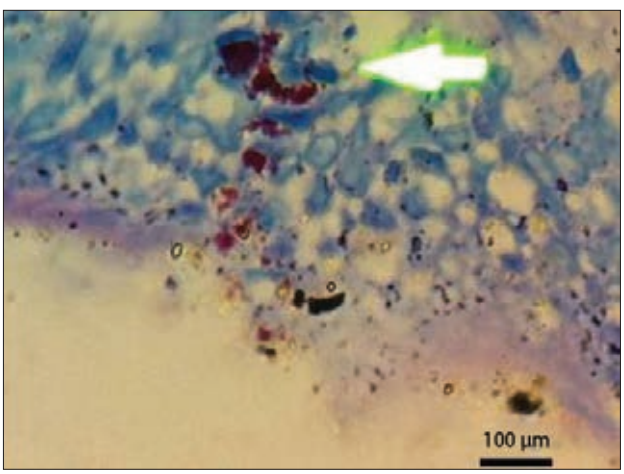

Figure 1. Acid-fast bacilli in the intestinal mucosa of a patient with Crohn's disease, with Ziehl-Neelsen staining.

Table 3. Relationship between IS*900* PCR results and clinical groups of patients

Group	Paraffin-embedded samples		Fresh samples		Total
	n	IS*900* PCR +	n	IS*900* PCR +	
CD	44	1 (2.3%)[a]	5	1 (20%)[b]	**49**
UC	49	2 (4%)[a]	8	1 (12.5%)[b]	**57**
nIBD	56	2 (3.5%)[a]	12	1 (8.3%)[b]	**68**
Total	**149**	**5 (3.3%)**	**25**	**3 (12%)**	**174**

Results followed by the same letters did not differ statistically according to Tukey's test at 5% probability. Paraffin-embedded samples: $F = 0.1211$, $P = 0.8860$; fresh samples: $F = 0.2051$, $P = 0.8161$. CD = Crohn's disease; UC = ulcerative colitis; nIBD = non-inflammatory bowel disease; PCR = polymerase chain reaction.

Table 4. Relationship between presence of acid-fast bacilli and clinical groups of patients included in the study

Group	Paraffin-embedded samples		Fresh samples		Total
	n	acid-fast bacilli +	n	acid-fast bacilli +	
CD	44	9 (20.4%)[a]	5	0 (0%)[c]	**49**
UC	49	1 (2%)[b]	8	1 (12.5%)[c]	**57**
nIBD	56	5 (8.9%)[a,b]	12	0 (0%)[c]	**68**
Total	**149**	**15**	**25**	**1**	**174**

Results followed by the same letters did not differ statistically according to Tukey's test at 5% probability. Paraffin-embedded samples: $F = 4.5879$, $P = 0.0117$; fresh samples: $F = 1.0686$, $P = 0.3607$. CD = Crohn's disease; UC = ulcerative colitis; nIBD = non-inflammatory bowel disease.

qRT-PCR

qRT-PCR was performed on eight samples that were positive according to PCR (five formalin-fixed paraffin-embedded and three fresh samples). Among the formalin-fixed paraffin-embedded samples, we observed values of 192.12 copies/μl in the CD group, 72.28 copies/μl in the UC group and 81.43 copies/μl in the nIBD group. Among the fresh samples, we observed values of 432.99 copies/μl, 167.92 copies/μl and 249.73 copies/μl in the CD, UC and nIBD groups, respectively (**Table 5**).

DISCUSSION

Studies that included children have been more likely to report a positive result for MAP than those with an adult population.[3] Dell'Isola et al.[19] suggested that if the initial MAP infection occurred during childhood, detection of this infection would be more likely in studies among children. However, in the present study, inclusion of children (formalin-fixed paraffin-embedded samples) did not influence our results.

MAP culturing from human intestinal biopsy material is quite difficult, even under optimal conditions. However, several research groups have been able to grow MAP from tissues from patients with CD, using classical culturing methods, with success rates ranging from 0-40%.[13]

MAP isolates from humans not only present the usual sample decontamination requirements and have very slow growth, but also occur in spheroplasts (a cell wall-deficient form), which are extremely hard to isolate, recover and maintain in sufficient numbers for studies.[20]

Additionally, MAP isolation may also have been negatively affected by the freezing of the samples. It was not possible to work with fresh samples because of the distance between HC/UFMG and LDBAC. Freezing of samples before processing was therefore necessitated and even though a cryoprotectant was used, the ideal would have been for the tissues to have been processed immediately.[6]

Although MAP was not isolated in this study, it is important to highlight that MAP has only been recovered from human tissues with CD. This microorganism has never been isolated from patients with UC or nIBD.[13]

Table 5. Relationship between qRT-PCR results and clinical groups of patients

Group	Paraffin-embedded samples		Fresh samples		Total
	n	qRT-PCR +	n	qRT-PCR +	
CD	1	192.12	1	432.99	**2**
UC	2	72.28	1	167.92	**3**
nIBD	2	81.43	1	249.73	**3**
Total	**5**		**3**		**8**

CD = Crohn's disease; UC = ulcerative colitis; nIBD = non-inflammatory bowel disease; PCR = polymerase chain reaction.

The PCR results regarding MAP detection have been inconclusive and conflicting. Reports have ranged from 0-100% detection in each group (CD, UC and nIBD) using a variety of different methodologies and target sequences.[3,4] Contrary to other studies in this field,[5-7] MAP was not detected more frequently among our patients with CD than among those with UC or nIBD. However, other research groups have shown that MAP detection in patients with CD occurs more frequently than in patients with UC or nIBD.[21,22]

In this study, we observed the presence of MAP DNA in intestinal biopsy specimens from eight patients among the 174 samples tested. Previous studies have demonstrated that MAP is difficult to detect reliably and reproducibly by means of PCR on DNA extracted from human tissues.[6] Thus, the use of non-optimal procedures in processing the samples may result in false-negative results. Bull et al.[6] indicated several important steps that should be followed in the DNA extraction method, such as processing of fresh tissues (i.e. which have never been frozen); mechanical disturbance to ensure access to MAP DNA; resuspension of the DNA overnight at 4 °C; and nested PCR. In this study, we followed these recommendations wherever possible. However, as previously mentioned, it was necessary for us to freeze the samples, and this could be one reason for the low MAP detection rate in our results.

Few studies have shown higher frequencies of detection of MAP or acid-fast bacilli in patients with CD.[23-26] This may be due to the difficulty in detecting MAP in tissue, given that MAP occurs in spheroplast form, and only small quantities of the microorganism are present in the tissues. For as long as these technical limitations remain unresolved, it will continue to be a challenge to demonstrate the presence of MAP in tissues of patients with CD.[13]

Considering the small number of PCR-positive samples that were tested for qRT-PCR, we could not make any statistical inferences about the quantities of DNA found in the three groups (CD, UC and nIBD), although we observed that CD patients had higher bacterial loads in both formalin-fixed paraffin-embedded and fresh samples.

Some studies have supported the theory that MAP is present in most individuals. However, it is found in greater quantities in people with CD, thus suggesting that MAP is an organism that is ubiquitous in the environment and that it is an opportunistic pathogen and not a primary cause of CD.[13]

In this study, the frequency of MAP detection by means of PCR did not differ between CD, UC and nIBD patients, and although the bacterial load was higher in patients with CD, it is not known whether higher bacterial loads cause higher inflammation scores or whether higher inflammation scores cause higher bacterial loads. One possible explanation may be that the

microorganism finds better conditions for replication in patients with CD than in patients with UC or nIBD. Immunological factors relating to MAP, in susceptible patients, may allow MAP to replicate in larger quantities, thereby increasing the bacterial load in patients with CD. This is corroborated by Lee et al.,[27] who showed that MAP gave rise to general colonization of the mucosa and suggested that there was simply an increase in mucosal surface colonization (dysbiosis) in CD cases that was unassociated with causality. Dysbiosis and reduced bacterial diversity of the intestinal microbiome in CD are likely to promote MAP growth and detection.[13]

Further investigations into the etiological role of MAP in CD are needed. Analysis on the human intestinal microbiome in healthy and CD patients would establish whether MAP belongs to the normal human microbiota or not. CD remains a debilitating disease that severely affects the quality of life of its sufferers. Further research is required in order to definitively answer the questions regarding the etiological nature of the disease.

CONCLUSION

MAP was present in all the groups of patients analyzed, although the greatest bacterial loads were observed in the CD group. This study supports the view that MAP is a ubiquitous organism that colonizes the mucosal surfaces of the gut, thereby resulting in increased detection in CD patients. This study does not provide evidence for any role played by MAP in Crohn's disease; its role remains controversial and inconclusive. This is the first report on the presence of MAP in biopsy specimens from the human gut in Brazil.

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Cross-cultural adaptation and content validation of START

Adaptação transcultural e validação de conteúdo do START

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KEY WORDS:
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PALAVRAS-CHAVE:
Idoso.
Preparações farmacêuticas.
Prescrições de medicamentos.
Saúde do idoso.
Uso de medicamentos.
Traduções.

ABSTRACT

CONTEXT AND OBJECTIVE: Non-treatment of diseases or clinical conditions has been considered to constitute omission of care in several countries. The aim of the present study was to develop a transcultural adaptation of the Screening Tool to Alert Doctors to the Right Treatment (START) to Brazilian Portuguese and to validate the tool's content.

DESIGN AND SETTING: Cultural adaptation and validation of the START criteria using the Delphi consensus technique.

METHOD: START was translated from its original language into Brazilian Portuguese, followed by back-translation and validation by means of the modified Delphi technique. For this, an electronic form was developed and sent to 20 experts, who were asked to use a Likert scale to assess the statements included in START, in relation to their pertinence to Brazilian realities. All of the statements that exhibited mean scores greater than 4.0 were considered to have attained consensus. The experts' identities were kept confidential throughout the validation process.

RESULTS: In the first phase of the validation process, 63.6% (14/22) of the statements in START attained consensus. The remaining statements were returned to the experts so that they could have the opportunity to review their comments and statements and to assess them again, based on the Likert scale used earlier. In this phase, 100% of the START instrument attained consensus.

CONCLUSION: The content of START was entirely validated for Brazil, with all of the original criteria maintained.

RESUMO

CONTEXTO E OBJETIVO: O não tratamento de doenças ou condições clínicas tem sido apontado como omissão no cuidado em diversos países. O objetivo deste estudo foi realizar a adaptação transcultural para o português brasileiro e sua validação de conteúdo do questionário START (Screening Tool to Alert Doctors to the Right Treatment).

TIPO DE ESTUDO E LOCAL: Adaptação cultural e validação dos critérios START através da técnica de consenso Delphi.

MÉTODO: O START foi submetido à tradução da língua original para o Português (Brasil), tradução reversa e validação de conteúdo por meio da técnica Delphi modificada. Para isso, um formulário eletrônico foi desenvolvido e enviado a 20 especialistas para o julgamento das proposições presentes na ferramenta START conforme sua pertinência para a realidade brasileira, utilizando uma escala de Likert. Foram consideradas consensuais todas as proposições que apresentaram média superior a 4,0. A identificação de cada especialista foi mantida em confidencialidade durante o todo o processo.

RESULTADOS: Na primeira fase da validação, foi obtido consenso em 63,6% (14/22) das proposições contidas na ferramenta START. As proposições não consensuais foram reencaminhadas para os especialistas, que tiveram a oportunidade de rever seus comentários e proposições e julgá-las com base na escala de Likert utilizada previamente. Nessa fase, foi obtido consenso em 100% do instrumento START.

CONCLUSÃO: O conteúdo do START foi validado para o Brasil na sua totalidade, com todos os critérios originais mantidos.

INTRODUCTION

Older adults are a heterogeneous group that usually presents a large number of chronic diseases, thus leading these individuals to use healthcare services and medications frequently.[1] Therefore, several researchers have formulated instruments to assess the appropriateness of drug prescribing among older adults.[2] According to Barry et al.,[3] a drug is rated inappropriate for older people when their tolerance to it has been scientifically and clinically shown to be poor, due to the physiological changes associated with aging. Such drugs may even exacerbate clinical problems. Page and Ruscin[4] considered a prescription to be inappropriate when it exhibited a significant risk of causing adverse events or when there was evidence that equally or more effective and safer alternatives existed for treating the same condition.

Most instruments published to date within this field have assessed inappropriate prescribing of medication to older adults, but few have evaluated errors of omission with regard to prescriptions.[3] START (Screening Tool to Alert Doctors to the Right Treatment) was formulated with the aim of detecting prescribing omissions among elderly patients. This instrument provides a method for systematic detection of prescribing omissions based on physiological systems, and it is considered to be valid, effective and easy to use.[5] The START criteria were formulated and validated in 2006 in the United Kingdom using the Delphi[6] consensus technique. The START criteria include 22 indicators of potential prescribing omissions among older adults, and its use for both outpatients and inpatients has become widespread across Europe.[7]

OBJECTIVE

The aim of the present study was to develop and validate a cross-cultural Brazilian Portuguese adaptation of START.

METHODS

Instrument

START is a published, evidence-based screening tool for detecting potential prescribing omissions among elderly patients. START categorizes prescribing omissions according to physiological systems within the following fields: cardiology, endocrinology, rheumatology, pneumology and neurology. The tool includes 22 indicators of potential prescribing omissions among older adults, but does not provide scores for each indicator.

Translation and cross-cultural adaptation

START was published by Gallagher et al.[5] Although this tool is in the public domain, the main author was contacted by e-mail to seek permission to adapt the content to Brazilian Portuguese and validate the adapted tool, and this permission was granted.

Firstly, the original version of the START criteria (in English) was translated into Brazilian Portuguese by a sworn translator who is a native Portuguese speaker. This translation was called version 1. This was then translated into English by a second translator, to produce a back-translation called version 2. This method of translation and transcultural adaptation followed the methodology of Guillemin et al.[8] Both of these translators were blinded to the study aims. The Delphi method[6] was used to validate the instrument.

The translations were compared by the authors of the present article. The three authors evaluated them independently. Inconsistencies were resolved by consensus to produce a START version in the Brazilian Portuguese language.

Validation of the instrument's content

The validation study was conducted in 2013, and it included Brazilian experts in the areas of geriatrics, cardiology, endocrinology, neurology, pulmonology and rheumatology. The modified Delphi technique was used to validate the instrument's content.[6]

The participating experts were specialists in their fields. They were living and working in Brazil and were known for their medical expertise and scientific production. Each participant was sent an invitation letter by e-mail that explained the study aims and the consensus technique that would be used.

After the participants signed an informed consent form, each of them was sent the electronic version of START by e-mail (Delphi round 1), taking their clinical specialization into consideration. Thus, before actually filling out the electronic form, each participant was ask to indicate his or her field of specialization, which granted him or her access to the statements relevant to his or her specialty only. Only the geriatrists had access to the full content of the instrument, which consisted of 22 statements.

The participants were asked to judge the information relating to the clinical situations described in the questionnaire and to record the answer that they considered to be most pertinent: 1. I fully disagree; 2. I partially disagree; 3. Indifferent; 4. I partially agree; or 5. I fully agree. Responses to each statement in START regarding prescribing omissions were provided by eight experts, namely five geriatrists and three specialists in the corresponding field.

Following the counting of responses and processing of comments, statements scoring less than the preset cutoff point (mean: 4.0), exhibiting confidence intervals (95% CI) less than the cutoff point and/or receiving substantial comments, as well as those for which changes in the information provided were requested, were sent back for reassessment (Delphi round 2).

Each participant was then given the opportunity to revise or confirm his or her previous position relative to the statements sent back for revision. During the first two *Delphi* rounds, the

participants were not informed of the identities of the remainder of the participants. A statement was considered to have attained consensus in round 2 when its mean score and 95% CI were higher than 4.0 (i.e. the cutoff point representing 80% agreement). When a statement score was less than 4.0 in round 2, because of the addition of comments made in round 1, the original content was maintained.

The data analysis included calculation of the mean scores assigned to each statement and the corresponding 95% CI. Analysis was performed using the SPSS software, version 22.0 (Chicago, IL, USA).

The study was approved by a local ethics committee.

RESULTS

Twenty-two experts were invited to participate in the study, and 20 agreed to participate, namely five geriatrists, three cardiologists, three endocrinologists, three pulmonologists, three neurologists and three rheumatologists. Approximately 60% (12/20) of the participants had a doctoral degree, 30% (6/20) had a master's degree and 10% (2/20) were accredited specialists only.

The first phase of the validation process lasted two months. No consensus was reached for eight of the 22 statements (36.4%). One of the geriatrists dropped out of the study for personal reasons during round two. The second phase also lasted two months, and consensus was reached for all eight statements discussed. The results relating to both Delphi rounds are presented in **Table 1**.

The START version validated and adapted for Brazilian realities is described in the **Supplementary Material** (in English and Portuguese).

DISCUSSION

No consensus was reached for 36.4% of the START statements in the first round of the Delphi survey. In the second round, all of the statements reached consensus. The likely reason for this finding was that although the START statements were published eight years ago, they exhibit current high-quality evidence supporting use of the drugs mentioned among older adults.

Several techniques are available for validating the content of clinical criteria, instruments or questionnaires. The Delphi technique aims to refine the opinions of an expert panel to achieve a consensus, by means of several questionnaires with controlled feedback.[6] It is a systematic method based on the participants' clinical experience, and therefore the level of expertise among the participants needs to be assessed before its application.[3,6,9] All of the START fields of expertise were assessed by a minimum of eight experts. The participants selected were well known for their medical expertise, as well as for the number of scientific articles that they had published in Brazilian and international journals. In addition, all of the participants had had significant experience in relation to care for older adults, and they were affiliated to higher education institutions. These features make it possible to obtain highly qualified contributions and to gather together experts with different experiences encompassing several specialties.

Two sworn translators were selected to perform the forward translation (first translator to the Brazilian Portuguese language) and back-translation (second translator) because these professionals were certified to perform translations, which therefore are officially attested for the entire territory of Brazil. This choice contributed towards improving the quality of the translated document, which is an important factor, because the document was

Table 1. Scores from the first and second phases of START content validation, by means of the modified Delphi technique

Statement	Mean Round 1	95% CI Round 1	Comments made in the first phase of the study	Mean Round 2	95% CI Round 2
Warfarin in the presence of chronic atrial fibrillation	4.00	2.91-5.09	EG1: Totally disagreed, but did not provide comment	3.86	3.03-4.69
Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but aspirin is not	4.13	2.99-5.23	EC2: Aspirin in the presence of chronic atrial fibrillation in patients with CHADS2 less than 2, when warfarin is contraindicated, but aspirin is not. If CHADS2 is less than or equal to 2, aspirin is clearly inferior to warfarin. Before choosing to prescribe aspirin, other non-contraindicated anticoagulants must be evaluated. Comment EG1: Currently, thrombin inhibitors and factor X inhibitors have been shown to be equal or superior to warfarin in elderly patients with preserved renal function and a creatinine clearance over 30	3.86	2.31- 5.41
Aspirin or clopidogrel with a documented history of coronary, cerebral or peripheral vascular disease in patients in sinus rhythm	4.38	3.20-5.55	EG1: Totally disagreed, but did not provide comments	4.57	4.08-5.01
Antihypertensive therapy where systolic blood pressure is consistently greater than 160 mm Hg	4.75	4.36-5.14	–	–	–

Table 1. Continuation

Statement	Mean Round 1	95% CI Round 1	Comments made in the first phase of the study	Mean Round 2	95% CI Round 2
Statin therapy in patients with a documented history of coronary, cerebral or peripheral vascular disease, where the patients'"functional status" remains independent for activities of daily living and life expectancy is more than 5 years	4.38	3.94-4.81	EC2: This would not differentiate the population. The evidence of long-term benefits of statins in cerebral or peripheral arterial atherosclerotic disease is weaker than the evidence supporting statin use in coronary disease, but the majority agree that therapy must be introduced, especially if LDL-C is over 100 mg/dl	4.43	3.93-4.92
Angiotensin-converting enzyme inhibitor therapy in chronic heart failure.	4.75	4.36-5.14	–	–	–
Angiotensin-converting enzyme inhibitor therapy following acute myocardial infarction	4.63	4.19-5.06	–	–	–
Beta-blocker therapy in chronic stable angina	4.50	4.05-4.95	–	–	–
Metformin with type 2 diabetes or metabolic syndrome (in the absence of renal impairment)	4.88	4.58-5.17	–	–	–
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in diabetes with nephropathy, i.e. overt proteinuria, microalbuminuria on urinalysis (higher than 30 mg/24 h) or renal impairment	4.00	–	–	–	–
Statin therapy in diabetes mellitus if one or more cardiovascular risk factors are present	4.63	4.19-5.06	–	–	–
Antiplatelet therapy in diabetes mellitus if one or more cardiovascular risk factors are present (hypertension, hypercholesterolemia, history of smoking)	4.50	4.05-4.95	–	–	–
Regular inhaled ß-2 agonist or anticholinergic agent for mild to moderate chronic obstructive pulmonary disease	4.25	3.86-4.64	EG4: Attempt to assay beta-2 antagonist by evaluating the weight of fragile elderly. There are reports of increased osteoporosis induced by long-term use of corticosteroid, even in inhalation therapy. At this point, there are controversies. EG6: Attempt for patients with cognitive deficits who may not be able to use inhaler devices	4.00	3.08-4.92
Regular inhaled steroid therapy in moderate-to-severe asthma or chronic obstructive pulmonary disease, where the forced expiratory volume in one second is less than 50%	4.88	4.58-5.17	–	–	–
Home continuous oxygen, where chronic type 1 respiratory failure (pO_2 < 60 mm Hg; pCO_2 < 48.75 mm Hg) or type 2 respiratory failure (pO_2 < 60 mm Hg; pCO_2 > 48.75 mm Hg) was documented	4.50	4.05-4.95	–	–	–
L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability	5.00	–	–	–	–
Antidepressants in the presence of moderate-to-severe depressive symptoms in the past three months	4.86	4.51-5.21	–	–	–
Disease-modifying anti-rheumatic drugs (DMARDs) with moderate to severe active disease in the past 12 weeks	4.63	4.19-5.03	–	–	–
Bisphosphonates in patients using oral glucocorticoid maintenance therapy	4.25	3.38-5.12	EG3, EG4 and EG6: Evaluate bone densitometry. Pay attention to osteomalacia	2.86	1.22-4.50
Calcium and vitamin D supplementation in patients with known osteoporosis (radiological evidence, previous fragility fracture or dorsal kyphosis)	4.63	3.74-5.51	EG3: Some studies show that vitamin D intake does not interfere with bone density	4.71	4.26-5.17
Proton pump inhibitors in the presence of severe gastroesophageal acid reflux or peptic stricture requiring dilatation	4.80	4.24-5.36	–	–	–
Fiber supplementation for chronic, symptomatic diverticular disease with constipation	4.60	3.92-5.28	EG6: If the patient is able to consume an adequate fluid intake	5.0	–

Legend: CI = confidence interval; renal dysfunction = glomerular filtration rate < 50 ml/minute; EC2 = Expert Cardiologist 2; EG1 = Expert Geriatrist 1; EG3 =: Expert Geriatrist 3; EG4 = Expert Geriatrist 4; EG6 = Expert Geriatrist 6; LDL = low-density lipoprotein cholesterol

thus officially recognized by public institutions and agencies and thus would be valid as an official or legal document.

Sworn translators are usually trained in the humanities and are approved for translating public edicts issued by the state boards of trade. Thus, such translators might be unacquainted with some medical terms, thus resulting in slight errors in translation. Such errors are expected, and therefore a review panel needs to be established in order to compare the original and translated versions before the process of content validation is started. In this manner, possible discrepancies can be resolved and the translation can be made fully understandable and can have satisfactory cross-cultural equivalence of scales.[8] The assessment performed by the reviewers enabled adaptation of technical terms relating to drug classes and units of measurements, before the Delphi consensus technique was applied, without the risk of compromising the study.

In the first phase of the study, consensus was not attained for the cardiology-related statements describing the use of warfarin for chronic atrial fibrillation. The main studies conducted with new anticoagulant agents have compared these agents with warfarin and have aimed to assess the benefits and risks associated with these agents.[10-12] However, most of these studies have been non-inferiority trials, i.e. comparative efficacy studies, which are performed to compare a new treatment with a traditional treatment in order to show that the new one is not inferior, but also not superior, to the existing treatment.[13]

Use of statins in cases with a known history of cerebral, peripheral or vascular disease, in which the patient remains functionally independent for activities of daily living and the life expectancy is more than five years, was also discussed and included for discussion in the second phase of the study. In this second phase, a consensus was achieved with regard to the evidence showing that the long-term benefit of statins in cerebral or peripheral atherosclerotic artery disease is poorer than that for coronary artery disease. Nevertheless, most of the participants agreed that statin therapy should be used, particularly when the low-density lipoprotein cholesterol (LDL-C) level is higher than 100 mg/dl.[12,14-17]

Furthermore, no consensus was reached in the first phase of the study in relation to the use of bisphosphonates in patients undergoing oral corticosteroid maintenance therapy. Bisphosphonates have antiresorptive action and increase bone mass. They are indicated for treatment and prevention of bone disorders. They are considered to be the first choice for treating osteoporosis and should be used together with calcium and vitamin supplements.[18,19]

A recent review failed to find any systematic reviews or meta-analyses of studies with three-year or longer follow-ups assessing fractures as outcomes associated with use of bisphosphonates. Nevertheless, case reports from Singapore and the United States have described occurrences of transverse fractures in the upper femoral shaft in patients treated with bisphosphonates. It is worth noting that most analyses on clinical trials or large datasets have failed to demonstrated higher total numbers of bone fractures among bisphosphonate users.[20] In the second phase of the present study, the experts agreed on the use of bisphosphonates, following comments made by their peers. Just as in the case of warfarin, lack of critical analysis about the issue discussed might have contributed to the failure to achieve consensus in the first phase, because case reports do not suffice to exclude the use of medications with proven efficacy and safety in previously performed, well-designed clinical trials. Under such circumstances, case reports may be considered to be a possible source of information on adverse reactions to drugs, and they could be useful in guiding the monitoring of the agents involved.

Additionally, the score for regularly inhaled ß-2 agonists or anticholinergic agents in mild-to-moderate asthma or chronic obstructive pulmonary disease was less than the cutoff point of the 95% CI in the first phase of the study. It was therefore discussed again in the second phase. Some studies conducted among older adults have shown that ß-2 agonists might reduce the risk of exacerbation of asthma or chronic obstructive pulmonary disease, in addition to improving the patient's survival.[19] ß-2 agonists were also used among older adults with cardiovascular and chronic obstructive pulmonary disease, and the results indicated that these drugs did not seem to influence the occurrence of cardiac and pulmonary events or death in that population.[21]

The lower limit of the confidence interval regarding the use of fiber supplementation for chronic, symptomatic diverticular disease with constipation was less than the preset cutoff point, and so it was included in the second round of discussion. All of the participants agreed with this statement in the second phase. Use of fiber supplementation for treating diverticular disease has been adopted in several studies, in which fiber intake seemed to be associated with better outcomes in comparisons among individuals who ate fiber-rich foods. Use of fiber-rich foods has also been associated with the development of diverticular disease, given that the likelihood of developing this disease seemed to be higher among individuals eating low-fiber diets.[22,23]

The reproducibility of this study will be evaluated through the master's degree project of one of the present authors.

Limitations of the study

In cases in which only one participant disagreed with a given statement, but he or she did not provide appropriate justification, the discussions among the experts were rather shallow. This was because the participants were not provided with arguments against the use of a given medication and they merely

held their previous positions due to the lack of new evidence requiring discussion. The Delphi consensus technique eliminates interpersonal factors that often influence consensus groups or committees, in which participants are face to face, and it encourages manifestation of honest opinions because of the lack of group pressure. The cost of applying the Delphi technique is low because there is no need for the participants to meet. The limitations of this technique derive from the doubts that are frequently cast on its scientific respectability, particularly regarding the selection and number of experts and the consensus criteria.[24] To minimize these problems, a larger number of experts were invited to participate, in comparison with the original criteria.[7] Regarding the consensus criteria, the cutoff point for accepting the experts' opinions was established before the start of the study.

Another limitation is that the study was not designed to add new statements to START. Doing so could have added the ability to screen for possible prescription omissions that were not described in the original instrument.

CONCLUSION

START was translated and adapted to Brazilian realities. Its validation by means of the Delphi consensus technique showed full agreement among the participants. START might be useful for other researchers and in clinical practice, with the aim of reducing the numbers of errors of omission with regard to prescriptions.

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Supplementary Material. START screening tool, adapted and validated by means of the modified Delphi technique

Statement	Field of expertise
Warfarin in the presence of chronic atrial fibrillation.	Cardiology
Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin.	Cardiology
Aspirin or clopidogrel with a documented history of coronary, cerebral or peripheral vascular disease in patients in sinus rhythm.	Cardiology
Antihypertensive therapy where systolic blood pressure is consistently greater than 160 mmHg.	Cardiology
Statin therapy in patients with a documented history of coronary, cerebral or peripheral vascular disease, where the patients' "functional status" remains independent for activities of daily living and life expectancy is more than five years.	Cardiology
Angiotensin-converting enzyme inhibitor therapy in chronic heart failure.	Cardiology
Angiotensin-converting enzyme inhibitor therapy following acute myocardial infarction.	Cardiology
Beta-blocker therapy in chronic stable angina.	Cardiology
Metformin with type 2 diabetes or metabolic syndrome (in the absence of renal impairment).	Endocrinology
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in diabetes with nephropathy, i.e. overt proteinuria, microalbuminuria on urinalysis (higher than 30 mg/24 h) or renal impairment.	Endocrinology
Statin therapy in diabetes mellitus if one or more cardiovascular risk factors are present.	Endocrinology
Antiplatelet therapy in diabetes mellitus if one or more cardiovascular risk factors are present (hypertension, hypercholesterolemia or history of smoking).	Endocrinology
Regular inhaled ß-2 agonist or anticholinergic agent for mild to moderate chronic obstructive pulmonary disease.	Pulmonology
Regular inhaled steroid therapy in moderate-to-severe asthma or chronic obstructive pulmonary disease, where the forced expiratory volume in one second is less than 50%.	Pulmonology
Home continuous oxygen, where chronic type 1 respiratory failure (pO_2 < 60 mm Hg; pCO_2 < 48.75 mm Hg) or type 2 respiratory failure (pO_2 < 60 mmHg; pCO_2 > 48.75 mmHg) was documented.	Pulmonology
L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability.	Neurology
Antidepressants in the presence of moderate-to-severe depressive symptoms in the past three months.	Neurology
Disease-modifying anti-rheumatic drugs (DMARDs) with moderate to severe active disease in the past 12 weeks.	Rheumatology
Bisphosphonates in patients using oral glucocorticoid maintenance therapy.	Rheumatology
Calcium and vitamin D supplementation in patients with known osteoporosis (radiological evidence, previous fragility fracture or dorsal kyphosis).	Rheumatology
Proton pump inhibitors in the presence of severe gastroesophageal acid reflux or peptic stricture requiring dilatation.	Gastroenterology
Fiber supplementation for chronic, symptomatic diverticular disease with constipation.	Gastroenterology

Anexo. Ferramenta de triagem START adaptada e validada por meio da técnica Delphi modificada

Proposição	Área de concentração
Varfarina na presença de fibrilação atrial crônica	Cardiologia
Aspirina na presença de fibrilação atrial crônica, onde varfarina é contraindicada, mas não a aspirina.	Cardiologia
Aspirina ou clopidogrel quando há história diagnosticada de doença arterial coronariana, doença vascular cerebral ou periférica em pacientes em ritmo sinusal.	Cardiologia
Terapia anti-hipertensiva quando pressão sistólica permanecer constantemente superior a 160 mmHg.	Cardiologia
Terapia com estatinas em pacientes com história diagnosticada de doença vascular periférica ou cerebral onde o "*status* funcional" do paciente permanece independente para as atividades diárias e expectativa de vida superior a cinco anos.	Cardiologia
Inibidor da enzima conversora de angiotensina na insuficiência cardíaca crônica.	Cardiologia
Inibidor da enzima conversora de angiotensina após infarto agudo do miocárdio.	Cardiologia
Beta-bloqueador na angina crônica estável.	Cardiologia
Metformina no diabetes tipo 2 ou síndrome metabólica (na ausência de disfunção renal).	Endocrinologia
Inibidor da enzima conversora de angiotensina ou bloqueador dos receptores da angiotensina em pacientes com nefropatia diabética, por exemploproteinúria ou microalbuminúria evidenciada em urinálise (maior que 30mg/24 horas) ou disfunção renal.	Endocrinologia
Terapia com estatinas no diabetes mellitus se um ou mais fatores de risco cardiovascular estiverem presentes.	Endocrinologia
Terapia antiagregante plaquetária no paciente com diabetes *mellitus* se um ou mais fatores de risco cardiovascular coexistir (hipertensão, hipercolesterolemia, história de fumo).	Endocrinologia
Inalação regular de agonista beta-2 ou agente anticolinérgico em casos de asma leve a moderada ou doença pulmonar obstrutiva crônica.	Pneumologia
Inalação regular de corticosteroides em casos de asma moderada a severa ou doença pulmonar obstrutiva crônica, onde o volume expiratório forçado em um segundo seja menor que 50%.	Pneumologia
Oxigênio domiciliar contínuo em insuficiência respiratória tipo 1 documentada (pO_2 < 60 mmHg, pcO_2 < 48.75 mmHg) ou insuficiência respiratória tipo 2 (pO_2 < 60 mmHg, pCO_2 > 48.75 mmHg).	Pneumologia
L-dopa em doença de Parkinson idiopática com disfunção funcional diagnosticada e resultando em incapacidade.	Neurologia
Medicamentos antidepressivos na presença sintomas depressivos moderados-severos durante os últimos três meses.	Neurologia
Medicamentos modificadores da doença reumática (DMARD) na doença moderada-severa ativa nas últimas 12 semanas.	Reumatologia
Bifosfonatos em pacientes em uso de terapia oral de manutenção com corticoides.	Reumatologia
Suplemento de cálcio e vitamina D em pacientes com osteoporose diagnosticada (evidência radiológica ou fratura devido fragilidade anterior ou cifose dorsal adquirida).	Reumatologia
Inibidores da bomba de prótons em doença do refluxo gastro-esofágico severa ou estenose péptica requerendo dilatação.	Gastroenterologia
Suplemento de fibras para doença diverticular sintomática crônica apresentando constipação.	Gastroenterologia

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Practical and conceptual issues of clinical trial registration for Brazilian researchers

Aspectos práticos e conceituais do registro de ensaios clínicos para pesquisadores brasileiros

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KEY WORDS:
Clinical trials as topic.
Database [publication type].
Information systems.
Publication bias.
Brazil.

PALAVRAS-CHAVE:
Ensaios clínicos como assunto.
Base de dados.
Sistemas de informação.
Viés de publicação.
Brasil.

ABSTRACT

CONTEXT AND OBJECTIVE: Clinical trial registration is a prerequisite for publication in respected scientific journals. Recent Brazilian regulations also require registration of some clinical trials in the Brazilian Clinical Trials Registry (ReBEC) but there is little information available about practical issues involved in the registration process. This article discusses the importance of clinical trial registration and the practical issues involved in this process.

DESIGN AND SETTING: Descriptive study conducted by researchers within a postgraduate program at a public university in São Paulo, Brazil.

METHODS: Information was obtained from clinical trial registry platforms, article reference lists and websites (last search: September 2014) on the following topics: definition of a clinical trial, history, purpose and importance of registry platforms, the information that should be registered and the registration process.

RESULTS: Clinical trial registration aims to avoid publication bias and is required by Brazilian journals indexed in LILACS and SciELO and by journals affiliated to the International Committee of Medical Journal Editors (ICMJE). Recent Brazilian regulations require that all clinical trials (phases I to IV) involving new drugs to be marketed in this country must be registered in ReBEC. The pros and cons of using different clinical trial registration platforms are discussed.

CONCLUSIONS: Clinical trial registration is important and various mechanisms to enforce its implementation now exist. Researchers should take into account national regulations and publication requirements when choosing the platform on which they will register their trial.

RESUMO

CONTEXTO E OBJETIVO: O registro dos ensaios clínicos é pré-requisito para publicação em revistas científicas de prestígio. Recentes mecanismos regulatórios brasileiros também exigem o registro de determinados ensaios clínicos na plataforma nacional (Registro Brasileiro de Ensaios Clínicos, ReBEC). Porém há pouca informação disponível sobre questões práticas envolvidas no processo de registro. Este trabalho discute a importância do registro de ensaios clínicos e aspectos práticos envolvidos nesse processo.

DESENHO DE ESTUDO E LOCAL: Estudo descritivo realizado por pesquisadores de um programa de pós-graduação em uma universidade pública em São Paulo, Brasil.

MÉTODOS: Informações foram obtidas em plataformas de registro de ensaios clínicos, referências dos artigos encontrados e *websites* (última busca: setembro, 2014) sobre os seguintes temas: definição de ensaio clínico, história, objetivo e importância das plataformas de registro, quais informações devem ser registradas e o processo de registro.

RESULTADOS: O registro de ensaios clínicos visa evitar viés de publicação e é exigido por revistas brasileiras disponíveis no LILACS, SciELO e revistas afiliadas ao Comitê Internacional de Editores de Revistas Médicas (ICMJE). Recentes normas brasileiras exigem que todos os ensaios clínicos (fases I a IV) envolvendo novos medicamentos no país sejam registrados no ReBEC. São discutidos os prós e contras da utilização de diferentes bases de registro de ensaios clínicos.

CONCLUSÃO: O registro de ensaios clínicos é importante e atualmente existem vários mecanismos que obrigam seu uso. Quando forem escolher em qual plataforma registrar seu ensaio clínico, os pesquisadores devem levar em consideração quais são as normas nacionais e as exigências para publicação.

INTRODUCTION

Registration of clinical trials has received increasing attention over the last few years. Discussions have progressed from theoretical issues, such as the importance of establishing trial registration platforms[1] and the creation of these registries, to regulatory issues involving enforcement of trial registration, such as through publication and legal restraints.[2-6] Many published papers on the history of trial registries are available at the Ottawa Group website,[7] including the 2004 Ottawa Statement, which presents the main principles for development of these registries.[8]

Over the last 14 years, the Brazilian government has recognized the strategic importance of scientific research for the country and has created mechanisms and structures to administer and encourage research.[9-11] In consonance with this plan, the Brazilian Clinical Trials Registry (ReBEC) has been created to register and provide information on clinical trials conducted in Brazil.[12]

Previous published papers have analyzed the importance of trial registries in general and of the ReBEC platform in particular for Brazilian researchers.[12-14] However, to the best of our knowledge, no previous papers have assessed the recent changes in the regulatory scenario of trial registries or provided any practical guidance for Brazilian researchers on how to register their trials. This gap motivated us to write this paper, which presents theoretical and practical issues relating to trial registration in Brazil.

OBJECTIVES

This study aimed to inform Brazilian researchers about the history and importance of clinical trial registration and to offer practical advice on how to use the ReBEC platform.

METHODS

This was a descriptive study. We searched MEDLINE (via PubMed), SciELO and LILACS from inception to September 30, 2014, for information on clinical trial registration, using the plain text "randomized controlled trial", OR "registry databases" OR "randomized controlled trial registration" and their corresponding Brazilian terms "Ensaio Clínico Controlado Aleatório", "Bases de Registros" and "Registro de Ensaio Clínico Randomizado", respectively. We complemented the search by screening the reference lists of articles selected for full text reading and by searching the websites of organizations with registry platforms or involved in the regulatory processes of this initiative, such as the International Committee of Medical Journal Editors (ICMJE),[15] the Cochrane Collaboration,[16] the World Health Organization (WHO),[17] the Ottawa group[1] and the Brazilian Registry of Clinical Trials (ReBEC).[18]

From these sources, we extracted information on 1) the definition of a trial, 2) the history and importance of trial registries and 3) details on where, when and how Brazilian researchers can register their trials.

RESULTS

What is a trial?

A trial is a study that prospectively assigns human beings or groups of human beings to one health-related intervention or to a series of such interventions, in order to assess the effects of the interventions on health.[15,17] A trial, also known as an interventional study, can test many different types of medical interventions used to modify health outcomes, such as drugs, biological products, surgical procedures, devices, behavioral treatments, preventive measures and healthcare protocols, among others.[19]

History and importance of trial registries

Before conducting a trial, researchers usually write a protocol that provides a brief contextual description of the problem or disease that will be investigated, the specific research question, the objectives of their study and some details on the methods that will be used, such as the participant selection criteria, a description of the intervention and the exact outcomes that will be assessed, as well as statistical issues such as sample size calculation and how the data will be analyzed.[20] Although this study protocol is naturally written by all investigators prior to actually beginning their study, until recently it was not mandatory to publish or register this protocol anywhere.

Registration of a trial protocol is an ethical pledge to ensure transparency in the execution and publication of studies.[3,6,8,12,13,15,21] WHO highlights that trial registries can also be sources of evidence on the efficacy and safety of health interventions.[22]

The main reasons for clinical trial registration are:

a) To avoid publication bias.[3,8,13-15] Registration of a trial protocol, in theory, ensures that the results of that study will be published, regardless of whether the findings were beneficial, harmful, inconclusive or even inefficacious.
b) To avoid selective reporting.[3,8,13-15] Registration of all essential details about outcomes that will be analyzed in the study protocol will preclude authors from selecting which outcome data will later be published.
c) To honor the ethical participant-investigator covenant.[3,8,12-15] In theory, registration of a trial ensures that both the methods and the results of the study will be published. Through publishing the study, the investigators will fulfill their ethical responsibility to the participants, because the data gathered in the study will be used to advance scientific knowledge.

Brazilian investigators have additional unique motivations for registration of their clinical trials, such as:

- To disseminate their work, thereby enabling greater visibility for Brazilian researchers.[6,12]
- To avoid language bias.[6,12,23] Non-English speaking researchers tend to only publish studies with positive results in English-language journals, thus limiting the dissemination of unfavorable results. Registration of the study protocol promotes dissemination of all trials, regardless of their findings since most clinical trial registries, included ReBEC bring both native language and English protocol versions.

Although discussions about mandatory registration of trial protocols date back to the 1960s,[1] this idea only gained momentum in the following century. In 2000, two large trial registries, ClinicalTrials.gov and Current Controlled Trials (ISRCTN), were created. Five years later, the ICMJE issued a recommendation on the use of these registries and many top medical journals, such as the Lancet, the British Medical Journal and BioMed Central journals, started to require prospective trial registration as a prerequisite for considering manuscripts for publication.[24,25] In 2007, this recommendation was also adopted by all Brazilian journals indexed in the Latin American and Caribbean Health Sciences Literature (LILACS) database and by those available through the Scientific Electronic Library Online (SciELO).[3]

Some years later, the Brazilian platform for the registration of clinical trials (Registro Brasileiro de Ensaios Clínicos, ReBEC) was created. ReBEC is administered by Fundação Oswaldo Cruz (FIOCRUZ), in association with the Brazilian Ministry of Health, the Pan-American Health Organization (PAHO) and the Latin American and Caribbean Center on Health Sciences Information (BIREME). This platform allows free open-access registration of any trial that started recruiting participants after January 2010. In 2008 and 2012, two Brazilian regulatory laws (RDC 39/2008 and RDC 36/2012) were passed.[4,5] Since 2012, all clinical trials (phases I to IV) involving new drugs to be marketed in Brazil must be registered on this trial platform.[4,5]

Where, when and how to register a trial

In 2007, the World Health Organization created a network of clinical trial registries called the International Clinical Trials Registry Platform (ICTRP).[26] This secondary platform combines 16 of the most popular primary trial registry platforms on a single webpage (apps.who.int/trialsearch).[27]

To meet the publication requirements of the ICMJE, the trial protocol must be registered in one of the primary registries of the ICTRP network.[15] Trial authors in any country can chose freely where to register their protocols in one of several primary trial registries available worldwide. Examples of these registries include the Brazilian platform (ReBEC),[18] the Australian New Zealand Clinical Trials Registry (ANZCTR),[28] the Chinese Clinical Trial Registry (ChiCTR),[29] the Cuban Public Registry of Clinical Trials (RPCEC),[30] the Pan-African Clinical Trial Registry (PACTR),[31] the EU Clinical Trials Register (EU-CTR)[32] and the International Standard Randomized Controlled Trial Number Register (ISRCTN.org),[33] among others. However, some platforms, such as ISRCTN, charge fees for registration of trial protocols while others, like the Pan-African Clinical Trials Registry and the EU Clinical Trials Registry, only register trials conducted locally. Once registered in any of the affiliated registries, the text of the trial protocol cannot be deleted and in some of them (e.g. ClinicalTrials.gov),[12,17] protocol amendments also become public.[34]

Before registering the trial protocol, the authors need to have obtained approval for their study through local or national ethics committees. The real recruitment of participants should only begin after the trial registration has been officially completed and is available online, since registration is not accepted after that point.[6,14] Clinical trials not registered from inception will face difficulties in the publishing process, since they will not be accepted by ICMJE-affiliated and probably many other journals.

The key elements needed for registering trials on these platforms are very simple and are usually part of any study protocol. **Box 1** describes key data required for registering a trial in the WHO network (ICTRP) of affiliated platforms.[35]

Practical advice on registration in ReBEC

Registration of a trial on the Brazilian platform follows steps that are similar to those of other trial registries. Details and answers to frequently asked questions are provided on the ReBEC website.[6]

We should nevertheless point out some inconvenient features of ReBEC, such as the need to fill out many free-text fields (**Figure 1**). Another problem is that the instructions on how to

Box 1. Main information required by World Health Organization (WHO) for registration of a trial in any International Clinical Trials Registry Platform (ICTRP) affiliated registries.[35]

• Study title
• Registry data and trial identification number*
• Source(s) of monetary or material support
• Contact for public queries
• Countries of recruitment
• Health condition(s) or problem(s) studied
• Interventions
• Control
• Key inclusion and exclusion criteria
• Study type
• Target sample size
• Date of first enrollment
• Recruitment status
• Primary outcome
• Key secondary outcomes

*generated by the system.

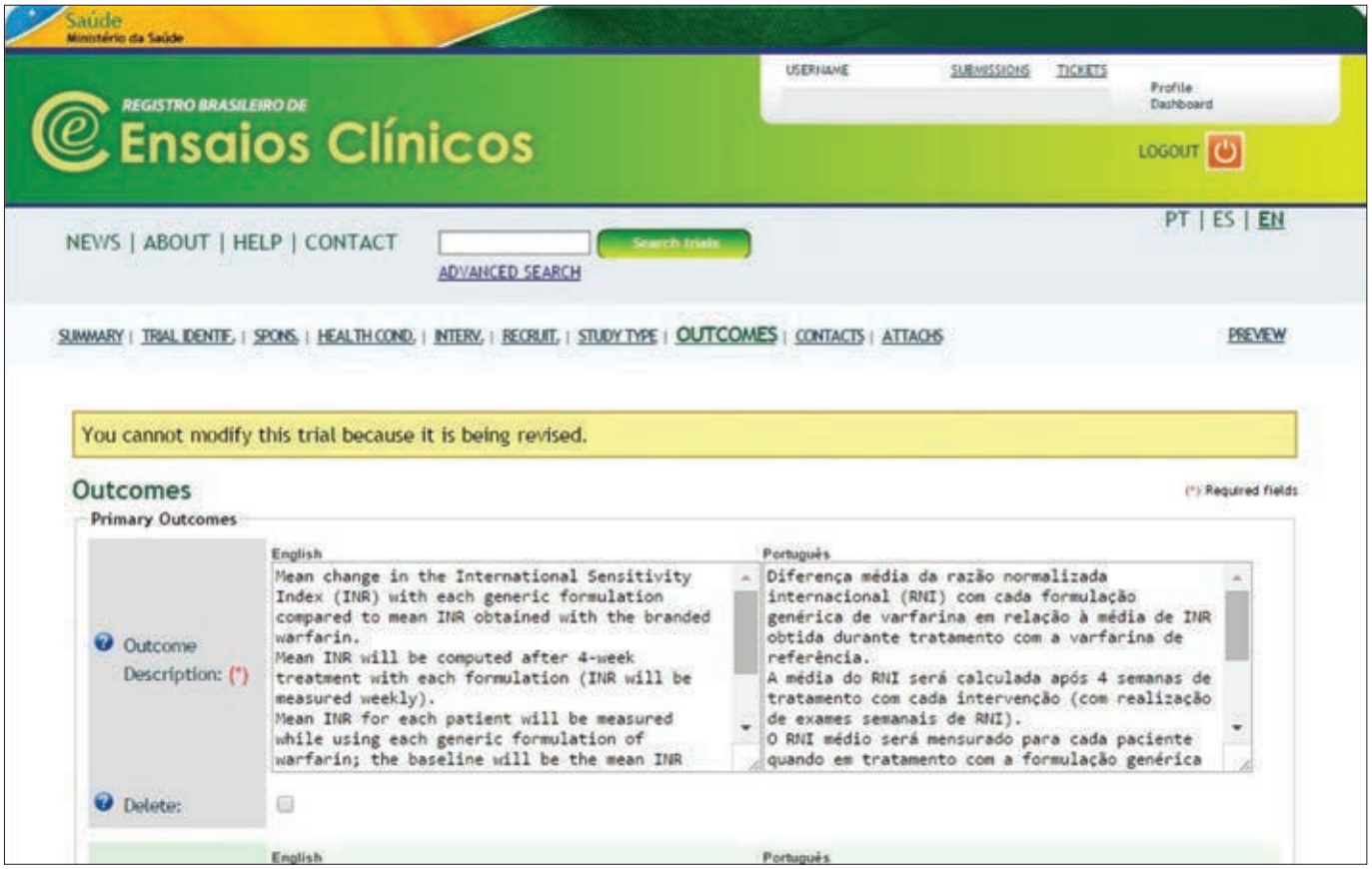

Figure 1. Screen shot of part of the Outcomes section of a Registro Brasileiro de Ensaios Clínicos (ReBEC) trial submission form. Outcomes are described in free-text fields.

fill out the fields are not very clear. As a result, the process of trial registration is prone to errors and this will lead to several bouts of revision dialogue between ReBEC and the applicant.

One of the present authors (CGF) compared the registration process of a trial already registered in ClinicalTrials.gov (identifier NCT02017197) with the registration process in ReBEC. While it took approximately one week between submission and publication of the trial register in ClinicalTrials.gov in 2013, the same study protocol, which was submitted to ReBEC in April 2014, has not yet been published online as of February 20, 2015. The reason for this delay may be that the ClinicalTrials.gov registration form, unlike that of ReBEC, has an interface with many closed questions, which probably speeds up the registration process. Not only that, since 2014 and until now (April 15) the homepage of ReBEC displays a message of staff shortage, which leads us to think that the registration process will be even slower.

DISCUSSION

This study describes the history and importance of clinical trial registry platforms and provides useful information for Brazilian researchers on where and how to register their trials. This pragmatic approach is one of the strengths of the study, since it responds to the needs of researchers who are usually not interested in extensive scientific discussions about clinical trial registration or specific characteristics of some registries but want practical information on this essential topic.[3,8,12-14,21] This need influenced our search strategy, which was not restricted to scientific articles, but included searches on relevant websites, along with a practical exercise on the Brazilian platform.

Registration of clinical trials emerged from scientific and ethical concerns on research transparency and is now going through a process of scientific and legal regulation aimed at enforcing its implementation.

We recommend that before selecting a specific platform for trial registration, researchers should pay attention to national regulations and laws, which may vary depending on their geographical setting. For Brazilian researchers, or foreign investigators conducting clinical trials in Brazil, the ReBEC platform is an option. ReBEC meets the requirements for publication both in Brazilian and in foreign journals and, in some cases (e.g. for registration of new drugs on the Brazilian market), it is mandatory to register trials on this platform. However, ReBEC has several

shortcomings because of its format, and this can considerably delay the process of trial registration. We think that many of the problems identified in ReBEC are probably due to the fact that this registry and the regulations on trial registration are relatively new in Brazil.

However, recent information regarding staff shortages at ReBEC means that improvement in its performance will not happen over the short term, which is highly detrimental to the reputation of the platform and also an impediment for companies that aim to register new drugs in Brazil.

CONCLUSIONS

Clinical trial registration has over 50 years of history and has received increasing attention over the last decade. Brazil has had a national trial registry (ReBEC) since 2010 and regulations have been created to encourage its use. However, this platform has some drawbacks. Researchers should take into account national laws and publication requirements when choosing the platform on which they will register their trial.

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Usefulness of the second heart sound for predicting pulmonary hypertension in patients with interstitial lung disease

Utilidade da segunda bulha cardíaca na predição de hipertensão pulmonar em portadores de doenças intersticiais pulmonares

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Ecocardiografia.
Fonocardiografia.

ABSTRACT

CONTEXT AND OBJECTIVE: P_2 hyperphonesis is considered to be a valuable finding in semiological diagnoses of pulmonary hypertension (PH). The aim here was to evaluate the accuracy of the pulmonary component of second heart sounds for predicting PH in patients with interstitial lung disease.

DESIGN AND SETTING: Cross-sectional study at the University of Brasilia and Hospital de Base do Distrito Federal.

METHODS: Heart sounds were acquired using an electronic stethoscope and were analyzed using phonocardiography. Clinical signs suggestive of PH, such as second heart sound (S_2) in pulmonary area louder than in aortic area; $P_2 > A_2$ in pulmonary area and P_2 present in mitral area, were compared with Doppler echocardiographic parameters suggestive of PH. Sensitivity (S), specificity (Sp) and positive (LR+) and negative (LR-) likelihood ratios were evaluated.

RESULTS: There was no significant correlation between S_2 or P_2 amplitude and PASP (pulmonary artery systolic pressure) (P = 0.185 and 0.115; P= 0.13 and 0.34, respectively). Higher S_2 in pulmonary area than in aortic area, compared with all the criteria suggestive of PH, showed S = 60%, Sp= 22%; LR+ = 0.7; LR- = 1.7; while $P_2 > A_2$ showed S= 57%, Sp = 39%; LR+ = 0.9; LR- = 1.1; and P_2 in mitral area showed: S= 68%, Sp = 41%; LR+ = 1.1; LR- = 0.7. All these signals together showed: S= 50%, Sp = 56%.

CONCLUSIONS: The semiological signs indicative of PH presented low sensitivity and specificity levels for clinically diagnosing this comorbidity.

RESUMO

CONTEXTO E OBJETIVO: Hiperfonese de P_2 tem sido considerada como achado valoroso no diagnóstico semiológico de hipertensão pulmonar (HP). O objetivo foi de avaliar a acurácia do componente pulmonar da segunda bulha cardíaca em predizer HP nos pacientes portadores de doenças intersticiais pulmonares.

TIPO DE ESTUDO E LOCAL: Estudo transversal na Universidade de Brasília e Hospital de Base do Distrito Federal.

MÉTODOS: Os sons cardíacos foram adquiridos com estetoscópio eletrônico e analisados por fonocardiografia. Os sinais clínicos sugestivos de HP, como B_2 mais intensamente audível em área pulmonar que aórtica, $P_2 > A_2$ na área pulmonar e P_2 presente em área mitral foram confrontados com parâmetros cardiográficos no exame de Doppler sugestivos de HP. Sensibilidade (S), especificidade (E), razões de verossimilhança positiva (RV+) e negativa (RV-) foram avaliados.

RESULTADOS: Não houve correlação significativa entre amplitude de B_2 e P_2 e a PSAP (pressão sistólica arterial pulmonar) (P = 0,185 e 0,115; P = 0,13 e 0,34; respectivamente). A análise da presença de B_2 mais intensa na área pulmonar que aórtica, quando comparada a todos os critérios sugestivos de HP, mostrou S = 60%; E = 22%; RV+ = 0,7; RV- = 1,7; enquanto $P_2 > A_2$ mostrou: S = 57%; E = 39%; RV+ = 0,9; RV- = 1,1; e P_2 no foco mitral mostrou: S = 68%; E = 41%; RV+ = 1,1; RV- = 0,7. Todos os sinais juntos mostraram S = 50%; E = 56%.

CONCLUSÃO: Os sinais semiológicos indicativos de HP apresentam baixos valores de especificidade e sensibilidade para diagnóstico clínico dessa comorbidade.

INTRODUCTION

Interstitial lung diseases are a heterogeneous group of disorders that affect the lung parenchyma. However, despite their differences, they all share chronic evolution associated with functional and structural deterioration of the pulmonary parenchyma.[1] This process is often also accompanied by pulmonary hypertension (PH), caused either by hypoxic pulmonary vasoconstriction or direct vascular impairment of vascular function, such as occurs in sarcoidosis.[2] The presence of PH is a predictor of mortality.[3]

Detecting the presence of PH is important because this disorder is a determining factor for various therapeutic measures, among them lung transplantation.[3] Moreover, a finding of PH may signal inapparent hypoxemia, such as occurs repeatedly during sleep or upon physical effort. Therefore, prompt and easy identification of factors that can provide additional information about the evolution of the disease is extremely important. In 1970, Harris[4] considered that both the intensity of the second heart sound (S_2) and its behavior during breathing deserved attention during routine auscultation. A change in its characteristics could be an early clinical sign of PH.[5]

In this scenario, splitting of S_2 mainly occurs because of delays in the pulmonary component (P_2), although there is a slight advance of the aortic component (A_2). This occurs even during expiration, with a delay of 0.02 to 0.03 seconds, and 0.02 in only 2% of the population, especially in children and young adults.[6]

Hyperphonesis of P_2 has traditionally been acknowledged in all semiology books as indicative of PH. However, there is little evidence to support this. It is defined as more accentuated presence of S_2 in the pulmonic area than in the aortic area[5] or, more specifically, as $P_2 > A_2$ in the pulmonic area. It shows highly variable sensitivity (S) (96% to 58%) and specificity (Sp) (46% to 19%).[5,7]

In fact, it is not uncommon for a semiological tradition to be established based on pathophysiological deductions, without proper clinical validation of the finding, including its perceived variability, which has a direct relationship with the credibility and routine application of this knowledge on a daily basis. For instance, the reliability of cardiac auscultation findings is rarely evaluated. Regardless of these issues, hyperphonesis of P_2 is still included in the guidelines for PH as an indicator of this condition.[8]

If, on the one hand, the benefits arising from a useful clinical finding, as a means for diagnosis that is doubly accessible in terms of both cost and speed of recognition, are enormous; on the other hand, acceptance of unproven validity can be harmful to the same extent. Therefore, it is increasingly important to determine the accuracy and real reliability of these clinical findings.

OBJECTIVE

In this study, we aimed to evaluate the pulmonary component of S_2 as a predictor of PH in patients with interstitial lung diseases. We also attempt to determine the pulmonary artery systolic pressure (PASP) value at which the pulmonary component of S_2 would be a more useful predictor of PH.

METHODS

This was a cross-sectional study from March to November 2011, in which 69 patients with various interstitial lung diseases seen in the outpatient care of a tertiary-level hospital were consecutively examined. This number was defined *a priori*, assuming an effect size of 0.4 *w* for the outcome, which represents a moderate to great effect, in addition to 80% power and an α value of 5%.[9] The study protocol was approved by our institution's ethics committee and all the participating subjects signed an informed consent form.

Each participating patient underwent cardiac auscultation in a quiet environment, in the supine position, with spontaneous breathing. The sounds were recorded using a 3MM Littmann electronic stethoscope, model 3200 (St. Paul, MN, USA) for further analysis. Next, the patient underwent color Doppler echocardiography carried out by a single examiner who was unaware of any of the clinical data. Electrocardiographic monitoring was done during the test.

We evaluated 69 patients aged between 21 and 86 years, with a mean age of 58 ± 16.6 years. Twenty-eight subjects (40.6%) were male and 41 (59.4%), female. Regarding the distribution of diseases, 15 patients (21.7%) had idiopathic pulmonary fibrosis, 22 (32%) had idiopathic interstitial diseases, 11 (16%) had interstitial lung disease associated with collagen-vascular disease, nine (13%) had sarcoidosis, seven (10.1%) had chronic hypersensitivity pneumonia and five (7.2%) presented other diffuse interstitial lung diseases.

Phonocardiogram

Phonocardiograms corresponding to heart sounds obtained by means of an electronic stethoscope were recorded in the aortic, pulmonic, mitral and tricuspid areas. The recording was done during spontaneous and continuous breathing.

The pulse tracings were transformed into signals by means of the Zargis Cardioscan heart sound analysis software (Princeton, NJ, USA) and were adjusted for reading in accordance with the same measurement scale. The amplitude of S_2 was measured (with or without splitting) and the amplitude of its P_2 component was measured separately; both measurements were obtained in the pulmonic area.

The parameters subsequently evaluated were the relative intensities of A_2 and P_2 in the pulmonic area; occurrences of

P_2 of greater amplitude than A_2 ($P_2 > A_2$); P_2 in the mitral area; absence of splitting of S_2; and, finally, simultaneous occurrence of all the parameters.

The analyses were performed by three independent examiners. They took into consideration the sounds, the pulse tracings and the additional features of the software, which made it possible to view the spectrums of the phonographic wave forms, among other things. Decisions were then based on the consensus reached among the examiners.

Phonocardiogram results were also compared with PASP measurements by means of Doppler echocardiography, using Doppler and additional criteria for diagnosing PH, as described below.

Transthoracic Doppler echocardiography

For transthoracic Doppler echocardiography evaluations, the patients were examined in the left lateral decubitus position, using standard echocardiographic projections. We used an ultrasound machine (model Vivid S5, General Electric. Milwaukee, WI, USA) with a multifrequency transducer and a frequency range from 2.5 to 3.5 MHz.

Measurements of variables relating to the heart chambers and ventricular function were obtained as established by the American Society of Echocardiography.[10]

Doppler analyses were performed in real time. Doppler color flow mapping in multiple views was used in order to more accurately measure tricuspid regurgitation. We used continuous wave Doppler ultrasound at a sweep speed of 50-100 mm/sec. Three to five measurements per pulse tracing were taken.

To calculate PASP by measuring tricuspid regurgitation, we used the modified Bernoulli equation. We then obtained the pressure gradient between the right ventricle (RV) and right atrium (RA). The estimated right atrial pressure was added to this parameter,[11,12] given that there was no right ventricular outflow tract obstruction.

Right atrial pressure was obtained by assessing the percentage collapse and the diameter of the inferior vena cava during spontaneous breathing. If the inspiratory collapse was greater than 50% and the diameter was less than 2.1 cm, the pressure added was 5 mmHg; if the inspiratory collapse was less than 50% and the diameter was greater than 2.1 cm, the pressure added was 10 mmHg; in patients where the inferior vena cava plethora was markedly greater than 2.1 cm and collapse was less than 50%, the pressure added was 20 mmHg.[13-15]

Pulmonary hypertension criteria

Pulmonary hypertension was considered "probable" when PASP was greater than 50 mmHg.[15,16] It was considered "possible" when PASP fluctuated between 37 and 50 mmHg, or when it was below 37 mmHg and accompanied by additional echocardiographic variables of PH, including the existence of dilation and/or hypertrophy of the right chambers, paradoxical movement of the interventricular septum or right ventricular dysfunction (analyzed in accordance with the recommendations of the American Society of Echocardiography for evaluating the right chambers).[15]

Data analysis

Continuous variables were described as the mean plus or minus standard deviation, along with the amplitude. Categorical variables were expressed as percentages. We conducted analyses on the correlations of the amplitudes of S_2 and P_2 in relation to PASP with the aim of assessing the influence of one variable on another. Since these variables did not show normal distribution according to the Shapiro-Wilk test, the Spearman correlation coefficient was used.

A receiver operating characteristic (ROC) curve with its components of sensitivity (S), specificity (Sp) and positive (LR+) and negative (LR-) likelihood ratios was constructed in order to determine the discriminatory power of each parameter studied. The area under the curve was expressed in terms of the 95% confidence interval (95% CI).

The findings were considered statistically significant when the probability P for two-tailed tests was $P < 0.05$. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 20 and Excel, both for the Mac OS X operating system.

RESULTS

The prevalence of PH in the sample, when all the echocardiographic criteria were taken into consideration, was 73% in patients with idiopathic pulmonary fibrosis, 41% in those with idiopathic diseases, 27% in those with collagen-vascular disease, 22% in those with sarcoidosis, 25% in those with chronic hypersensitivity pneumonia and 25% in those with other diffuse lung diseases. In these patients, the forced vital capacity (FVC) showed a mean of 67 ± 22.7%, with a minimum value of 18% and maximum of 110%. Hemoglobin oxygen saturation (SpO_2) in ambient air showed a mean of 93.4 ± 4.8% and a minimum value of 70% and maximum of 99%.

PASP estimated by means of Doppler echocardiography (which was feasible in all tests) was normal in 41 patients (59.4%), while 17 (24.7%) had additional echocardiographic criteria that, together with PASP, were suggestive of PH (possible PH). In 11 patients (15.9%), the PASP values measured by means of Doppler indicated PH (probable PH). Therefore, the combination of all the criteria measured through the examination led us to observe PH in 28 patients (40.6%).

Table 1 shows the frequencies of the clinical findings studied. For each analysis of S and Sp, we observed low values for

all phonocardiographic parameters, in comparison with Doppler echocardiographic criteria, as shown in **Tables 2** and **3**.

From observing the behavior of the maximum amplitude of S_2 on phonocardiography (with or without splitting) and the amplitude of P_2, in relation to the variation of PASP, we obtained a weak and not statistically significant correlation. The correlation index ρ was 0.185 for S_2 (P = 0.13) and 0.115 for P_2 (P = 0.34).

In assessing the ROC curve, the best cutoff point for PASP was defined as 53 mmHg. At this pressure, simultaneous presence of the three clinical signs studied showed LR+ = 2.32 and LR- = 0.88. The area under the curve was 0.518 (95% CI: 0.376 to 0.659; P = 0.80). This value was very close to the limit set for probable PH. Considering the pretest probability to be the prevalence of PH above 53 mmHg within the sample studied (which was 13%), the post-test probability would increase to 26%. For each clinical sign isolated, there were no points on the curve that yielded LR+ greater than 2 or LR- less than 0.5.

Table 1. Frequencies of clinical findings surveyed

Phonocardiography	Sign present n = 69	Sign absent n = 69
S_2 more intense in the pulmonic area than in the aortic area	49 (71.0%)	20 (29.0%)
$P_2 > A_2$	41 (59.4%)	28 (40.6%)*
P_2 in the mitral area	43 (62.3%)	26 (37.7%)
All signs present simultaneously	32 (46.4%)	37 (53.6%)

*Splitting was not observed in 9 patients (13%).

Table 2. Comparison between clinical findings predictive of pulmonary hypertension (probable)

	S	Sp	LR+	LR-	P
S_2 more intense in the pulmonic area than in the aortic area	63%	27%	0.9	1.3	0.50
$P_2 > A_2$	63%	41%	1.0	0.9	0.90
P_2 in the mitral area	63%	37%	1.0	0.9	0.90
All signs present simultaneously	63%	57%	1.4	0.6	0.20

S = sensitivity; Sp = specificity; LR+ = positive likelihood ratio; and LV- = negative likelihood ratio.

Table 3. Comparison between clinical findings predictive of pulmonary hypertension (possible and probable)

	S	Sp	LR+	LR-	P
S_2 more intense in the pulmonic area than in the aortic area	60%	22%	0.7	1.7	0.12
$P_2 > A_2$	57%	39%	0.9	1.1	0.70
P_2 in the mitral area	68%	41%	1.1	0.7	0.40
All signs present simultaneously	50%	56%	1.1	0.9	0.60

S = sensitivity; Sp = specificity; LR+ = positive likelihood ratio; and LV- = negative likelihood ratio.

DISCUSSION

This study included patients with several types of interstitial lung diseases, with different FVC values and degrees of hypoxemia at the time of evaluation. We observed a range of situations: normal PASP values, mild degrees of PH and also markedly elevated levels of the disease, which constituted the later stages of this comorbidity.

The prevalence of PH in these diseases varies widely according to the diagnosis and pulmonary involvement. It is also a predictor of morbidity and mortality.[17-19]

Doppler echocardiography has been used in other clinical studies to trace PH, in which the prevalence of this disorder was between 5.7% and 73.8% when pulmonary involvement was due to sarcoidosis.[20] In interstitial diseases relating to collagenosis, especially scleroderma, the prevalence of PH was around 18.1%.[21] In idiopathic pulmonary fibrosis, these data are not yet well defined, with the possibility of reaching 84% in patients with advanced degrees of pulmonary involvement.[22] Other authors have also demonstrated its occurrence in one third of patients with IPF (interstitial pulmonary fibrosis).[23] In the present study, the prevalence rates of PH were in agreement with the range of values previously reported.

Since the recognition of inspiratory splitting of the second heart sound by Potain[24] 100 years ago, numerous studies have tried to explain how these heart sound variations occur and whether these changes can be attributed to various disorders. Analyses have been conducted with the aim of comparing traditional phonocardiograms with intracardiac pressure measurements made through cardiac catheterization, in order to relate pressure values to semiological findings.

There are no studies comparing intracardiac pressure measurements obtained using Doppler echocardiography with digital phonocardiogram pulse tracings obtained using an electronic stethoscope, in which patients with interstitial lung disease were specifically targeted. However, the reasons that would lead to increased PASP and possible semiological changes would be similar to those found in other diseases.

The relative intensities of heart sounds are still an integral part of auscultation. In cases of PH, the explanation for findings that the pulmonary component of the second heart sound presents greater intensity than that of the aortic component is believed to be associated with hemodynamic concepts and factors relating to the anatomy of the pulmonary artery.[25] However, there is still controversy about the exact mechanism of this phenomenon.

Earlier studies[25-27] indicated that the amplitude of the P_2 component in PH may not differ significantly from that of A_2. This would be explained by the fact that although the diastolic pressure gradient in the right ventricle is elevated in this condition, it would not exceed the gradient of the left chamber. In this regard, increased amplitude of the P_2 component could only be

expected in those few patients with PH in the later stages of the disease, in which the rate of increase of this gradient would be extremely high. Nevertheless, the analysis on this component did not show statistical significance.[25]

One anatomical factor that could also contribute towards greater amplitude of P_2 in cases of PH would be greater surface area of the pulmonary valve and higher pulmonary artery distensibility, which would produce intense vibration of the semilunar valves, in comparison with the aortic valve. The combination of these factors was significant.[26,27] The data from our study were consistent with the facts previously described and also showed no relationship between higher amplitude of the P_2 component measured by means of phonocardiography and elevated PASP levels measured by Doppler echocardiography.

The PASP values estimated by means of color Doppler echocardiography showed a good correlation with invasive measurements (r = 0.92). The S and Sp values for predicting PH ranged from 79 to 100% for S and from 60 to 98% for Sp, in a study showing high prevalence of PH.[28]

Through evaluating the presence of clinical findings suggestive of PH and comparing the data with measurements of PASP by means of Doppler echocardiography, we noted that our values for S and Sp and the ratios for LR+ and LR- were of low clinical relevance, even when the pulmonary pressure levels were high. The findings from clinical studies that did not report any relationship between the relative intensities of the components of S_2 found through phonocardiography and measurements of pulmonary pressure through catheterization[29] are in agreement with these data. Other clinical findings such as P_2 with higher amplitude than A_2 and the presence of P_2 in the mitral area were also compared in other studies in which pressure measurements were made by means of catheterization. There was no relationship between elevated measurements and the existence of these signs. In this context, the S and Sp values for high-amplitude P_2 components were respectively 58-96% and 19-46%, thus demonstrating a wide variation.[5,7]

So far, the results from rigorous analysis on the S and Sp of semiological findings predictive of PH that were associated with the second heart sound have not been conclusive. However, our results showed that the discriminatory power of each of the clinical parameters evaluated was not very important for the diagnostic suspicion of PH "at the bedside".

It should be noted that even the data from the NIH registry, which was a relevant prospective study, refer to the existence of an accentuated pulmonary component of the second heart sound, seen on clinical examination in more than 90% of the patients with PH, irrespective of its cause.[30] However, the NIH study aimed to investigate factors associated with survival in this population. The only concern was to report the clinical findings, without determining the S and Sp of these semiological findings.

Thus, considering a context in which the prevalence of PH is high, findings of physical signs with high Sp would increase the likelihood of the disease post-test. Absence of signs showing high S would practically dismiss this possibility, and this would be useful for tracing. Our data demonstrated that these signs do not have the capacity to confirm the presence or absence of the disease. Other methods such as Doppler echocardiography are required in order to diagnose this complication.

CONCLUSIONS

Therefore, we can conclude that, in the context of symptomatic evaluation for predicting PH in patients with interstitial diseases, clinical signs are not useful. Their pathophysiological concepts would only be useful for academic thinking. These signs cannot take on the function of reaching a diagnosis.

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Translation, cultural adaptation and reproducibility of the Oxford Shoulder Score questionnaire for Brazil, among patients with rheumatoid arthritis

Tradução, adaptação cultural e reprodutibilidade do questionário Oxford Shoulder Score para o Brasil em pacientes com artrite reumatoide

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PALAVRAS-CHAVE:
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Qualidade de vida.
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ABSTRACT

CONTEXT AND OBJECTIVE: Although shoulder questionnaires validated for Brazil do exist, none of them are aimed at populations with rheumatic disease. We believe that the Oxford Shoulder Score (OSS) may be useful in this population. The objective of this study was to translate the OSS, adapt it to Brazilian culture and test its reproducibility.

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

METHODS: The OSS was translated into Portuguese by two English teachers and was then retranslated into English by two native English teachers. These translations were reviewed by a committee to establish the version of OSS-Brazil to be administered to 30 patients with rheumatoid arthritis (RA) and shoulder pain, in order to test the cultural adaptation. The validity and reproducibility was tested among another 30 patients with RA and shoulder pain, of both genders and aged 18 to 65 years. The internal consistency and reproducibility were analyzed. The following instruments were evaluated: OSS-Brazil; a numerical scale for shoulder pain; DASH; HAQ and SF-36.

RESULTS: The internal consistency was 0.957 and the intra and inter-rater reproducibility was 0.917 and 0.861, respectively. A high level of correlation was found between OSS-Brazil and the following: HAQ (-0.663), DASH (-0.731) and the SF-36 domains of functional capacity (0.589), physical aspects (0.507), pain (0.624), general state of health (0.444), vitality (0.634) and mental health (0.578).

CONCLUSION: OSS-Brazil was successfully translated and adapted, and this version exhibited good internal consistency, reliability and construct validity.

RESUMO

CONTEXTO E OBJETIVO: Apesar de existirem questionários de ombro validados para o Brasil, nenhum deles é voltado para a população com doenças reumáticas. Acreditamos que o Oxford Shoulder Score (OSS) possa ser útil nessa população. O objetivo deste estudo foi traduzir, adaptar à cultura brasileira e testar a reprodutibilidade do OSS.

TIPO DE ESTUDO E LOCAL: Estudo de validação realizado nos ambulatórios da universidade.

MÉTODOS: Foi realizada a tradução para o português por dois professores de inglês e depois a retradução para o inglês por dois professores nativos da língua inglesa. Essas traduções foram revisadas por um comitê para estabelecer a versão do OSS-Brasil, que foi aplicada em 30 pacientes com artrite reumatoide (AR) e dor no ombro para testar a adaptação cultural. A validade e a reprodutibilidade foram testadas em outros 30 pacientes com AR e dor no ombro de ambos os gêneros com idade entre 18 a 65 anos. Foram analisadas a consistência interna e a reprodutibilidade. Foram avaliados os seguintes instrumentos: OSS-Brasil; escala numérica de dor no ombro; DASH; HAQ e SF-36.

RESULTADOS: A consistência interna foi 0,957 e a reprodutibilidade intra-avaliador e interavaliador foi 0,917 e 0,861, respectivamente. Foi observado alto nível de correlação do OSS-Brasil com HAQ (-0,663), DASH (-0,731) e os domínios do SF-36: capacidade funcional (0,589); aspectos físicos (0,507); dor (0,624); estado geral de saúde (0,444); vitalidade (0,634); saúde mental (0,578).

CONCLUSÃO: O OSS-Brasil foi traduzido e adaptado com sucesso, com boa consistência interna, confiabilidade e validade de construção.

INTRODUCTION

The impact of chronic diseases on individuals has led to development of quality-of-life instruments in order to better measure physical and mental factors, social wellbeing and factors that preserve function or control symptoms. Shoulder dysfunction is an important cause of mortality and incapacity,[1] and is one of the most common peripheral complications in the general population.[2,3] It is known that activities that use the arms or hands increase the risk of development of shoulder pain.[3] It has been estimated that the incidence of shoulder problems ranges from 7 to 25 cases per 1,000 consultations with general practitioners.[4] The prevalence of shoulder pain among adults under 70 years of age is between 7% and 27%, and it is between 13.2% and 26% for the over-70s.[5]

The Oxford Shoulder Score (OSS) is an instrument that specifically evaluates pain and quality of life in relation to inflammatory and degenerative shoulder diseases.[6] It is a short, practical, reliable and valid questionnaire that is also sensitive to clinically important changes. However, it has not been adapted and validated for use among the Brazilian population. It may be important for detecting shoulder alterations and for measuring the impact of treatment.

Despite the existence of validated Portuguese-language shoulder questionnaires, none are directed towards the population with rheumatological diseases. The OSS was originally validated for several diseases including osteoarthritis and inflammatory arthritis.[6] We believe the OSS may be very helpful in relation to clinical treatment of patients with rheumatological diseases.

Almost 12% of rheumatoid arthritis (RA) patients may have involvement of the shoulder joint, which can lead to pain and disability.[7] No specific instrument for measuring shoulder abnormalities in RA patients currently exists.

OBJECTIVE

The objective of this study was to translate the OSS, adapt it to Brazilian culture and test its reproducibility.

METHODS

The study was performed in two stages: firstly, the original questionnaire was translated and adapted for Portuguese; and secondly, its reproducibility and external validity were tested in relation to the Brazilian population with rheumatoid arthritis and shoulder pain.

Translation and adaptation process

The original authors of the OSS questionnaire authorized its use for cultural adaptation. The translation and cultural adaptation followed the standardization model proposed by Guillemin et al.[8,9]

The questionnaire was independently translated by two English teachers who provided two separate Portuguese translations. Both versions were presented to a committee of specialists consisting of a rheumatologist and two physiotherapists with experience in rheumatology rehabilitation. The committee analyzed the translations to check for errors, and then chose one version for each translated question, thereby creating an agreed consensus version.

After this process, the consensus version was back-translated into English by two native-speaker English teachers who were also proficient in Portuguese and had not had any contact with the original instrument. During this stage, the translators were not given any information about the study or the questionnaire.

The two English versions were then presented to the review committee and compared against the original questionnaire. This analysis showed that the original questionnaire and the consensus version were semantically equivalent, and the latter was then accepted as the final version. The final version of the questionnaire (**Appendix 1**) was used on 30 patients with RA and shoulder pain, in order to test its comprehensibility.

Patients

Sixty patients with RA and shoulder pain complaints were selected consecutively at the Rheumatology Outpatient Clinic of the Federal University of São Paulo (Universidade Federal de Sao Paulo, UNIFESP): 30 in the first stage and 30 in the second stage. The study included male and female patients aged between 18 and 65 years who were classified as presenting RA under the criteria of the American College of Rheumatology (ACR),[10] and who reported having shoulder pain within the last month.[11] The study excluded individuals presenting any of the following: reduced shoulder range of motion due to skin lesions (e.g. burns), other autoimmune rheumatological diseases, neurological diseases, other upper-limb musculoskeletal diseases, shoulder trauma within the last week or shoulder instability; and also any patients who did not understand Portuguese.

This study was approved by the Ethics Committee of the UNIFESP, and all the patients who participated signed a written informed consent form.

Evaluations

For the inter-observer reproducibility, the evaluations were performed during a single day by two physiotherapists and for the intra-observer reproducibility, the evaluations were carried out between 7 and 15 days after the initial evaluation, by the same physiotherapist.

Evaluation instruments

- Oxford Shoulder Score – A questionnaire containing 12 questions for patients with inflammatory and degenerative shoulder diseases. It is not appropriate for patients with shoulder instability. Each question has 5 potential answers; carrying

a score of between 0 and 4. The total score can range from 0 (worst) to 48 (best).[12] The questions investigate pain and quality of life. The questionnaire is short, practical, reliable and valid, and is sensitive to clinically important changes.[6]

- Numerical Pain Scale (NPS) – A subjective evaluation of pain on a numerical scale of 0 to 10 centimeters, such that 0 represents absence of pain and 10 unbearable pain.[13]
- Disabilities of the Arm, Shoulder and Hand (DASH) scale – An instrument containing three modules: Module 1 (Q1) relates to sports and musical activities; Module 2 (Q2) relates to work; and Module 3 (Q3) relates to performance of activities. intensity of pain, symptoms of weakness, rigidity and paresthesia, negative effects on social activities, difficulty in sleeping and psychological harm, with reference to the previous week. Modules Q1 and Q2 each contain 4 questions, while Q3 is made up of 30 questions. Each question is scored using 5 scoring levels, and the final score of Q3 is calculated using the sum of the first 30 questions, from which the number of questions answered is subtracted and divided by 1.2; whereas for Q1 and Q2 the sum is subtracted by 4 and divided by 0.15.[14]
- Health Assessment Questionnaire (HAQ) – Evaluation of functional capacity: 20 questions split into 8 subscales relating to different aspects of activities within daily life in which the upper and lower limbs are used. The score is obtained by adding the highest scores from each subdivision and then dividing this partial result by 8. The scores range from 0 to 3, and the higher the resultant score is, the worse the individual's functional capacity is.[15]
- Short Form-36 (SF-36) – Thirty-six questions divided into 8 domains that evaluate quality of life, covering factors relating to: functional capacity, physical limitations, pain, general state of health, vitality, social factors, emotional factors and mental health. The scores can range from 0 (worst) to 100 (best), and the higher the score is, the better the individual's quality of life is.[16]
- The time taken to apply each questionnaire is noted.

Statistical analysis

The sample was descriptively analyzed using means, standard deviations and percentages. Intraclass correlation coefficients were used to analyze inter and intra-observer reproducibility and the Spearman correlation test was used to ascertain the correlation between the OSS and the following: NPS scores for shoulder pain, DASH, HAQ and SF-36.

Cronbach's alpha test was used to evaluate the internal consistency of the OSS. All questionnaire items were examined for correlations with the general score. Cronbach's alpha test was also calculated through eliminating a single item from the total of 12 questions.[6]

All the data were analyzed using the SPSS software for Windows, version 17.0.

RESULTS

A total of 221 patients classified as RA in accordance with the criteria of the American College of Rheumatology (2010), who reported having shoulder pain, were interviewed. Of these, 60 were included in the present study: 30 in the first stage and 30 in the second stage (**Table 1**). Most of the interviewees did not fulfill the inclusion criteria because they did not present shoulder pain or had juvenile idiopathic arthritis.

For the cultural adaptation, the final version of the OSS was used among 30 patients in order to evaluate their comprehension of each question. Since the questions were understood by more than 90% of the patients interviewed, all the questions were retained without the need for any changes.

Regarding reproducibility, the patients answered all the questionnaires at the first evaluation and the times taken were recorded. **Table 2** presents the absolute values of all the scores and the average times taken to apply the questionnaires. In relation to inter-observer reproducibility, no differences in the measurements made by the two evaluators were detected (P = 0.073) and the intraclass correlation coefficient (ICC) was 0.92, thus showing strong agreement between the evaluators. In relation to intra-observer reproducibility, no differences in the two measurements were detected (P = 0.290) and the intraclass correlation coefficient (ICC) was 0.86.

The internal consistency was high (Cronbach's alpha = 0.93). Elimination of one answer item from each of the 12 questions in

Table 1. Demographic and clinical characteristics of the patients

	Cultural equivalence mean ± SD	Reproducibility mean ± SD
	n (30)	n (30)
Age (years)	56.00 ± 9.05	53.83 ± 8.86
Gender (%)		
Male	10	13
Female	90	87
Schooling (years)	7.56 ± 4.15	7.43 ± 4.62
Illiterate	0	1
Primary	3	3
Junior high school	27	26
Senior high school and beyond	0	0
Dominant hand (%)		
Right	93	97
Left	7	3
Time since diagnosis (years)	13.00 ± 7.77	14.46 ± 9.76
Profession (%)		
Manual worker	-	63
Non-manual worker	-	17
Retired	-	20
BMI (kg/m^2)		26.47 ± 4.92

Data are expressed as mean ± standard deviation (SD); BMI = body mass index.

the questionnaire resulted in Cronbach's alpha values of > 0.96. Item-total correlation analyses yielded coefficients greater than or equal to 0.52 in all cases (**Table 3**).

Construct validity was tested using Spearman's correlation coefficient (r = 0.75). Significant correlations between the Brazilian OSS and the HAQ, DASH and SF-36 questionnaires were observed, except in the domains of social factors and limitations due to emotional factors (**Table 4**).

Table 2. Scores and time taken for the instruments used

Variable	Mean ± SD n (30)	Average time (minutes: seconds) ± SD
Numerical pain scale (cm)		-
Right	5.96 ± 1.92	
Left	5.30 ± 2.85	
SF-36		
Physical functioning	44.67 ± 19.07	
Role - physical	16.67 ± 30.32	
Bodily pain	45.73 ± 17.78	
General health	50.33 ± 11.74	6:04 ± 1:02
Vitality	50.33 ± 20.36	
Social functioning	63.70 ± 28.12	
Role - emotional	30.80 ± 40.77	
Mental health	57.73 ± 20.68	
HAQ	1.14 ± 0.54	2:48 ± 0:51
DASH		
Module relating to work	7.92 ± 16.32	
Module relating to performance of activities	38.25 ± 16.35	6:27 ± 1:34
OSS	26.17 ± 8.96	2:26 ± 0:27

Data are expressed as mean ± standard deviation (SD); SF-36 = Medical Outcome Study Short Form-36 Health Survey; HAQ = Health Assessment Questionnaire; DASH = Disabilities of the Arm, Shoulder and Hand; OSS = Oxford Shoulder Score.

Table 3. Oxford Shoulder Score internal consistency

Question	Mean score ± SD	Correlation with total number of items	Alpha if item removed
1	2.27 ± 0.85	0.79	0.97
2	1.53 ± 1.02	0.73	0.96
3	1.00 ± 0.97	0.73	0.96
4	1.23 ± 1.17	0.56	0.97
5	1.90 ± 1.45	0.84	0.96
6	1.37 ± 1.17	0.76	0.96
7	2.10 ± 1.25	0.87	0.97
8	3.10 ± 0.91	0.55	0.97
9	1.90 ± 1.25	0.72	0.97
10	1.27 ± 0.89	0.76	0.96
11	2.47 ± 1.09	0.52	0.97
12	2.70 ± 0.90	0.54	0.97

SD = standard deviation.

Table 4. Correlations* between OSS and the NPS, HAQ, DASH and SF-36 domains

Instruments	P-value	r
NPS	-	-
HAQ	< 0.001	-0.663
DASH	< 0.001	-0.731
SF-36		
Physical functioning	0.001	0.589
Role - physical	0.004	0.507
Bodily pain	< 0.001	0.624
General health	0.014	0.444
Vitality	< 0.001	0.634
Social functioning	-	-
Role - emotional	-	-
Mental health	0.001	0.578

OSS = Oxford Shoulder Score; NPS = Numerical Pain Scale; HAQ = Health Assessment Questionnaire; DASH = Disabilities of the Arm, Shoulder and Hand; SF-36 = Medical Outcome Study Short Form-36 Health Survey; p > 0.05. *All correlations were analyzed using Spearman's test. Spearman correlation r = -0.25 to 0 or 0 to 0.25 was considered to be small or null; r = -0.50 to -0.25 or > 0.25 to 0.50, weak correlation; r = -0.75 to -0.50 or > 0.50 to 0.75, moderate correlation; and r = -1.00 to -0.75 or > 0.75 to 1.00, strong correlation.

DISCUSSION

The overall presence of RA in the general population ranges from 0.5% to 1% and approximately 11.5% of RA patients may have shoulder dysfunctions.[4,7] Until now, no specific instrument was available in Brazil for evaluating the shoulders in RA cases. The instrument normally used for evaluating the upper limbs is DASH, which has been translated and validated for use among patients with RA. However, this instrument is generic and evaluates the entire upper limb,[14] and is also lengthy and difficult to understand, as was observed in the current study. After making a comprehensive review of the literature, we chose the OSS for the translation and cultural adaptation process because it presents adequate validity and reproducibility and is also quick to apply, given that it is made up of easily comprehensible questions.[6]

Recently, a systematic review evaluated the development process, psychometric properties and administration of specific instruments for shoulder assessment. Its authors concluded that the OSS questionnaire should be the first choice for measuring function and disability among patients with shoulder dysfunction. Moreover, this instrument has shown high reproducibility, validity and responsiveness and is easy to administer, which makes it highly recommended.[17] The OSS exists in several languages, including German, Italian, Dutch, Turkish, Korean and Danish.[18-23]

The importance of translating and validating a questionnaire for which the psychometric properties have already been tested comes from its unification of the language of clinical research. Through doing this, studies can be conducted around the world

using the same evaluation instrument. This also facilitates comparison of data from different populations around the world.

Falcão et al. proposed a method for translation and cultural adaptation of instruments in order to reduce the time taken and cost of these studies.[23] However, we chose to use Guillemin's methodology, which is a specific method for translation and cultural adaptation of instruments. This methodology has been used in several studies and their criteria are internationally recognized.[8,9]

We chose to apply the questionnaire using interviewers because our patients' low educational level would make self-administered questionnaires difficult to understand and answer. Our participants presented an average of 7.43 years of schooling, thus constituting a population of low educational level. This is common among patients using the Brazilian national health system (Sistema Único de Saúde, SUS), who generally have an average of 4 years of schooling, such that they know how to read and write.[24]

The original Oxford Shoulder Score presented a scoring range from 12 to 60 points. However, the questionnaire was recently revised and the scoring system changed such that the range is now from 0 to 48 points. Thus, this was the system of calculation that we used in our study.[6,12]

The average OSS scores obtained by interviewers I and II in the evaluations were similar. These results suggest that the functional involvement of these patients in relation to the shoulder was moderate, i.e. similar to the findings from other studies.[18,21]

In the present study, the intraclass correlation coefficient was 0.92 for intra-observer reproducibility. This figure is the same as the level in the original instrument, which was also 0.92. This shows that the questionnaire has good reproducibility.[6]

The inter-observer evaluation was performed after an interval of 7 to 15 days. This period was chosen because it was highly unlikely that the patient would remember the content of the questionnaire or that any substantive changes in their disease would have occurred during that time. Other studies have used shorter intervals of between 24 and 48 hours in order to avoid occurrences of changes to the participants' state of health. Despite our use of a longer interval than those used in other studies, this did not affect the ICC result, as compared with the findings from other studies.[6,18,21]

According to the present study, the internal consistency was high, with Cronbach's alpha of 0.93, which was similar to that of the original version, with a value of 0.87. In the correlations using the total number of items, Cronbach's alpha was higher than 0.52 for all questions, thus showing a good level of differentiation. After elimination of one item from the total of 12 questions, the Cronbach's alpha results were 0.96 or 0.97. These results were similar to those in the Italian version, which showed Cronbach's alpha of 0.93, while the correlation using the total number of items was greater than 0.57.[21]

The correlation between the OSS and the DASH, HAQ and SF-36 questionnaires was moderate. This level of correlation was expected because DASH, HAQ and SF-36 also evaluate function and quality of life. The OSS had a positive correlation with SF-36, and a negative correlation with DASH and HAQ, i.e. it was inversely proportional, since higher score are better in DASH and HAQ.

The correlation between the OSS and the NPS was not significant, and this finding was similar to that of the original questionnaire because the purpose of the OSS is to measure quality of life and function. We expected to find a correlation between these variables, from the principle that with reductions in pain, there would be a positive response in relation to function and quality of life, although this is not always present in medical practice.

In relation to the average time taken to apply the questionnaires used, we noted that the OSS and HAQ took longer than the other questionnaires. However, HAQ evaluates overall function in patients with RA.

Within the study limitations, the greater prevalence of females in our sample may be explained by the greater prevalence of RA among females. However, we believe that this does not prevent the use of this instrument among male patients.[25] The lack of a sensitivity test in the present study can also be considered to be a limitation, because this could detect changes as a result of interventions. This would make the instrument validation process more robust.

CONCLUSION

The Oxford Shoulder Score questionnaire in Portuguese is a valid and reliable instrument for evaluating the quality of life and function of patients with rheumatoid arthritis and shoulder pain.

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APPENDIX 1

Nome:_____ Data: ___/___/_____

PROBLEMAS COM OS OMBROS

Por favor marque com um (X) apenas uma resposta para cada pergunta:

1. **Nas últimas 4 semanas ...**
   Como você descreveria a pior dor que sentiu no ombro?
   ( ) Nenhuma ( ) Fraca ( ) Média ( ) Forte ( ) Insuportável
2. **Nas últimas 4 semanas...**
   Você teve alguma dificuldade para vestir-se por causa do ombro?
   ( ) Nenhuma dificuldade ( ) Um pouco de dificuldade ( ) Dificuldade moderada
   ( ) Dificuldade extrema ( ) Impossibilidade total
3. **Nas últimas 4 semanas...**
   Você teve alguma dificuldade para entrar ou sair de carros ou no uso de transporte público por causa do ombro?
   ( ) Nenhuma dificuldade ( ) Um pouco de dificuldade ( ) Dificuldade moderada
   ( ) Dificuldade extrema ( ) Impossibilidade total
4. **Nas últimas 4 semanas...**
   Você conseguiu usar garfo e faca ao mesmo tempo?
   ( ) Sim, com facilidade ( ) Com pouca dificuldade ( ) Com dificuldade moderada
   ( ) Com dificuldade extrema ( ) Não Conseguiu
5. **Nas últimas 4 semanas...**
   Você conseguiu fazer as compras da casa sozinha?
   ( ) Sim, com facilidade ( ) Com pouca dificuldade ( ) Com dificuldade moderada
   ( ) Com dificuldade extrema ( ) Não Conseguiu
6. **Nas últimas 4 semanas...**
   Você conseguiu atravessar um cômodo carregando uma bandeja com um prato de comida?
   ( ) Sim, com facilidade ( ) Com pouca dificuldade ( ) Com dificuldade moderada
   ( ) Com dificuldade extrema ( ) Não Conseguiu
7. **Nas últimas 4 semanas...**
   Você conseguiu pentear ou escovar seu cabelo com o braço afetado?
   ( ) Sim, com facilidade ( ) Com pouca dificuldade ( ) Com dificuldade moderada
   ( ) Com dificuldade extrema ( ) Não Conseguiu
8. **Nas últimas 4 semanas...**
   Como você descreveria a dor que habitualmente sentiu no ombro?
   ( ) Nenhuma ( ) Muito fraca ( ) Fraca ( ) Moderada ( ) Intensa
9. **Nas últimas 4 semanas...**
   Você conseguiu pendurar suas roupas no guarda-roupa, usando o braço afetado?
   ( ) Sim, com facilidade ( ) Com pouca dificuldade ( ) Com dificuldade moderada
   ( ) Com dificuldade extrema ( ) Não Conseguiu
10. **Nas últimas 4 semanas...**
    Você conseguiu lavar e secar a axila dos dois braços?
    ( ) Sim, com facilidade ( ) Com pouca dificuldade ( ) Com dificuldade moderada
    ( ) Com dificuldade extrema ( ) Não Conseguiu
11. **Nas últimas 4 semanas...**
    Quanto você diria que a dor no ombro interferiu no seu trabalho habitual, incluindo trabalho doméstico?
    ( ) Nada ( ) Pouco ( ) Moderadamente ( ) Muito ( ) Totalmente
12. **Nas últimas 4 semanas...**
    Você enfrentou dificuldade para dormir por causa da dor no ombro?
    ( ) Nenhuma noite ( ) 1 ou 2 noites ( ) Algumas noites ( ) A maioria das noites
    ( ) Todas as noites

Por favor certifique-se que você respondeu todas as questões.
Muito obrigado!

Escore de 0 a 19 → Pode indicar artrite severa no ombro.
Escore de 20 a 29 → Pode indicar artrite grave no ombro.
Escore de 30 a 39 → Pode indicar artrite leve a moderada no ombro.
Escore de 40 a 48 → Pode indicar uma função satisfatória no ombro.

Abandonment of nicotine dependence treatment: A cohort study

Abandono do tratamento da dependência à nicotina: Um estudo de coorte

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KEY WORDS:
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PALAVRAS CHAVE:
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Transtorno por uso de tabaco.
Abandono do uso de tabaco.
Motivação.

ABSTRACT

CONTEXT AND OBJECTIVE: Non-adherence to treatment is one of the hindering factors in the process of smoking cessation. This study aimed to compare sociodemographic characteristics, smoking status and motivation among smokers who maintained or abandoned treatment to stop smoking, and to analyze associations between sociodemographic factors and smoking.

DESIGN AND SETTING: Cohort study on 216 smokers who were attended at healthcare units in Cuiabá, Mato Grosso.

METHODS: The instruments used were the Fagerström, URICA and CAGE questionnaires. Data from the initial evaluation was analyzed using the two-proportion test ($\alpha < 0.05$). The patients were monitored for six months and those who abandoned treatment were accounted for. Bivariate analysis was conducted, using crude prevalence ratios and 5% significance level ($P < 0.05$), with abandonment of treatment as the outcome variable. Associations with $P < 0.20$ were selected for multiple robust Poisson regression (RPa).

RESULTS: The abandonment rate was 34.26%. Males and individuals in the 20-39 age group, in employment, with low motivation, with shorter time smoking and lower tobacco intake predominated in the dropout group. In the final model, gender (RPa 1.47; 95% CI: 1.03-2.10) and age group (RPa 3.77; 95% CI: 1.47-9.67) remained associated with abandonment.

CONCLUSION: Males and individuals in the 20-39 age group, in employment, with low motivation, with shorter time smoking and lower tobacco intake more frequently abandoned the treatment. Male gender and younger age group were associated with abandonment of nicotine dependence treatment.

RESUMO

CONTEXTO E OBJETIVOS: A não adesão ao tratamento é um dos fatores dificultadores do processo de cessação do tabagismo. Este estudo objetiva comparar características sociodemográficas, *status* do tabagismo e motivação entre fumantes que abandonaram ou não o tratamento do tabagismo e analisar a associação entre fatores sociodemográficos e uso do tabaco.

TIPO DE ESTUDO E LOCAL: Estudo de coorte, com 216 fumantes atendidos em unidades de saúde de Cuiabá, MT.

MÉTODOS: Instrumentos: foram utilizados os questionários Fagerström, URICA e CAGE. Dados da avaliação inicial foram analisados via teste de duas proporções ($\alpha < 0.05$) e os pacientes foram acompanhados por seis meses, contabilizando-se os que abandonaram o tratamento. Foi realizada análise bivariada, utilizando a razão de prevalência bruta, com nível de significância 5% ($P < 0,05$); tendo como desfecho o abandono do tratamento. As associações com $P < 0,20$ foram selecionadas para a regressão de Poisson múltipla robusta (RPa).

RESULTADOS: A taxa de abandono foi de 34,26%. O predomínio no grupo abandono foi do gênero masculino, na faixa etária 20-39 anos, trabalhadores, com baixa motivação, menor tempo de fumo e de carga tabágica. No modelo final, gênero (RPa 1,47; IC 95% 1,03-2,10) e faixa etária (RPa 3,77; IC 95% 1,47-9,67) permaneceram associados ao abandono.

CONCLUSÃO: Indivíduos do gênero masculino, na faixa etária de 20-39, que trabalham, com baixa motivação, menor tempo de fumo e de carga tabágica abandonaram mais o tratamento. Gênero masculino e faixa etária jovem estão associados ao abandono do tratamento da dependência à nicotina.

INTRODUCTION

Both as a risk factor and as a chronic disease, smoking is one of the great evils of humanity. It has become a worldwide public health problem, since it causes roughly six million deaths a year through direct consumption of tobacco and its derivatives or through exposure to environmental tobacco smoke.[1]

In Brazil, the prevalence of smoking has been declining over the years, ever since public policies were implemented through the National Tobacco Control Program (Programa Nacional de Controle do Tabagismo, PNCT) in 1989.[2] Currently, this program is called the National Program for Controlling Tobacco and Other Risk Factors for Cancer (Programa Nacional de Controle do Tabagismo e Outros Fatores de Risco de Câncer, PNCTOFR). PNCTOFR is recognized worldwide as one of the most effective programs for controlling tobacco, through its development of multiple actions, and it is an international reference.[3]

The program involves two main action groups: the first one targets prevention of starting to smoke, focusing on children and adolescents; and the second one aims at encouraging smokers to quit smoking.[4] Tobacco treatment was added to the Brazilian National Health System (Sistema Único de Saúde, SUS) through an agreement with the Tripartite Interagency Commission (Comissão Intergestores Tripartite, CIT), which has created ordinances approving an implementation plan for addressing and treating smoking within SUS, with clinical protocols and therapeutic guidelines for nicotine dependence.[2]

The recommended treatment for smoking is based on psychological support (cognitive-behavioral therapy, CBT) and on the use of medications to control abstinence syndrome.[4] The consensuses on the treatment of smoking have recommended the medications used by the PNCT as first rate: transdermal nicotine patches, nicotine chewing gum and bupropion hydrochloride.[5]

However, these consensuses have not achieved the desired therapeutic success, with low success rates in clinical trials.[6] Another problem is the high rates of abandonment during treatment. A high number of patients who are enrolled in programs abandon treatment without having participated in the necessary number of CBT meetings and discontinue their use of medication. These patients are therefore accounted for in surveys as patients presenting treatment failure or relapses during treatment.[7]

The issues surrounding abandonment of treatment have been poorly studied and need to be taken more seriously, given that each patient who gives up the program and continues to smoke will suffer the direct harm caused by tobacco and the impact of morbidity and mortality resulting from diseases related to tobacco consumption. Moreover, abandonment of treatment generates an economic and social burden. Smoking causes an annual loss of R$ 338.6 million to SUS.[8]

In the city of Cuiabá, Mato Grosso, the program functions in accordance with the guidelines and standards of the PNCT, with actions aimed at education and promoting health.[3] However, one of the difficulties that healthcare professionals find in practice when implementing these actions is that even though the demand for this service is high, the rate of abandonment of treatment during the process of smoking cessation is significant. Some of the hypotheses that can be cited are the level of motivation and the smoker's occupation and sociodemographic characteristics, which show that there is a need to deepen this understanding in order to propose actions and approaches for treating dependence that are more efficient.

OBJECTIVE

The objective of this study was to investigate the associations between abandonment of treatment for nicotine dependence and a set of clinical and sociodemographic variables, among a sample of patients seen at healthcare units in the city of Cuiabá, Mato Grosso.

METHODS

A cohort study was conducted among patients who were over 18 years old and sought or were referred to the smoking cessation programs of four healthcare units in Cuiabá, Mato Grosso (Júlio Müller University Hospital, Campo Velho Healthcare Center and Coxipó and Planalto Polyclinics). All the smokers who enrolled in the initial phase of these programs, from May to August 2012, were invited to participate in this study. Those who agreed were included and their research records were numbered sequentially, thus making up the population of this present study, totaling 216 participants.

The criteria for inclusion were that the subjects needed to be smokers, be over 18 years old and have the desire to quit smoking. These subjects were enrolled in the initial phase of the cessation program. Participants who had cognitive limitations, were dependent on other psychoactive substances, except caffeine, or were pregnant or breastfeeding women were excluded from this study.

In this study, the size of the population (N) and the proportion of smokers who would be able to abandon cigarettes in the city of Cuiabá during the data collection were unknown. Therefore, in order to determine the approximate size of the sample (n), an expression taking the coefficient of reliability to be 95% and the sampling error to be 7.00% (d = 0.07) was used.[9-11] This indicated that the distance between the sample estimate and the population parameter should not exceed this value, with a proportion of 0.5 (P = 0.5). This value was used because of what was not known about the prevalence of the outcome, and also because this value provided greater variance and made it possible to obtain a sample of larger size with a given fixed precision.[12]

From using the expression (1), the size of the sample obtained was 196 participants. Considering a percentage loss of 10%, the final sample size was 216 individuals. Thus, all the patients who had enrolled in the programs since May 2012 participated in this study, and the data collection ended when the number of patients needed for the sample was reached.

$$n = \frac{(z_{\alpha/2})^2 \, p(1-p)}{d^2} \quad (1)$$

The same treatment protocol was used in this study for all the patients: nicotine replacement therapy (NRT) + bupropion + cognitive behavioral therapy (CBT). The participants who remained in the program were followed up by a doctor during the initial phase, for 30 days after starting to take medication, and at monthly evaluations until completing six months of treatment. After the initial evaluation conducted by a psychologist and after the evaluation instruments had been applied, all of the participants were invited to attend CBT, consisting of four group sessions (each with 10 to 15 patients), lasting one hour and a half, once a week over a four-week period.[4] Subsequently, there were five follow-up meetings: after 15 days, 30 days, 60 days, 90 days and 180 days.

The instruments used in the initial individual interview with a psychologist for data collection were the following:

1. **Sociodemographic profile questionnaire:** This was specifically designed for this study and was constructed based on the model used and distributed by INCA/MS (National Cancer Institute, Ministry of Health). It contains two parts: Part I – identification and sociodemographic data, with the following variables: gender, age, marital status, occupation, education and family income; and Part II – status of tobacco use, with the following variables: time spent smoking, number of cigarettes per day, age when smoking started and the number of attempts to quit.
2. **Fagerström Test for Nicotine Dependence (FTND):**[13] This is used for analysis on nicotine dependence, such that scores higher than the median (≥ 6) are categorized as having high dependence, and those with values below 6, as having low dependence.
3. **CAGE (Cut-down, Annoyed, Guilty and Eye-opener) questionnaire:** This was designed for detecting suspected alcoholism. It was developed in 1974[14] and validated in Brazil in 1983.[15]
4. **URICA (University of Rhode Island Change Assessment),[16] reduced version:** This evaluates the motivational stage (precontemplation, contemplation, preparation and action) in relation to drug-using behaviors. The Transtheoretical Model of Behavioral Change (TMBC), based on the internships of the American James O. Prochaska, was validated and standardized for the Brazilian population in relation to illicit drugs, with transcription to tobacco.[17] A previous study was used as a reference to dichotomize the data into precontemplation/contemplation and preparation/action.[18]

After the instruments had been fully administered, the data obtained were checked and entered twice into the Epidata software, version 3.1. In the present study, the results from the instruments in the initial evaluation were analyzed, and the patients were monitored for six months, taking into account the number of people who abandoned the program. Abandonment was defined as a situation in which after a smoker had attended the medical consultation and the initial evaluation with the psychologist, he or she did not attend the first CBT session or gave up the treatment at a subsequent session.

The data analysis consisted initially of descriptive analysis using position and variation measurements (means, medians and standard deviations) and proportions, for the smoking variables, considering the categories of abandonment and non-abandonment of treatment. Subsequently, inferential analysis on the data was carried out using the technique of comparison of two proportions, considering the normal distribution with its respective 95% confidence interval. Therefore, in order to test the difference between these two proportions, the test was used with a significance level of 0.05 ($\alpha < 0.05$).[19]

To determine whether the data on the six quantitative variables relating to smoking presented normal distribution, the Shapiro test was used. Through this test, it was found that the data did not have normal distribution. To analyze the difference between the group that abandoned treatment and the group that did not abandon it, the nonparametric Mann-Whitney test was used for both categories, comparing the differences between the average levels of the variables relating to the patient's smoking. In this comparison, the significance level was taken to be 0.05.

Bivariate analysis was conducted, taking the crude prevalence ratio as a reference, with a confidence interval of 95% and significance level of 5% ($P < 0.05$). The variables with significance levels lower than 20% ($P < 0.20$), as shown by the chi-square test, were retained for testing in a multiple Poisson regression model with strong variance (RPa), in which the variables that presented P values lower than 5% ($P < 0.05$) remained in the final model.

The Poisson model was chosen because this has been preferred in the epidemiological literature for estimating the relative risk in cross-sectional or longitudinal studies, using the prevalence ratio.[20]

The dependent variable (outcome) was treatment dropout, and the independent variables considered in the model were gender, age group, motivational level, occupational level, number of

years of schooling, CAGE score, psychiatric disorders, physical activity and religion.

This study was submitted to our institution's Research Ethics Committee on May 9, 2012, under submission certificate (CAAE) no. 0106612.6.0000.5541, and was approved through the committee's resolution no. 19548.

RESULTS

Out of the 216 initial patients, 74 (34.26%) gave up the treatment during the process, and 142 completed the treatment within six months (65.74%) (**Figure 1**).

The results from comparisons of the sociodemographic variables, CAGE scores, psychiatric treatments and motivational levels of the participants in both groups (abandonment and non-abandonment) are presented in **Table 1**. This table shows that there were statistically significant differences ($P < 0.05$) in the proportions of four variables, for which the P values are highlighted in bold type. These variables are described below.

Differences were found in relation to gender, age group, occupation and motivational level. For these variables, the categories that most significantly contributed to abandonment and non-abandonment were male gender ($P = 0.030$ and $\Delta = 15.01$), belonging to the 20-39 year age group ($P = 0.011$ and $\Delta = 16.17$), having employment ($P = 0.016$ and $\Delta = 15.93$) and having lower motivational level ($P = 0.008$ and $\Delta = 12.31$). On the other hand,

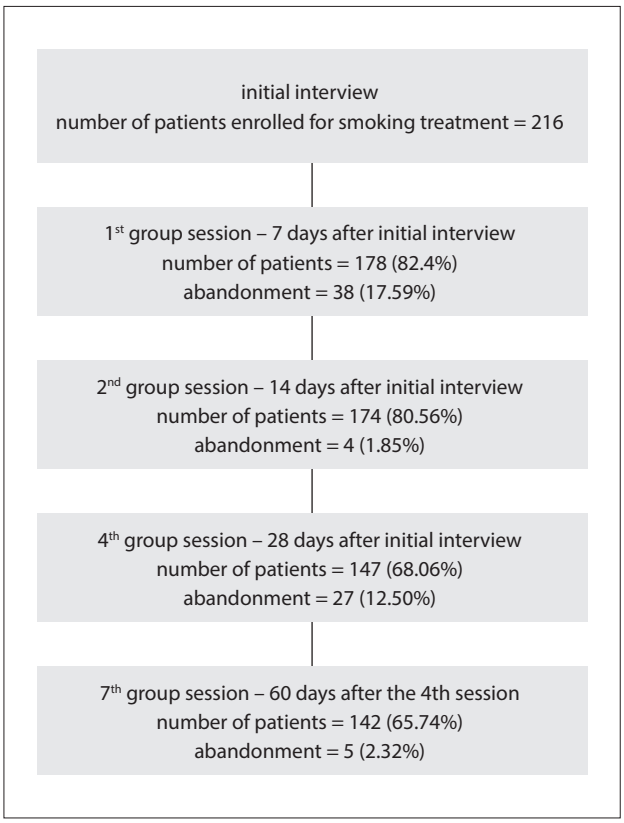

Figure 1. Monitoring of abandonment of treatment among patients during the process.

Table 1. Numbers and percentages of participants, comparing abandonment with non-abandonment of nicotine dependence treatment, according to sociodemographic variables. Cuiabá, Mato Grosso, 2013

Variables	Category	Smokers				Δ_p	*95% CI
		Abandonment		Non-abandonment			
		n	%	n	%		
Gender	Male	33	44.59	42	29.58	15.01	**[1.43; 28.60]**
	Female	41	55.41	100	70.42	-15.01	**[-28.60; -1.43]**
Age group	20-39 years	25	33.78	25	17.61	16.17	**[3.71; 28.64]**
	40-59 years	45	60.81	90	63.38	-2.57	[-16.23; 11.09]
	60 years or over	4	5.40	27	19.01	-13.61	**[-21.87; 5.35] F**
Years of education	≤ 8	24	32.43	40	28.17	4.26	[-8.72; 17.24]
	> 8	50	67.57	102	71.83	-4.26	[-17.24; 8.72]
Occupation	In work	20	27.03	61	42.96	-15.93	**[-28.92; -2.94]**
	Out of work	54	72.97	81	57.04	15.93	**[2.94; 28.92]**
Religion	Catholic	45	60.81	97	68.31	-7.50	[-21.00; 6.00]
	Other	29	39.19	45	31.69	7.50	[-6.00; 21.00]
Physical activity	Performing	10	13.51	21	14.79	-1.28	[-11.01; 8.46]
	Non-performing	64	86.49	121	85.21	1.28	[-8.46; 11.01]
CAGE	Positive	18	24.32	31	21.83	2.49	[-9.41; 14.40]
	Negative	56	75.68	111	78.17	-2.49	[-14.40; 9.41]
Previous psychiatric disorder	Had	32	43.24	52	36.62	6.62	[-7.17; 20.42]
	Did not have	42	56.76	90	63.38	-6.62	[-20.42; 7.17]
Motivation level	Precontemplation /contemplation	68	91.89	113	79.58	12.31	**[3.22; 21.40]**
	Preparation/action	6	8.11	29	20.42	-12.31	**[-21.40; -3.22]**

Δ_p = estimate of the difference in the proportions. Δ_m = estimate of the difference in the means. SD = standard deviation. *95% CI = 95% confidence interval for difference in proportions. F = Fisher's exact test.

the variables of number of years of schooling, religion, physical activity, CAGE score and previous psychiatric disorders did not present statistically significant differences between the two groups.

Table 2 presents the average levels of the values for the variables relating to smoking, for the groups that abandoned treatment and did not abandon it. The difference in the average levels of the groups regarding time spent smoking was statistically significant. However, no differences were observed among the groups for the other variables that were studied: smoking history, age when smoking started, number of cigarettes per day, attempts to stop smoking and Fagerström score, taking the significance level to be 0.05.

The associations between abandonment of treatment of smoking and sociodemographic variables are shown in **Table 3**. Abandonment was associated with male gender (PR = 1.51; 95% CI: 1.05-2.18), lower age group (PR = 3.88; 95% CI: 1.49-10.08), having employment (PR = 1.62; 95% CI: 1.05-2.50) and motivational levels in the precontemplation and contemplation phases (PR = 2.19; 95% CI: 1.03-4.65). There were no associations between abandonment of treatment and schooling level (P = 0.515), religion (P = 0.270), physical activity (P = 0.80), CAGE score (P = 0.678) or psychiatric disorders (P = 0.343).

Table 4 presents the variables that remained associated with abandonment of treatment after analysis of the final model of

Table 2. Average levels ($\overline{R_i}$) of the variable values relating to smoking per group. Cuiabá, Mato Grosso, 2013

Variables	Groups	n	Average level	P
Time spent smoking	Abandonment	74	92.09	**0.005**
	Non-abandonment	142	117.05	
Age at start of smoking	Abandonment	74	114.51	0.306
	Non-abandonment	142	105.37	
Number of cigarettes per day	Abandonment	74	110.23	0.766
	Non-abandonment	142	107.60	
Smoking history	Abandonment	74	99.03	0.108
	Non-abandonment	142	113.44	
Attempts to quit	Abandonment	74	105.05	0.548
	Non-abandonment	142	110.30	
Fagerström	Abandonment	74	111.64	0.589
	Non-abandonment	142	106.86	

P = value associated with the Mann-Whitney test.

Table 4. Adjusted prevalence ratio for robust Poisson regression (RPa), for the variables associated with abandonment of smoking among 216 patients, with their respective 95% confidence intervals and the P values for variables selected using the backward method. Cuiabá, MT, 2013

Variables	RPa	95% CI
Gender		
Male	1.47	1.03 to 2.10
Female	1.00	
Age Group		
20–39 years	3.77	1.47 to 9.67
40–59 years	2.68	1.06 to 6.77
60 years or more	1.00	

RPa = adjusted prevalence ratio in the Poisson regression model with variable selection; CI = confidence interval.

Table 3. Association between abandonment of smoking and sociodemographic factors. Cuiabá, Mato Grosso, 2013

Variables	Category	Smoker				PR_c	95% CI
		Abandonment		Non-abandonment			
		n	%	n	%		
Gender	Male	33	44.00	42	56.00	1.51	**[1.05; 2.18]**
	Female	41	29.08	100	70.92	1.00	-
Age group	20-39 years	25	50.00	25	50.00	3.88	**[1.49; 10.08]**
	40-59 years	45	33.33	90	66.66	2.58	**[1.01; 6.65]**
	60 years or over	4	12.90	27	87.10	1.00	-
Years of education	≤ 8	50	32.89	102	67.11	0.88	[0.59; 1.30]
	> 8	24	37.50	40	62.50	1.00	-
Occupation	Employed	54	40.00	81	60.00	1.62	**[1.05; 2.50]**
	Not employed	20	24.62	61	75.31	1.00	
Religion	Other	29	39.19	45	60.81	1,24	[0.85; 1.80]
	Catholic	45	31.69	97	68.31	1.00	-
Physical activity	Performing	64	34.59	121	65.40	1.07	[0.82; 1.85]
	Non-performing	10	32.26	21	67.74	1.00	-
CAGE	Positive	18	36.73	31	63.27	1.10	[0.72; 1.68]
	Negative	56	33.53	111	66.47	1.00	-
Psychiatric disorder	Had	32	38.09	52	61.90	1.20	[0.84; 1.66]
	Did not have	42	31.82	90	68.18	1.00	-
Motivation level	Precontemplation/contemplation	68	37.57	113	67.66	2.19	**[1.03; 4.65]**
	Preparation/action	6	17.14	29	82.86	1.00	-

PR = crude prevalence ratio. 95% CI = 95% confidence interval. P = significance level, considering the chi-square distribution.

robust multivariate Poisson regression. The participants presented greater risk of abandonment of treatment when they were male (RPa = 1.47; 95% CI: 1.03-2.10) and were in the 20 to 39 and 40 to 59 year age groups (RPa = 3.77; 95% CI: 1.47-9.67; and RPa = 2.68; 95% CI: 1.06-6.77).

DISCUSSION

The rate of abandonment of nicotine dependence treatment in the population studied after six months of observation was high (34.26%), and the majority of the abandonment occurred before CBT was started. These results are similar to those found in other studies.[21,22] It is noteworthy that among the participants who were considered to have abandoned their treatment, two groups can be identified: those who did not attend the first CBT session and those who quit during the treatment process. At first glance, these two groups seem to be different from each other; nevertheless, the statistical analysis showed that there were no differences between them regarding the main variables studied here (sociodemographic factors, smoking status, motivational level and CAGE score). Therefore, they were homogeneous and were considered to be a single group, i.e. abandonment.

Some of the variables studied could explain the outcomes that were found, and among these were the sociodemographic characteristics (gender, age group and occupation), those relating to smoking status (duration of tobacco use) and motivational level. It was noteworthy that male participants abandoned treatment more often, thus remaining associated with failure in the final model. There are various plausible explanations for this result. It is a fact that most of the smokers who seek nicotine dependence treatment programs are female.[23,24] It is possible that this predominance of females seeking help and then remaining in the programs is due, in large part, to women's greater concern for their own health, given that there is a difference in health concern depending on gender: women live longer and use healthcare services more frequently than do men, who have a hard time accepting that they are sick.[24] There are some other important factors that hinder smoking cessation, which the female gender presents with greater intensity: they have more mood disorders, more marked withdrawal syndromes and slower nicotine metabolism; and their weight gain through cessation is more distressing.[24-26] Added to this, there is the fact that abandonment was also more prevalent among the participants who were employed. Since males formed the largest workforce and income groups in this population, it is possible that professional commitments were hindering their attendance at the scheduled appointments.[26,27] It has been shown that male smokers are embarrassed about being absent from their employment to attend such programs, even if that can obtain a declaration of presence at the healthcare unit.[21]

Another important variable that was associated with the final model for abandonment of treatment was the age group. The youngest group (20-39 years) presented the highest abandonment rate. It is possible to imply that abandonment among young people may have occurred because they still did not feel "sick", and thought that the harmful effects of smoking would take a long time to appear, such that they would still have plenty of time to decide when to quit definitively.[28] Studies on licit and illicit drug users have reported that the younger the users are, the lower the chances are that they will remain in treatment.[29]

The degree of success of and adherence to treatment among young individuals presenting substance abuse depends on variables such as severity of dependence and motivation to change behavior, among other things. These two variables proved to be important in the present study. Young people believe that their problems are not related to drugs, and that everything will be all right and nothing bad will happen to them.[30] Thus, it is necessary to review how to approach these patients in order to achieve higher treatment adherence. This will perhaps not just involve addressing tobacco-related diseases, given that these are still not present and that these individuals have not even envisioned this reality yet. One option would be to work on the esthetic harm caused by chronic use of nicotine (teeth, skin and odor), in an attempt to raise awareness and motivate these young people, who are concerned about their image and appearance.[31]

In relation to the participants in the other age groups, it was observed that they did not abandon treatment so frequently. Despite ambivalence (they felt unable to quit smoking, even though they knew that it was necessary), the older individuals sought support and acceptance, thus suggesting that the decision to seek help occurs at a time of greater maturity, when there is an awareness of the health risks that smoking entails.[26,32]

Comparisons between the averages relating to occupation and abandonment of dependence treatment should be viewed with caution. Firstly, the results showed that abandonment occurred more often among those who had an occupation, and this was similar to the findings from other studies.[24,26] This issue may be related to the times (morning/afternoon) at which controlled visits and program sessions occurred, which are times at which many patients have professional commitments. This may have prevented attendance and may thus have significantly influenced abandonment. The question that arises, therefore, is whether greater schedule flexibility, with appointments in the evenings and/or on weekends, would influence this variable. On the other hand, it is important to remember that the highest smoking prevalence rates are among individuals with lower educational levels who undertake heavy manual labor activities, and these are the very ones who struggle to adhere to extended treatment.[33]

Regarding the variables relating to smoking status, less time spent smoking influenced the abandonment of treatment. This finding shows that the longer the period spent smoking, the more a person will decide to invest in the treatment, perhaps because of the possibility of starting to feel the effects of the diseases caused by tobacco. One of the main reasons why individuals decide to quit smoking relates to the deterioration of health conditions caused by tobacco-related diseases.[34]

Comparison of the average tobacco intake levels showed that the participants who abandoned treatment had lower average levels than those who did not abandon, but the difference was not statistically significant. These results agree with the statement that the higher the dependence is, the greater the search for professional monitoring and the use of medications will be.[35] Perhaps this reinforces the result in terms of age, in that the younger the age group, the shorter the time spent smoking and the lower the tobacco intake are, the greater the abandonment rate will be. On the other hand, the results found here differ from another study in which dependence levels were not associated with treatment abandonment.[23]

Regarding motivational level, the results show that the participants who were in the precontemplation or contemplation phase were the ones who most abandoned treatment. This result reinforces the established knowledge that individual motivation is the most decisive factor in the process of quitting smoking.[36] It is known that patients who go to healthcare units for treatment without motivation are a challenge for the therapists, because addictive disorders are essentially motivational.[37] These results are consistent with those from a study on adolescents who were undergoing treatment for illicit drug use, in which most of those who did not adhere to the program (69.3%) were in the precontemplation phase.[38]

Motivation for change is multifactorial and occurs differently for each human being at given moments in his/her life history.[39] Perhaps those who do not abandon treatment and stay until the end, even though they do not quit smoking, are patients with high motivational levels. Motivated smokers who are in the preparation or action phase are open to making changes to their behavior, and to taking the necessary steps to do so, and they accept discussion and selection of strategies for the process to be successful.[40] This motivational level towards quitting smoking encourages smokers to remain in the treatment group, whereas those with low motivational levels (precontemplation or contemplation) tend to abandon the treatment.[41]

Since having a high motivational level is fundamental for non-abandonment and for increasing the chances of adherence to treatment, the whole healthcare team should work on their patients' motivation. One strategy that has already been tested is the adoption of motivational interviewing, which consists of individualized interventional techniques focused on the patient and tailored to each stage, with the aim of reinforcing the motivation towards change and increasing the treatment adherence.[42] However, working with motivational interviews requires specialized training for healthcare professionals, because their success depends on the style of those who apply this method, which can directly interfere in the treatment.[43] Another strategy could be a closer approach to the smoker, so as to stimulate him continuously and show that it is possible to live without smoking and in a healthier way. If necessary, those who did not attend the CBT sessions or the treatment monitoring control appointments could be contacted in person or by telephone.[44]

The major limitation of this study might be the non-characterization of the two groups that initially seemed to be distinct, i.e. the outright abandoners (those who did not even participate in the first session of CBT) and the more resistant individuals (those who abandoned the treatment while it was in progress). It is possible that the number of participants who abandoned the treatment did not allow us to find the differences between them. To further our knowledge of abandonment of nicotine dependence treatment, more studies will be necessary, bearing in mind the distinction between smokers who abandon treatment outright and those who are more resistant.

CONCLUSIONS

We conclude that in comparing individuals who abandoned nicotine dependence treatment and those who did not abandon it, there are higher dropout rates among male patients and among individuals who belong to the 20-39 age group, have employment, have low motivational levels and have spent shorter periods of time smoking.

Abandonment of treatment for smoking is associated with male gender and a younger age group. Identifying which is the best approach towards dealing with these patients and working with their concerns in order to assist them in carrying out the program is the fundamental key to adherence to treatment of nicotine dependence.

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Screening for physical inactivity among adults: the value of distance walked in the six-minute walk test. A cross-sectional diagnostic study

Triagem para inatividade física em adultos: o valor da distância percorrida no teste de caminhada de seis minutos. Um estudo transversal diagnóstico

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KEY WORDS:
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PALAVRAS-CHAVE:
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Acelerometria.
Curva ROC.
Índice de massa corporal.

ABSTRACT

CONTEXT AND OBJECTIVES: Accelerometry provides objective measurement of physical activity levels, but is unfeasible in clinical practice. Thus, we aimed to identify physical fitness tests capable of predicting physical inactivity among adults.

DESIGN AND SETTING: Diagnostic test study developed at a university laboratory and a diagnostic clinic.

METHODS: 188 asymptomatic subjects underwent assessment of physical activity levels through accelerometry, ergospirometry on treadmill, body composition from bioelectrical impedance, isokinetic muscle function, postural balance on a force platform and six-minute walk test. We conducted descriptive analysis and multiple logistic regression including age, sex, oxygen uptake, body fat, center of pressure, quadriceps peak torque, distance covered in six-minute walk test and steps/day in the model, as predictors of physical inactivity. We also determined sensitivity (S), specificity (Sp) and area under the curve of the main predictors by means of receiver operating characteristic curves.

RESULTS: The prevalence of physical inactivity was 14%. The mean number of steps/day (≤ 5357) was the best predictor of physical inactivity (S = 99%; Sp = 82%). The best physical fitness test was a distance in the six-minute walk test and ≤ 96% of predicted values (S = 70%; Sp = 80%). Body fat > 25% was also significant (S = 83%; Sp = 51%). After logistic regression, steps/day and distance in the six-minute walk test remained predictors of physical inactivity.

CONCLUSION: The six-minute walk test should be included in epidemiological studies as a simple and cheap tool for screening for physical inactivity.

RESUMO

CONTEXTO E OBJETIVOS: A acelerometria fornece medida objetiva do nível de atividade física, porém não é viável na prática clínica. Assim, foram investigados testes de aptidão física capazes de predizer inatividade física em adultos.

DESENHO E LOCAL: Estudo de teste diagnóstico, desenvolvido em laboratório universitário e uma clínica de diagnósticos.

MÉTODOS: 188 participantes assintomáticos tiveram o nível de atividade física avaliado por acelerometria, ergoespirometria em esteira, composição corporal por bioimpedância, função muscular isocinética, equilíbrio postural em plataforma de força e teste de caminhada de seis minutos. Foram realizadas análise descritiva e regressão logística múltipla, incluindo idade, sexo, consumo de oxigênio, gordura corporal, centro de pressão, pico de torque de quadríceps, distância percorrida no teste de caminhada de seis minutos e passos/dia no modelo como preditores da inatividade física. Adicionalmente, foram determinadas a sensibilidade (S), especificidade (Sp) e área abaixo da curva dos principais preditores por meio de curvas de característica de operação do receptor.

RESULTADOS: A prevalência da inatividade física foi 14%. O número médio de passos/dia (≤ 5357) foi o melhor preditor da inatividade física (S = 99%, Sp = 82%). O melhor teste de aptidão física foi a distância no teste de caminhada de seis minutos e ≤ 96% dos valores preditos (S = 70%; Sp = 80%). A gordura corporal > 25% também foi significativa (S = 83%, Sp = 51%). Após regressão logística, passos/dia e a distância no teste de caminhada de seis minutos permaneceram preditores da inatividade física.

CONCLUSÃO: O teste de caminhada de seis minutos deve ser incluído em estudos epidemiológicos como ferramenta simples e barata para triagem da inatividade física.

INTRODUCTION

Physical inactivity is an important risk factor for many diseases, particularly cardiovascular diseases.[1] It has been suggested that the appropriate level of physical activity is associated with a significant reduction in mortality from all causes.[2] With aging, the prevalence of physical inactivity increases, thus making its epidemiological evaluation fundamental in designing preventive strategies.[3]

Insufficiently active or totally inactive individuals are those who perform physical activities, but in quantities and at intensities that are insufficient to allow them to be classified as active, since they do not comply with the recommendations of at least 150 minutes/week of moderate to vigorous physical activity.[4]

Questionnaires and self-reporting have been often used to assess the level of physical activity in population-based cohort studies. However, validation studies using accelerometry indicate that the accuracy of the questionnaires is limited, especially in estimating physical activity of milder intensity. Thus, questionnaires may also result in information recall bias.[5]

Alternatively, motion sensors are instruments that are used to detect body movement and can be used to objectively quantify the level of physical activity for a period of time. However, assessment of physical activity within daily life by means of motion sensors is not feasible in clinical practice because the equipment is expensive and the evaluation takes several days to be completed. Another widespread concern around motion sensors is adherence to the evaluation, although this only requires simple care from the individual.[6]

Walking tests have been shown to be closely related to activities of daily life and has been applied to older individuals with and without chronic diseases because of their simplicity with less cognitive demand. Whether functional exercise capacity assessed by field walking tests might be useful for predicting physical inactivity requires further clarification, especially among healthy participants in the general population. Moreover, it has not yet been determined which physical fitness test for screening for physical inactivity would be the most suitable.

OBJECTIVE

We aimed to identify the best physical fitness test capable of predicting physical inactivity in adults.

METHODS

One hundred and eighty-eight participants (mean age: 41 ± 14 years; 91 men) used an accelerometer (Actigraph GT3x+) for seven days. The participants were selected from the EPIMOV study (Epidemiological Study of Human Movement and Hypokinetic Diseases). Briefly, the EPIMOV study is a population-based cohort study with the main objective of investigating the longitudinal association shown by sedentary behavior and physical inactivity in relation to occurrences of hypokinetic diseases, especially cardiorespiratory diseases. The volunteers were selected through dissemination in social networks, folders displayed in the universities of the region, local magazines and newspapers. All participants in the EPIMOV study were potentially eligible to form part of the convenience sample of the present study. In the early clinical evaluation, personal and demographic data were collected and participants with previous self-reported diagnoses of heart disease, lung disease or musculoskeletal disorders were not excluded from the present study.

Physical inactivity was defined as less than 150 min/week of moderate to vigorous physical activity in daily life. We excluded swimmers from the analysis because they did not use the device during their training. We evaluated the cardiopulmonary exercise test, body composition (bioelectrical impedance), isokinetic muscle function of the upper and lower limbs, handgrip strength, postural balance (force platform) and six-minute walk test.

The participants were informed about the possible risks and discomforts of this study and signed a consent form. The local Ethics Committee for Research on Humans approved this study.

Initial clinical evaluation

In the early clinical evaluation, personal and demographic data were collected. In addition, participants answered the physical activity readiness questionnaire (PAR-Q).[7] Cardiovascular risk stratification for events during exercise was then performed in accordance with the system of the American College of Sports Medicine (ACSM)[8] and a respiratory questionnaire based on the American Thoracic Society (ATS) questionnaire was administered.[9]

Anthropometric and body composition evaluation

Body weight and height were measured and the body mass index (BMI) was calculated. Body composition was determined by means of bioelectrical impedance (310e Biodynamics, Detroit, USA), following the procedure described by Kyle et al.[10,11] Lean body mass and body fat mass were calculated using the regression equations developed for healthy individuals.[12]

Cardiorespiratory fitness

Functional exercise capacity was assessed by means of the six-minute walk test, which was performed rigorously in accordance with the American Thoracic Society guidelines.[13] The six-minute walking distance was recorded in meters and as a percentage of predicted values.[14]

The maximum and symptom-limited exercise capacities were assessed through a cardiopulmonary exercise test (CPET), using a treadmill ramp protocol (ATL, Inbrasport, Curitiba, Brazil). After 3 min at rest, the speed and inclination were automatically incremented in accordance with the estimated maximal

oxygen consumption ($V'O_2max$), with the aim of completing the test within about 10 minutes.[15] Cardiovascular, ventilatory and metabolic variables were analyzed breath by breath, using a gas analyzer (Quark PFT, Cosmed, Pavona di Albano, Italy). Oxygen uptake ($V'O_2$), carbon dioxide production ($V'CO_2$), R ($V'CO_2/V'O_2$), minute ventilation (V'E) and heart rate (HR) were monitored throughout the test. The data were filtered every 15 seconds for further analysis. The anaerobic threshold was obtained in accordance with the standardized v-slope technique.[16] Two experienced observers independently obtained this index. In cases of disagreement between evaluators, the opinion of a third experienced assessor was considered.

Balance evaluation

Balance was evaluated from kinetic data at the center of pressure, using a force platform (400 BIOMEC, EMGSystem, Brazil). The frequency of data acquisition on the platform was 100 Hz. The participants were instructed to remain as static as possible, standing with weight borne on both feet, with both eyes open, and then again with both eyes closed. Each position was maintained for 30 seconds.

Muscle function

Muscle function was assessed using an isokinetic dynamometer (Biodex, Lumex Inc., Ronkonkoma, NY, USA). Peak torque in Nm was evaluated through two trials of five movements at 60°/s. After a rest period of at least three minutes, the participants performed an isometric force test twice, recorded in Nm against fixed resistance over a 60° range of flexion. After another similar rest period, the participants performed 30 movements at 300°/s to record the total work, in kJ. The highest value was selected for analysis in all the abovementioned tests. These tests were applied to the quadriceps femoris and biceps brachii.

Muscle function was also assessed by means of handgrip strength. The handgrip strength of the dominant hand was assessed using a hydraulic dynamometer (JAMAR), in accordance with the methods described by Mathiowetz et al.[17] Three measurements were made, with a minimum interval of 30 seconds between them, and the highest value obtained was subjected to analysis.

Level of physical activity in daily life

The level of physical activity in daily life (LPADL) was assessed using a triaxial accelerometer that had previously been validated (ActiGraph, MTI, Pensacola, FL, USA).[18-20] The participants were asked to wear the device over their dominant hip on an elasticized belt for 7 days. Days of use were considered to be valid if the participants had worn the device for at least 12 h. They were instructed to remove it for water-related activities, such as bathing or swimming, and to remove it at bedtime. The triaxial ActiGraph measures the duration and intensity of physical activity. Only the data from participants who used the accelerometer for at least four valid days were analyzed.

Physical activity in sedentary, low-intensity, moderate-intensity, vigorous and very vigorous strata was defined as described by Freedson et al.[21] The minimum level of physical activity in terms of quantity and intensity was considered to be 150 min/week of moderate to vigorous physical activity during the monitoring.[15,22] Individuals who did not reach this level of physical activity were considered to be physically inactive. For descriptive purposes, we also stratified the participants into three categories of amounts of physical activity, as recommended by ACSM,[22] i.e. less than 30 min/day, 30-59 min/day and 60 min/day or more.

Statistical analysis

The sample size was calculated using the OpenEpi free tool (openepi.com). Based on our initial experiences from the EPIMOV study, we found that the prevalence of physical inactivity was about 14%. We took this to be the prevalence among the 450,000 residents of the city of Santos, São Paulo, Brazil, where the present study was developed. Assuming a 95% confidence interval for precision, alpha of 0.05 and beta of 0.20, we concluded that 185 participants would be enough to develop the receiver operating characteristic (ROC) curves proposed in the present study.

We firstly conducted a descriptive analysis on the data, which included determination of frequencies, histograms, central trend measurements and variability. In order to identify the best physical fitness index capable of predicting physical inactivity, ROC curves were determined and the area under the curve was calculated as representing good combinations of sensitivity and specificity. Areas under the curve greater than or equal to 0.8 were considered to be excellent values.

We calculated the sensitivity, specificity, positive and negative predictive values and accuracy for each predictor. Sensitivity identifies the proportion of individuals who truly do have the disease (in the case of this study, physical inactivity) and present a positive test result and specificity identifies the proportion of individuals who truly do not have the disease and present a correct negative test result. The positive and negative predictive values, respectively, are the proportions of positive and negative results in statistics and diagnostic tests that are true positive and true negative results.

Reduced models were used as a modeling strategy for logistic regression, using physical inactivity as the outcome variable. The physical fitness variables were included in the model as predictors. The model was also adjusted according to demographic and anthropometric variables and also confounding comorbidities. Odds ratios and the 95% confidence interval of the odds ratios were calculated. The probability of alpha error was set at 5%.

RESULTS

One hundred and eighty-eight adults aged over 20 years participated in the study (**Table 1**), and these represented the totality of subjects invited (there were no refusals). Twenty-two percent of the participants performed less than 30 min/day of moderate to vigorous physical activity, whereas 49% performed 30 to 59 min/day and 29% performed 60 min/day or more. As expected, the average number of steps/day (≤ 5357) was the best predictor of physical inactivity (**Table 2**). The best physical fitness test for predicting physical inactivity was a six-minute walking distance ≤ 511 m (**Figure 1A**; **Table 2**) and ≤ 96% of predicted values (**Figure 1B**; **Table 2**). Body fat mass > 25% was also significant (**Figure 1C**; **Table 2**). All these tests showed high values for the area under the curve. Using multiple logistic regression, the average number of steps/day and the six-minute walking distance remained significant predictors of physical inactivity (**Table 3**). The correlation between steps/day and six-minute walking distance was moderate but significant ($r = 0.415$; $P < 0.05$).

Table 1. Demographic, anthropometric, lung function, oxygen uptake, static balance, muscle function, walking capacity and physical activity level characteristics of the subjects

Age (years)	41 ± 14
Gender	
Female	97 (51.6%)
Male	91 (48.4%)
Body mass (kg)	74.8 ± 18.3
Height (cm)	166 ± 10
Body mass index (kg/m^2)	27 ± 5.5
Lean body mass (kg)	54 ± 12.3
Body fat mass (% total)	27.1 ± 8.75
Forced vital capacity (% of predicted)	97.5 ± 14.4
Forced expiratory volume in 1 second (% of predicted)	96 ± 13.9
Forced expiratory volume in 1 second/forced vital capacity (%)	81.2 ± 8.3
Peak oxygen uptake (ml/min)	2486 ± 873
Peak oxygen uptake (ml/min/kg)	33.7 ± 11.1
Peak oxygen uptake (% of predicted)	104 ± 23
Center of pressure — eyes opened (cm^2)	0.98 (0.61-1.58)
Center of pressure — eyes closed (cm^2)	0.99 (0.65-1.84)
Peak torque quadriceps (Nm)	147.8 ± 60.2
Peak torque biceps (Nm)	36.4 ± 21.8
Handgrip strength (kgf)	35.27 ± 10.25
Six-minute walking distance (m)	611 ± 84.42
Six-minute walking distance (% of predicted)	105.7 ± 12.7
Steps/day (count)	7894 ± 3065

Data presented as mean ± standard deviation or as median (with interquartile range).

DISCUSSION

The present study showed that the six-minute walk test has adequate sensitivity and specificity for diagnosing physical inactivity among adults who are free from chronic diseases. To our knowledge, no studies have previously found this association among healthy and asymptomatic subjects.

Physical activity is a complex behavioral pattern, and choosing a tool to assess it is challenging. Accordingly, it has yet to be established what would constitute a reasonable gold standard method. Doubly labeled water is considered to be one of the best ways for assessing energy expenditure, but it does not have the capacity to measure the duration, frequency and intensity of activity-related energy expenditure. Accelerometers have been considered to be the tool that has the greatest capability for assessing LPADL. They are precise enough to quantify the physical activity and are cheap enough for use in large epidemiological studies. They have been used as the instrument of choice for validating physical activity questionnaires.[23] Since there is no defined gold standard method for measuring LPADL, triaxial accelerometry has been recognized as the best method for validating other methods, e.g. the six-minute walk test in the present study.

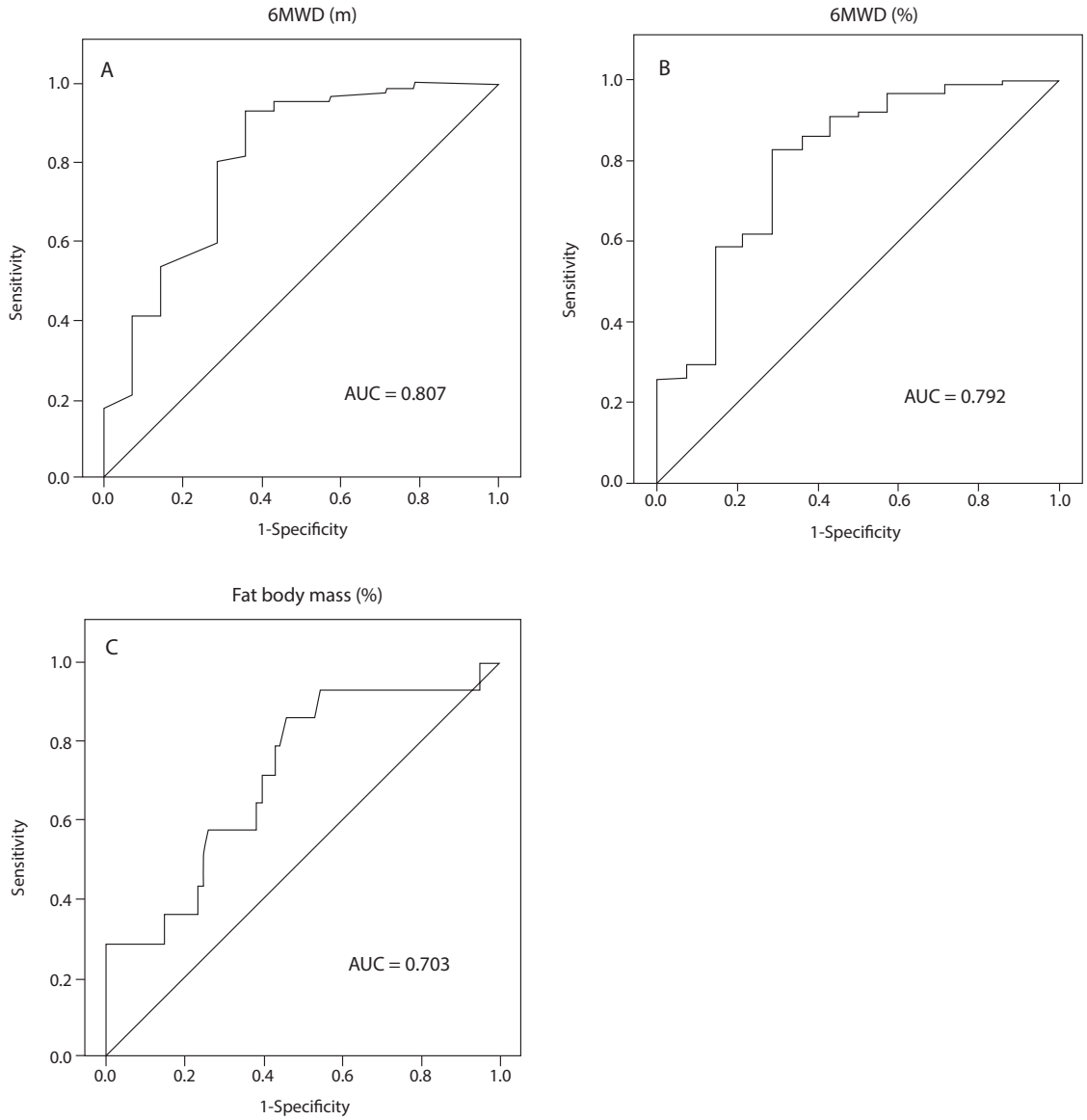
In our previous study, we found that the six-minute walk test can be described as a moderate to high-intensity exercise in which $V'O_2$ and HR of approximately 80% of the maximum may occur. Furthermore, the peak $V'O_2$ in CPET was accurately predicted by the six-minute walking distance ($R^2 = 0.76$), through the equation derived.[24] Although this tool is suitable for evaluating the functional exercise capacity of the majority of middle-aged and older adults, some studies have failed to demonstrate any association between self-reported physical activity and six-minute walking distance.[25,26] This inconsistency may be due to self-reported physical activity. In the present study, the six-minute walking distance was significantly correlated with LPADL, as evaluated through accelerometry.

The ability to walk as far as possible is associated with better health status among patients with chronic diseases and

Table 2. Sensitivity, specificity, positive and negative predictive values and accuracy

Variables	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Steps/day (count)	99 (78-100)	82 (73-90)	50 (31-68)	100 (95-100)	84.38
Six-minute walking distance (m)	64 (35-87)	91 (85-97)	60 (32-83)	94 (86-98)	87.22
Six-minute walking distance (% of predicted)	70 (41-91)	80 (72-89)	40 (21-61)	94 (86-98)	78.60
Body fat mass (%)	83 (57-98)	51 (42-65)	24 (13-38)	95 (85-99)	55.48

Data presented as mean and 95% confidence interval (lower limit – upper limit).



AUC = area under the curve.

Figure 1. Receiver-operator characteristic (ROC) curves for six-minute walking distance (6MWD) and body fat mass as predictors of physical inactivity.

Table 3. Predictors of physical inactivity after multiple regression analysis

Predictors*	Unadjusted model				Adjusted model			
	Odds ratio	95% confidence interval for odds ratio		P	Odds ratio	95% confidence interval for odds ratio		P
		Lower limit	Upper limit			Lower limit	Upper limit	
Age (years)	1.048	1.010	1.087	0.014	0.983	0.916	1.055	0.637
Sex (male/female)	0.585	0.185	1.852	0.362	0.057	0.003	0.997	0.050
Peak oxygen uptake (ml/min/kg)	0.908	0.854	0.966	0.002	0.962	0.82	1.127	0.636
Body fat mass (%)	1.062	1.011	1.115	0.016	1.206	0.961	1.512	0.106
Center of pressure (cm^2)	1.357	0.931	1.980	0.113	0.889	0.455	1.736	0.731
Quadriceps peak torque (Nm)	0.998	0.989	1.008	0.697	1.006	0.987	1.025	0.539
Six-minute walking distance (m)	0.984	0.975	0.992	0.000	0.987	0.976	0.999	0.034
Steps/day (count)	0.997	0.996	0.998	0.000	0.998	0.997	0.999	0.026

*Model adjusted for race, hypertension, diabetes, dyslipidemia, obesity and smoking.

asymptomatic older adults.[27] We found that a six-minute walking distance ≤ 511 m was the best predictor of physical inactivity, although this absolute value could be questioned, since it is influenced by factors such as height, weight and age. However, the absolute distance proved valid for predicting LPADL because the six-minute walking distance as a percentage of the predicted value was also reduced in individuals who walked less than 511 m in the six-minute walk test.

Our findings from asymptomatic subjects were similar to those described for patients with chronic obstructive pulmonary disease (COPD). Steele et al.[28] used a triaxial accelerometer to measure LPADL in 47 patients with COPD. The authors observed a significant correlation between the six-minute walking distance and accelerometry (r = 0.74). Pitta et al.[29] also used a triaxial motion sensor among 50 patients with COPD, and a strong correlation between walking time in daily life and six-minute walking distance (r = 0.76) was observed. In the same study, patients who walked less than 400 m in the six-minute walk test were considered to be extremely inactive in daily life.

According to univariate analysis in the present study, body fat mass was able to predict physical inactivity. The sensitivity for predicting physical inactivity was 85% among individuals with body fat mass > 25%. However, in the multivariate analysis, body composition was no longer a significant predictor of physical inactivity. In fact, the area under the curve and the specificity of 54% that was found may not be considered to be promising results. This low specificity reflects the inability of body fat mass determinations to identify physical inactivity among individuals with values ≤ 25%. We may suggest that body fat mass is not a good predictor for physical inactivity, since adiposity relates to multiple factors, such as diet, lifestyle, metabolism, genetics and socioeconomic level.[30]

Muscle function was not able to determine physical inactivity in the present study, and our results are in agreement with the previous literature. Garcia et al.[31] reported that there was only a moderate correlation between these variables. Likewise, $V'O_2$ obtained during CPET was not selected as a determinant of physical inactivity in the present study. The walking velocity reached during the six-minute walk test possibly reproduces the LPADL of the general population better, and therefore, the six-minute walking distance is more suitable for predicting physical inactivity than is the peak $V'O_2$ obtained at the end of the treadmill CPET.[32]

This study has limitations that need to be considered. The LPADL can be determined through sociocultural and economic factors that were not evaluated in this study and were not adjusted for, in the multiple logistic regression model. Triaxial accelerometry is not the gold standard method for assessing the LPADL, and therefore its use may have introduced bias into our analysis. However, a gold standard method remains to be established.[23] This instrument is most often used as a reference in validating other methods. For this reason, we suggest caution when extrapolating our results. Nevertheless, we are confident about the usefulness of the six-minute walking distance for screening for physical inactivity in the general population.

Functional exercise capacity (i.e. the six-minute walk test) is a suitable strategy for screening for physical inactivity among adults. The six-minute walk test should be included in epidemiological studies as a simpler and cheaper tool for screening for physical inactivity.

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Self-administered versus interview-based questionnaires among patients with intermittent claudication: Do they give different results? A cross-sectional study

Questionários autoadministrados *versus* administrados por entrevistador para pacientes com claudicação intermitente: Os resultados são diferentes? Um estudo transversal

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KEY WORDS:
Intermittent claudication.
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PALAVRAS-CHAVE:
Claudicação intermitente.
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Estudos de validação.
Doença arterial periférica.

ABSTRACT

CONTEXT AND OBJECTIVE: Many clinical investigations use generic and/or specific questionnaires to obtain information about participants and patients. There is disagreement about whether the administration method can affect the results. The aim here was to determine whether, among patients with intermittent claudication (IC), there are differences in the Walking Impairment Questionnaire (WIQ) and European Quality of Life-5 Dimension (EQ-5D) scores with regard to: 1) the questionnaire administration method (self-administration versus face-to-face interview); and 2) the type of interviewer (vascular surgeon, VS, versus general practitioner, GP).

DESIGN AND SETTING: Cross-sectional observational multicenter epidemiological study carried out within the Spanish National Health Service.

METHODS: 1,641 evaluable patients with IC firstly completed the WIQ and EQ-5D questionnaires and then were interviewed by their doctor on the same day. Pearson correlations and Chi-square tests were used.

RESULTS: There was a strong correlation ($r > 0.800$; $P < 0.001$) between the two methods of administering the WIQ and EQ-5D questionnaires, and between the VS and GP groups. Likewise, there was a high level of concordance ($P > 0.05$) between the different dimensions of the WIQ-distance and EQ-5D (self-administration versus face-to-face) in the VS and GP groups.

CONCLUSION: There was no difference between the different methods of administering the WIQ and EQ-5D questionnaires, among the patients with IC. Similarly, the two types of interviewers (VS or GP) were equally valid. Therefore, it seems unnecessary to expend effort to administer these questionnaires by interview, in studies on IC.

RESUMO

CONTEXTO E OBJETIVO: Muitas investigações clínicas usam questionários genéricos e/ou específicos para obter informações sobre os participantes e pacientes. Não se sabe se o modo de administração pode afetar os resultados. O objetivo foi determinar se, nos pacientes com claudicação intermitente (CI), existem diferenças nas pontuações do Walking Impairment Questionnaire (WIQ) e do European Quality of Life-5 Dimension (EQ-5D) no que diz respeito a: 1) a forma de administrar o questionário (autoadministrado *versus* entrevista presencial); e 2) o tipo de entrevistador: cirurgião vascular (CV) ou médico generalista (MG).

TIPO DE ESTUDIO E LOCAL: Estudo epidemiológico observacional, transversal, multicêntrico realizado no Serviço Nacional de Saúde espanhol.

METODO: 1.641 pacientes avaliáveis com CI completaram inicialmente o WIQ e questionários EQ-5, e depois, no mesmo dia, foram entrevistados pelo seu médico. Foram utilizados correlações de Pearson e testes de qui-quadrado.

RESULTADOS: Houve forte correlação ($r > 0{,}800$; $P < 0{,}001$) entre os dois métodos de administração do WIQ e EQ-5D; e entre os grupos CV e MG. Também houve alto nível de concordância ($P > 0{,}05$) entre as diferentes dimensões do WIQ-distância e EQ-5D (autoadministrado *versus* entrevista presencial), nos grupos CV e MG.

CONCLUSÃO: Em pacientes com CI, não há diferenças entre as diferentes formas de administrar os questionários WIQ e EQ-5D. Da mesma forma, os dois tipos de entrevistador (CV ou MG) foram igualmente válidos. Portanto, não parece necessário despender esforço para administrar esses questionários através de entrevista, em estudos de CI.

INTRODUCTION

Many epidemiological and clinical studies, including clinical trials, use information directly reported by study participants. There are many generic and disease-specific questionnaires reported in the medical literature that are used by researchers to obtain relevant information about their patients. Research into peripheral arterial disease (PAD) and, specifically, intermittent claudication (IC) also uses generic or specific questionnaires to measure outcomes such as deterioration in walking or health-related quality of life (HRQOL). The former include the Walking Impairment Questionnaire (WIQ), while in the European context, the European Quality of Life-5 Dimensions (EQ-5D) is recommended for evaluating HRQOL among patients with IC.[1,2]

Most of these questionnaires have been validated from the original version to other languages; for example, the WIQ has been validated in Portuguese and Spanish.[3-5] The WIQ and EQ-5D were originally designed to be self-administered and have been used in that way in most studies on IC.[6,7] However, these questionnaires may be completed by other means; for example, with the aid of an interviewer (face-to-face or by telephone). While the latter methods have the advantage of directly controlling the process and thereby offer the possibility of obtaining superior-quality results, self-administration methods (in the consultation room or at home, and returned by post or e-mail) do not require research staff, enable lower research costs and allow patients greater freedom to express their responses to the questions. However, only Conley et al. have evaluated the effects of the two methods of administering the WIQ.[8] Thus, while some studies (not on IC) have shown differences between administration formats,[9-12] others have found no statistically significant differences.[13-17] For these reasons, in some epidemiological studies, self-administered and interviewer-led questionnaires are available to accommodate the preferences, physical impediments or literacy of the participants.

OBJECTIVE

Our study aimed to examine whether, in a large cohort of patients with IC who had completed the WIQ and EQ-5D questionnaires, there were systematic differences in the scores that could be attributed to: 1) the administration method of the questionnaire (self-administration versus interview-based); and 2) the type of interviewer (vascular surgeon versus general practitioner).

METHODS

A cross-sectional observational multicenter epidemiological study on IC in Spain was carried out between May and December 2011, using previously published data.[18]

Vascular surgeons (VSs) and general practitioners (GPs) were identified through the scientific societies participating in the study. All the physicians had previously taken part in epidemiological studies about some type of vascular pathology. Patients were recruited during visits to hospitals (in the case of the VSs) or health centers (in the case of the GPs) within the National Health Service. Each researcher was obliged to include 3-4 consecutive patients affected by IC. The diagnosis of IC was made through the clinical history (including a positive Edinburgh questionnaire result), physical examination and ankle-brachial index (ABI < 0.90 or > 1.3, in diabetic patients), following previously described methods.[19,20] The ABI of each extremity was calculated by dividing the highest pressure obtained in either of the leg arteries by the maximum brachial value. In the records of each patient, only the claudicant limb, or the lower ABI in the bilateral cases, was taken into account.[21]

Each physician compiled the information on a data collection sheet covering the demographic and clinical characteristics of the patient. Two questionnaires were completed on the same occasion: WIQ and EQ-5D.

The WIQ is a questionnaire specific to IC that evaluates four parameters: pain, distance covered, speed and stair-climbing ability.[6] For each domain, a score for the ranked difficulty of doing each of the items is calculated, ranging from 0 (total incapacity) to 100 (full capacity). The Spanish version of the questionnaire was used.[5]

The EQ-5D questionnaire is an instrument designed by a European group for measuring HRQOL.[7] It is a generic questionnaire that is widely used in research because of its ease of use. It has three components. The first evaluates five factors: mobility, self-care, everyday activities, pain/discomfort and anxiety/depression. The scores obtained are summarized as an overall index from 0 (worst state of health) to 1 (best state of health). The second part consists of a visual analogue scale (VAS), in the form of a thermometer, with end points of "worst" and "best" imaginable state of health (scored from 0 to 100, respectively). The third part (patient preference values) was not evaluated. The Spanish version, which has also been validated for use in primary care, was used.[22,23]

Both questionnaires were administered through two methods: self-administration (before the start of the aforementioned consultation), and a subsequent face-to-face interview by the physician (VS or GP). We applied the questionnaire in these two forms without any relevant time interval between them. Initially, the patients completed the WIQ and EQ-5D, in that order, without any help. Once that phase was completed, they filled in the questionnaires in the same order with the help of the doctor. We can consider the latter phase to be the 'ideal means of applying the questionnaires' or to be a control for the former phase. The formats of the self-administered and interview-based questionnaires were identical.

Statistical analysis

A data file was created in PASW (version 18; IBM, New York, NY, USA). Continuous variables were summarized as means and standard deviations; categorical variables were expressed as percentages. Normally and non-normally distributed continuous variables were compared using Student's t test and the Mann-Whitney U test, respectively. Categorical variables were examined using the χ^2 or Fisher's exact test; the latter was used when the expected frequencies of one or more categories was less than 5. The Pearson correlation coefficient (r) of each dimension of the WIQ and EQ-5D was calculated for each of the two methods of questionnaire administration. Values of r were interpreted as follows: 0.0-0.19, very weak correlation; 0.20-0.39, weak; 0.40-0.59, moderate; 0.60-0.79, strong; and 0.80-1.0, very strong.[24] All comparisons were based on a 95% confidence interval. Results were taken to be statistical significant when $P < 0.05$.

Ethics approval for the study

The study was approved by the Scientific and Ethics Committees of the Hospital Clinic (Barcelona, Spain) on March 10, 2011 (Protocol: SEA-NUL_2011_01).

RESULTS

Six hundred and twenty-five researchers provided information from 2,127 consecutive patients affected with IC, of whom 486 patients (22.8%) were removed from the study because their data were incomplete. Thus, 1,641 patients were evaluated: 920 patients from 249 VSs and 721 from 247 GPs. The reasons for exclusion and removal are shown in **Table 1**. Patients and researchers were selected from across the entire country, including urban and rural areas.

The demographic and clinical characteristics of the groups are summarized in **Table 2**. Patients in the VS group had lower ABI than those in the GP group (0.63 versus 0.71; $P < 0.001$).

The scores for the various components of the WIQ, self-administered and administered through an interview with a VS or GP, are shown in **Table 3**. The group of patients interviewed by the VSs had significantly worse scores for the dimensions of pain (47.1% versus 50.4%; $P < 0.001$) and distance covered (34.1% versus 36.4%; $P = 0.007$).

Table 1. Patients with intermittent claudication (IC) and criteria for inclusion, exclusion and withdrawal*

Criterion	Number of patients	VS group	GP group
Patient with IC	2,257	1,261	996
Exclusion	130 (5.8)	69 (5.5)	61 (6.1)
Inclusion	2,127 (94.2)	1,192 (94.5)	935 (93.9)
Removed	486 (22.8)	272 (22.8)	214 (22.9)
Evaluated	1,641(77.2)	920 (77.2)	721 (77.1)
Cause of removal			
Incomplete data	23 (4.7)	11 (4.0)	12 (5.6)
Uncompleted questionnaires	463 (95.3)	261(96.0)	202 (94.4)
Reasons			
EQ-5D self	85 (18.4)	46 (17.6)	39 (19.3)
EQ-5D interview	25 (5.4)	15 (5.7)	10 (4.9)
WIQ self	210 (45.4)	118 (45.2)	92 (45.5)
WIQ interview	35 (7.6)	22 (8.4)	13 (6.4)
EQ-5D + WIQ (all)	108 (23.3)	60 (23.0)	48 (23.8)

*Number (percentage).

EQ-5D = European Quality of Life-5 Dimension; WIQ = Walking Impairment Questionnaire.

Table 2. Baseline characteristics of patients with intermittent claudication

	VS group	GP group
Number of patients	920	721
Male*	717 (77.9)	518 (71.8)
Age (years), mean ± SD	68.2 ± 9.8	68.6 ± 8.9
Body mass index, mean ± SD	27.6 ± 3.6	28.2 ± 3.7
Cohabitation*		
Alone	197 (21.4)	150 (20.8)
Couple/family	666 (72.4)	522 (72.4)
Others	47 (5.1)	40 (5.5)
Not known/answered	10 (1.1)	9 (1.2)
Place of residence (numbers of inhabitants)*		
< 50,000	297 (32.3)	312 (43.3)
50,000-200,000	279 (30.3)	248 (34.4)
200,000-500,000	191 (20.8)	99 (13.7)
500,000-1,000,000	52 (5.6)	33 (4.6)
> 1,000,000	97 (10.5)	26 (3.6)
Not known/answered	4 (0.4)	3 (0.4)
Employment situation*		
Active working	176 (19.1)	153 (21.2)
Unemployed/off work	131 (14.2)	78 (10.8)
Retired	613 (66.6)	487 (67.5)
Not known/answered	1 (0.1)	3 (0.4)
Family history of cardiovascular disease*		
Yes	541 (58,8)	380 (52,7)
No	351 (38.1)	272 (37.7)
Not known/answered	28 (3.1)	69 (9.6)
Cardiovascular risk factor*,†		
None	23 (2.5)	29 (4.0)
Only one	159 (17.3)	129 (17.9)
Two	343 (37.3)	266 (36.9)
Three	302 (32.8)	236 (32.7)
All (four)	93 (10.1)	61 (8.5)
Associated cardiovascular pathology*		
Cardiac insufficiency	86 (9.3)	61 (8.5)
Ischemic cardiopathy (angina)	278 (30.2)	118 (16.4)
Arrhythmias	85 (9.2)	55 (7.6)
Valvular heart diseases	33 (3.6)	29 (4.0)
Stroke	23 (2.5)	19 (2.6)
Renal insufficiency	77 (8.4)	33 (4.6)
Ankle-brachial index, mean ± SD	0.63 ± 0.19	0.71 ± 0.19

*Number (percentage) or mean ± standard deviation (SD).

VS = vascular surgeon; GP = general practitioner; †(tobacco, diabetes mellitus, arterial hypertension and dyslipidemia).

The WIQ scores obtained from both types of interviewer were somewhat higher on average than those obtained through self-reporting. However, only the higher score in the VS group (mean score 2.04 points higher) was statistically significant ($P < 0.05$).

The correlations between self-administration and interview-based methods of completing the questionnaire were very strong ($r = 0.820$-0.905), even when considering the two types of interviewer separately (**Table 3**).

The overall scores from the EQ-5D questionnaire were almost identical (0.58 ± 0.21) when administered through self-reporting and through interview with a VS, and likewise when the interviewer was a GP (0.57 ± 0.21). There were no differences between the VS and GP groups ($P = 0.429$). The correlation between the two methods of administering the questionnaire was very strong, whether the interviewer was a VS ($r = 0.850$; $P < 0.001$) or a GP ($r = 0.828$; $P < 0.001$).

Tables 4 and **5** compare the results from the various dimensions of the WIQ and EQ-5D obtained through self-administration and through interviews conducted by a VS or GP. No differences were found between these methods ($P > 0.05$).

DISCUSSION

Our results demonstrate that self-administration and interview by a physician are both valid approaches for evaluating patients with IC using the WIQ and EQ-5D questionnaires. Likewise, the correlation between the two modes of administering the questionnaires was high for both types of interviewer (VS and GP).

These findings are highly important, since if the different ways of administering a particular questionnaire were to produce different results in an epidemiological study or clinical trial, the estimates of the associations or the effects of the treatment investigated could be affected, thus raising the possibility of incorrect conclusions being drawn.

Table 3. Walking Impairment Questionnaire (WIQ) and EuroQol (EQ-5D). Survey mode

	Self administration	Interview	Correlation (r) Self-adm. versus interview	P-value
WIQ, mean (SD)				
Vascular surgeon				
Pain	47.12 ± 20.40*	49.16 ± 19.37	0.820	< 0.001
Distance	34.07 ± 26.77†	35.13 ± 26.68	0.890	< 0.001
Speed	35.43 ± 23.01	36.24 ± 22.88	0.893	< 0.001
Stair climbing	41.16 ± 28.54	42.06 ± 28.34	0.905	< 0.001
EQ-5D				
Vascular surgeon				
Overall, mean (SD)	0.58 (0.21)	0.58 (0.21)	0.850	< 0.001
Current health (%)	55.04 (21.30)	Not applicable	-	-
General practitioner				
Overall, mean (SD)	0.57 (0.20)	0.57 (0.19)	0.823	< 0.001
Current health (%)	53.79 (19.71)	Not applicable	-	-

*P < 0.001, between pain assessed by vascular surgeon and pain assessed by general practitioner; †P = 0.007, between distance assessed by vascular surgeon and distance assessed by general practitioner.
SD = standard deviation.

Table 4. Walking Impairment Questionnaire: distance dimensions (%) through self-administration or interview, by vascular surgeons and general practitioners

	Vascular surgeons			General practitioners		
	Self	Interview	P	Self	Interview	P
1. Walking indoors						
Very high	0.7	0.4		0.4	0.2	
High	2.9	2.4		2.1	1.8	
Medium	8.9	8.4	0.75	8.6	8.2	0.80
Low	21.0	19.7		32.0	30.9	
Any	66.5	69.1		56.9	58.9	
2. Walk 15 m						
Very high	1.7	1.5		1.5	1.1	
High	3.7	3.3		2.6	2.4	
Medium	11.2	10.4	0.66	12.3	12.3	0.96
Low	24.3	22.1		33.3	33.6	
Any	59.1	62.7		50.3	50.6	
3. Walk 50 m (half square)						
Very high	4.3	3.6		3.5	3.2	
High	9.2	8.8		6.7	6.4	
Medium	20.9	19.9	0.80	24.8	24.3	0.97
Low	24.9	24.7		33.5	33.1	
Any	40.7	43.0		31.5	33.0	
4. Walk 100 m (1 square)						
Very high	9.1	8.2		5.8	5.5	
High	18.9	18.0		16.8	16.0	
Medium	27.4	25.3	0.59	31.9	31.9	0.98
Low	21.8	23.7		29.3	29.4	
Any	22.8	24.8		16.2	17.2	
5. Walk 200 m (2 squares)						
Very high	19.3	18.4		12.6	12.1	
High	27.0	25.5		26.2	26.6	
Medium	25.5	25.9	0.84	34.1	34.0	0.98
Low	15.7	17.3		19.1	19.8	
Any	12.5	12.9		8.0	7.5	
6. Walk 300 m (3 squares)						
Very high	34.5	32.3		25.1	23.7	
High	29.7	29.8		32.0	33.7	
Medium	18.2	19.8	0.73	26.6	26.7	0.96
Low	10.5	11.6		12.9	12.6	
Any	7.1	6.5		3.4	3.3	
7. Walk 500 m (5 squares)						
Very high	51.7	50.5		40.8	40.5	
High	24.2	24.7		31.9	33.7	
Medium	14.1	14.2	0.90	19.4	18.3	0.90
Low	8.0	9.0		6.2	6.3	
Any	2.0	1.6		1.7	1.2	

Self = self-administration.

It is possible to measure an individual's capacity to walk. The treadmill widely used by VSs enables objective measurement of the walk of patients with IC and evaluation of the changes following an intervention program. Introduction of the WIQ has helped GPs measure the walking capacity of their patients without the need for sophisticated equipment. The WIQ has become a widely used instrument for evaluating the walking capacity of patients with claudication,[25] and its scores correlate well with more objective measurements.[26,27] The WIQ has been used jointly with various HRQOL questionnaires, thereby providing excellent overall information about the limitations of these patients.

IC patients have significantly poorer HRQOL than healthy controls, especially with regard to the physical domains. Of the various questionnaires that measure HRQOL, the EQ-5D has the great advantages of being simple to use (only five dimensions) and of being validated for IC, despite its generic nature.[28,29]

As Puhan et al. noted,[15] most questionnaires of this type tend to be self-completed. Indeed, the WIQ and EQ-5D were originally designed to be self-administered, although they may also be completed through personal interview, over the telephone or by post. The aforementioned advantages and disadvantages make it necessary to compare these methods.

With regard to the WIQ, we are aware of only one study, by Coyne et al.,[8] that has compared the different administration methods. Although their study included a relatively small sample of 60 patients, it sought to validate the questionnaire for self-administration and telephone interviews, and found no significant differences in the scores on the four subscales of the WIQ (pain severity, distance, speed and stair-climbing), compared with control interviews. Our study also found no differences in the results obtained through the various forms of administration. In this type of study, in which a degree of psychological influence may be expected, a correlation coefficient of 0.70 or more can be considered to be very strong.[30]

Nevertheless, there were two notable observations:

1. As in other studies, albeit on other pathological conditions,[31] we noted numerically higher scores when the questionnaires were administered by an interviewer, although the difference was only significant for the pain domain of the WIQ. This is commonly explained as being the result of social desirability bias,[32] in which participants may state that they are less affected when interviewed by research staff than when the questionnaires are self-administered.
2. As in the study by Mahe et al.,[33] there was also a substantial number of errors and missing responses in the self-administered WIQ questionnaires. These patients were excluded from the study. In order to avoid any bias that may arise as a consequence, completion of the questionnaire would have to be supervised. In our study, the excluded and included patients did not differ with regard to items that might influence the socioeconomic characteristics of the two groups: age, sex, cohabitation, place of residence and type of job.

Table 5. EuroQol (EQ-5D) dimensions (%) through self-administration or interview, between vascular surgeons and general practitioners

	Vascular surgeons			General practitioners		
	Self	Interview	P	Self	Interview	P
1. Mobility						
I have no problems in walking about	11.5	12.0		13.2	11.5	
I have some problems in walking about	85.9	85.3	0.94	85.3	87.4	0.48
I am confined to bed	2.6	2.7		1.5	1.1	
2. Self-care						
I have no problems with self-care	71.8	70.7		63.7	61.6	
I have some problems washing or dressing myself	26.0	27.5	0.69	34.5	37.0	0.43
I am unable to wash or dress myself	2.2	1.8		1.8	1.4	
3. Everyday activities						
I have no problems with performing my usual activities	39.3	40.4		37.6	37.4	
I have some problems with performing my usual activities	53.7	53.6	0.61	57.1	58.2	0.74
I am unable to perform my usual activities	7.0	6.0		5.3	4.4	
4. Pain/discomfort						
I have no pain or discomfort	16.8	16.4		14.8	13.0	
I have moderate pain or discomfort	67.5	70.8	0.18	71.3	75.5	0.19
I have extreme pain or discomfort	15.7	12.8		13.9	11.5	
5. Anxiety/depression						
I am not anxious or depressed	58.3	55.8		51.0	49.5	
I am moderately anxious or depressed	32.8	36.3	0.22	41.5	43.6	0.70
I am extremely anxious or depressed	8.9	7.9		7.5	6.9	

Self = self-administration.

Although the EQ-5D has been widely used in cardiovascular studies,[34,35] there are no published studies comparing the different formats for administering this questionnaire to patients with this type of pathological condition. The best match for the EQ-5D has been found among HIV patients, whose scores were very similar for the different administration methods (self-reporting versus interview) and types of interview (face-to-face versus telephone).[13]

Our study has some limitations. Apart from the considerable number of excluded patients, the study was also limited because it was not possible to carry out treadmill tests to measure the IC objectively. The use of ergometers is time-consuming and costly and requires control by specialist professionals. However, this omission may not be too important, since clinical manifestations and the WIQ can be used as an alternative to treadmill testing for objectively assessing functional walking ability. Forty percent of the patients recruited came from non-hospital consultations, thus justifying the use of the WIQ.

Another limitation of our study was the absence of a washout period between the two forms of administration of the questionnaires. In our study, this was sequential: first, self-administration (trial form); second, face-to-face (ideal application or control). Our aim was not to evaluate either of the questionnaires but to measure the equivalence between the two forms of administration. Evidently, when patients arrived at the interview they already had previous (and recent) experience, but this was minimized due to the doctor's influence on filling out the questionnaires. On the other hand, the doctor would have a decisive influence, were the sequence to be interview first, followed by self-administration.

CONCLUSION

Our study, which was carried out on a large sample of patients with intermittent claudication, provides evidence that the format of administration of the WIQ and EQ-5D questionnaires has no significant effect on the measurements, provided that the patient is able to fill out a self-applicable form. Consequently, it is not necessary to take into consideration the different formats of administration in this type of study, in analyzing the results within this scenario. This is fortuitous in that it avoids having to do unnecessary work. However, researchers should carefully consider the format of administration used, in order to avoid bias arising from the application method of the questionnaire chosen.

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The role of diagnostic laparoscopy in gynecology

O papel da laparoscopia diagnóstica em ginecologia

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KEY WORDS:
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PALAVRAS-CHAVE:
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Endoscopia.

ABSTRACT

CONTEXT AND OBJECTIVES: Laparoscopy is a diagnostic method that is currently becoming consolidated for therapeutic use. It consists of endoscopically viewing the abdominal cavity. The aim here was to evaluate the indications for diagnostic videolaparoscopy and the intraoperative findings in an endoscopic gynecology clinic at a tertiary-level hospital over the last five years.

DESIGN AND SETTING: Retrospective descriptive study on all diagnostic videolaparoscopy procedures of the last five years carried out in the endoscopic gynecology clinic of a tertiary-level hospital.

METHODS: The medical records of 618 women who underwent diagnostic laparoscopy between 2008 and 2012 were analyzed. The clinical characteristics of these women, the indications for videolaparoscopy and the intraoperative findings were evaluated.

RESULTS: The women's mean age was 32 ± 6.4 years. Most of the women had already undergone at least one previous operation (60%), which was most frequently a cesarean. The indications for performing videolaparoscopy were infertility in 57%, chronic pelvic pain in 27% and others (intrauterine device, adnexal tumor, ectopic pregnancy or pelvic inflammatory disease) in 16%. The main laparoscopic findings were tubal alterations in the group with infertility (59.78%) and peritoneal alterations in the group with chronic pelvic pain (43.54%).

CONCLUSION: The main indications for videolaparoscopy in gynecology were infertility and chronic pelvic pain. However, in most procedures, no abnormalities justifying these complaints were found.

RESUMO

CONTEXTO E OBJETIVOS: A laparoscopia é um método diagnóstico que atualmente se consolida como terapêutico e se caracteriza pela visão endoscópica da cavidade abdominal. O objetivo foi avaliar as indicações de videolaparoscopia diagnóstica e os achados intraoperatórios no serviço de videolaparoscopia ginecológica de um hospital terciário nos últimos cinco anos.

DESENHO E LOCAL: Estudo retrospectivo descritivo com todos os procedimentos videolaparoscópicos diagnósticos dos últimos cinco anos realizados no serviço de ginecologia endoscópica de um hospital terciário.

MÉTODOS: Foram analisados 618 prontuários de mulheres submetidas à laparoscopia diagnóstica entre os anos de 2008 a 2012. Foram avaliadas as características clínicas dessas mulheres, bem como as indicações da videolaparoscopia e os achados intraoperatórios.

RESULTADOS: As mulheres tinham em média 32 ± 6.4 anos. A maioria das mulheres já tinha feito pelo menos uma cirurgia anterior (60%), sendo que a mais frequente foi a cesárea. As indicações para a realização da videolaparoscopia foram 57% por infertilidade, 27% por dor pélvica crônica e 16% outras (dispositivo intrauterino, tumor anexial, gravidez ectópica e doença inflamatória pélvica). Os principais achados laparoscópicos foram alterações tubárias no grupo com infertilidade (59.78%) e alterações peritoneais no grupo com dor pélvica (43.54%).

CONCLUSÃO: As principais indicações da videolaparoscopia em ginecologia são infertilidade e dor pélvica crônica; mas na maior parte dos procedimentos não foram encontradas alterações que justifiquem essas queixas.

INTRODUCTION

Laparoscopy is a diagnostic method that has become consolidated for therapeutic use. It consists of endoscopic viewing of the abdominal cavity by means of distention provided by artificial pneumoperitoneum. The first description of laparoscopy was by Ott and Kelling in 1901.[1]

Diagnostic laparoscopy is traditionally carried out in an operating theatre under general anesthesia. The procedure takes between 20 and 30 minutes and the patients are usually discharged from the hospital on the same day. Although laparoscopy is a simple technique, it is not free from complications, such as infections, hemorrhage and injuries of other abdominal-pelvic organs (bowel or bladder, for example). It has been shown that laparoscopy can diagnose pelvic pathological conditions in approximately 50% of the cases.[2]

The indications for diagnostic laparoscopy are infertility, chronic pelvic pain, pelvic tumors, pelvic inflammatory disease, genital tuberculosis and ectopic pregnancy.[1] The present study evaluated the indications for diagnostic laparoscopy in a university hospital over the last five years.

OBJECTIVE

To evaluate the indications for diagnostic laparoscopy and the intraoperative findings in the endoscopic gynecology clinic of a tertiary-level hospital in Campinas over the last five years.

METHODS

A retrospective descriptive study was conducted in the Department of Gynecology and Obstetrics of a tertiary-level hospital in Campinas. A total of 618 medical records, from all diagnostic laparoscopy procedures performed in the endoscopic gynecology clinic between 2008 and 2012, were analyzed. The clinical characteristics of these women, the indications for laparoscopy and the intraoperative findings were evaluated. The protocol for this study was approved by our institution's Review Board, under number 342.431/2013.

Descriptive analysis (frequencies, means and standard deviations) was performed on the categorical variables. To evaluate associations between the variables, the Kruskal-Wallis test was used. The significance level for statistical tests was 5%. SAS version 9.2 was used.

RESULTS

The women's mean age was 32 ± 6.4 years and their mean body mass index (BMI) was 25.6 ± 4.8 kg/m^2. Among these women, 3% were menopausal and 39% were nulligravid. Diabetes was presented by 1.4%, hypertension by 3.8% and hypothyroidism by 3.4%, and 6.6% were smokers. Most of the women had already undergone at least one operation previously (60%), which was most frequently a cesarean.

The indications for laparoscopy were infertility in 57%, chronic pelvic pain in 27% and others (intrauterine device, adnexal tumor, ectopic pregnancy or pelvic inflammatory disease) in 16%.

The mean age of the women presenting infertility was 32 ± 4.4 years and, among the women with chronic pelvic pain, it was 34 ± 6.9 years (P = 0.04). There was no significant difference in body mass index (BMI) between these groups (P = 0.27). Among the women with infertility, the ultrasound examination was altered in 8.5% of the cases (uterine fibroids or adnexal cyst). Among the women with chronic pelvic pain, this was seen in 45.18% of the cases (uterine fibroids or adnexal cyst).

In laparoscopic procedures to treat chronic pelvic pain, 74% of the women presented no alterations, 11% had endometriosis and 15% had adhesions. In the laparoscopic procedures on the infertility group, 47% presented no alterations, 24% had tubal sterilization, 17% had tubal alterations, 5% had endometriosis and 7% had adhesions.

The findings during laparoscopy in the group of women with infertility were: 14.16% with adnexal alterations (simple cyst, endometriomas or adhesions); 19.83%, uterine abnormalities (fibroids, adenomyosis or absence); 18.98% peritoneal alterations (endometriosis or adhesions); and 59.78%, tubal alterations (dilatation and tortuosity, adhesion, tubal sterilization or absence). In the women with chronic pelvic pain, the findings during laparoscopy were: 14.45% with adnexal alterations (simple and hemorrhagic cysts, endometriomas and adhesions); 28.92%, uterine abnormalities (fibroids, adenomyosis or absence); 35.54%, peritoneal alterations (endometriosis or adhesions); and 25.30%, tubal alterations (dilatation and tortuosity, adhesion or tubal sterilization) (**Table 1**).

Table 1. Laparoscopic findings according to the indication

Laparoscopic findings	Infertility (n = 353) n (%)	Chronic pain (n = 166) n (%)
Ovarian		
Without alterations	303 (85.84)	142 (85.55)
Cysts (simple or hemorrhagic)	32 (9.06)	15 (9.03)
Endometrioma	8 (2.27)	8 (4.82)
Adhesion	10 (2.83)	1 (0.60)
Absence	0 (0)	0 (0)
Uterine		
Without alterations	283 (80.17)	118 (71.08)
Adenomyosis	18 (5.10)	24 (14.46)
Fibroids	51 (14.45)	17 (10.24)
Absence	1 (0.28)	7 (4.22)
Peritoneal		
Without alterations	286 (81.02)	107 (64.46)
Endometriosis	37 (10.48)	24 (14.46)
Adhesion	30 (8.50)	35 (21.08)
Tubal		
Without alterations	142 (40.22)	124 (74.70)
Dilated and tortuous	101 (28.61)	18 (10.84)
Adhesion	24 (6.80)	13 (7.83)
Sterilization	84 (23.80)	11 (6.63)
Absence	2 (0.57)	0 (0)

DISCUSSION

Our study showed that the main indications for diagnostic laparoscopy were infertility (57%) and chronic pelvic pain (27%). Most of the laparoscopic procedures did not show any abnormalities, but the primary findings were tubal alterations in the group of women with infertility and peritoneal alterations (endometriosis or adhesion) in the group of women with chronic pelvic pain.

Similar results can also be seen in the literature. A study on 1654 diagnostic laparoscopic procedures showed that the main indications for the procedure were infertility (98%) and chronic pelvic pain (2%).[2] Laparoscopy is indicated in 89% of the cases of infertility in the United States, while in Canada it is indicated in 63% of the cases.[3] In cases of chronic pelvic pain, laparoscopy is indicated in 40%.[4]

Our study showed that in infertility cases, tubal alterations were the most prevalent finding from laparoscopy. In another study on 206 women with infertility, laparoscopy showed that 20.4% had pelvic adhesions, 13.6% tubal obstruction and 5.8% endometriosis.[5] Another study on 328 infertile women showed that laparoscopy diagnosed that 16% had pelvic adhesions, 19% tubal obstruction, 26% endometriosis and 13% pelvic infection.[6] In the literature, in cases in which laparoscopy was indicated due to infertility, the main findings were tubal alterations and endometriosis.[3,7]

Although most of the laparoscopic procedures carried out in the group of women with chronic pelvic pain did not show any abnormalities, the main findings were endometriosis and adhesions. Chronic pelvic pain is characterized by a painful sensation in the lower abdomen or pelvis, which may be either intermittent or constant, with or without a cyclic nature, lasting for at least six months and intense enough to lead the woman to seek medical care. Its prevalence has been estimated as between 12% and 29%.[8]

Laparoscopy in cases of chronic pelvic pain can be useful for diagnosing diseases such as endometriosis, adhesions, ovarian cysts and pelvic inflammatory disease. In cases of endometriosis, laparoscopy is the gold standard for diagnosis, in addition to enable staging (endometriosis grades 1, 2, 3 and 4). Laparoscopy can be used to evaluate subserosal fibroids and differentiate them from ovarian cysts. It can be used to diagnose abnormal uterine findings such as congenital uterine malformations (septate, bicornuate or didelphys uterus), which is not always possible with ultrasound.[1]

In our clinic, 74% of the laparoscopy procedures for investigating for chronic pelvic pain did not present any alterations. This leads us to discuss the importance of better clinical approaches and imaging studies before indicating the procedure. Despite the low complication rate of laparoscopy, it is an invasive method that entails great costs. One of the reasons why laparoscopy might not find any alterations is that abdominal myofascial syndrome might be present, resulting from a change to the abdominal wall, usually secondary to a previous cesarean.

In one study that evaluated 44 women with chronic pelvic pain in comparison with 31 women without pain, laparoscopy found that 88.4% of the group with pelvic pain and 42% of the group without pain presented alterations. In the literature, the incidence of laparoscopic findings among women with chronic pelvic pain was between 35% and 83%.[5] In a recent study on 85 women with chronic pelvic pain, laparoscopy showed that 20% had pelvic tuberculosis, 13% endometriosis, 9% adhesions and 7% adnexal cysts.[4]

Laparoscopy may be indicated in emergencies, in cases of acute pelvic pain, to identify pelvic inflammatory disease, adnexal torsion, ruptured ectopic pregnancy and ruptured hemorrhagic cysts. It also enables evaluation of the pelvic cavity and the uterus in cases of uterine perforations during surgery or insertion of a intrauterine device.[1]

However, there are still some conditions that limit the use of laparoscopy, due either to a permanent or to a temporary health condition presented by the patient. Such conditions might make it impossible to perform any surgery or might require open surgery because of technical difficulties or because better results are sought. Among these conditions are serious diseases such as heart disease, hemodynamic instability (septic or hypovolemic shock) and severe respiratory diseases, which may worsen through pneumoperitoneum caused by laparoscopy. Intracranial hypertension can also be aggravated by the head-down position in laparoscopy. Other conditions that limit the use of laparoscopy include the presence of distended bowels, which can be damaged by the equipment; presence of a large abdominal mass; advanced pregnancy; histories of several previous surgeries, which might distort the anatomy and hinder viewing; and obesity, which can make it impossible to implement pneumoperitoneum.[1]

Because laparoscopy is a technique that presents little risk, low complication rates and shorter duration of operations, and enables diagnosis and treatment procedures, it has become very important and widely used in the field of gynecology. Thus, knowing what the indications for laparoscopy are, along with the results from this procedure and the profile of the women who would benefit from it, can be beneficial.

Since this study was retrospective, it has limitations due to the lack of data in many records. Thus, we were unable to assess whether differences in socioeconomic level among the women could be a factor interfering in our results. We can infer that the population was homogeneous with regard to economic status, given that our clinic provides healthcare for the general population with low financial power.

CONCLUSION

The main indications for laparoscopy in gynecology were infertility and chronic pelvic pain. However, in most procedures, no abnormalities justifying these complaints were found. This suggests that there is a need for better clinical research before indicating laparoscopy.

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Retractions in general and internal medicine in a high-profile scientific indexing database

Retratações em medicina geral e interna em um indexador científico de alta visibilidade

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KEY WORDS:
Databases, Bibliographic.
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PALAVRAS-CHAVE:
Bases de dados bibliográficas.
Bibliometria.
Retratação de publicação.
Má conduta científica.
Fator de impacto.

ABSTRACT

CONTEXT AND OBJECTIVE: Increased frequency of retractions has recently been observed, and retractions are important events that deserve scientific investigation. This study aimed to characterize cases of retraction within general and internal medicine in a high-profile database, with interest in the country of origin of the article and the impact factor (IF) of the journal in which the retraction was made.

DESIGN AND SETTING: This study consisted of reviewing retraction notes in the Thomson-Reuters Web of Knowledge (WoK) indexing database, within general and internal medicine.

METHODS: The retractions were classified as plagiarism/duplication, error, fraud and authorship problems and then aggregated into two categories: "plagiarism/duplication" and "others." The countries of origin of the articles were dichotomized according to the median of the indicator "citations per paper" (CPP), and the IF was dichotomized according to its median within general and internal medicine, also obtained from the WoK database. These variables were analyzed using contingency tables according to CPP (high versus low), IF (high versus low) and period (1992-2002 versus 2003-2014). The relative risk (RR) and 95% confidence interval (CI) were estimated for plagiarism/duplication.

RESULTS: A total of 86 retraction notes were identified, and retraction reasons were found for 80 of them. The probability that plagiarism/duplication was the reason for retraction was more than three times higher for the low CPP group (RR: 3.4; 95% CI: [1.9-6.2]), and similar results were seen for the IF analysis.

CONCLUSION: The study identified greater incidence of plagiarism/duplication among retractions from countries with lower scientific impact.

RESUMO

CONTEXTO E OBJETIVO: Recente aumento da frequência de retratações tem sido observado, e retratações são eventos importantes que merecem investigação científica. O objetivo do estudo é caracterizar casos de retratação na área de medicina geral e interna em banco de dados de alta visibilidade, com interesse no país de origem do artigo e no Fator de Impacto (FI) da revista que realizou a retratação.

TIPO DE ESTUDO E LOCAL: O estudo consistiu em revisão das notas de retratação no indexador Web of Knowledge (WoK) Thomson Reuters, na área "Medicina Interna e Geral".

MÉTODOS: As retratações foram classificadas como: plágio e duplicação, erro, fraude e problemas de autoria e, em seguida, agregadas em duas categorias: "plágio e duplicação" e "outros". Os países de origem dos artigos foram dicotomizados pela mediana do indicador "citações por artigo" (CPP), e o FI foi dicotomizado por sua mediana para a área de pesquisa "medicina interna e geral", também obtida a partir do WoK. Essas variáveis foram analisadas em tabela de contingência de acordo com os grupos CPP (alto x baixo), FI (alto x baixo) e período (1992-2002, 2003-2014). Riscos relativos (RR) e intervalos de confiança de 95% (IC 95%) foram estimados para plágio-duplicação.

RESULTADOS: Um total de 86 notas de retratação foi identificado, com razões de retratação disponíveis para 80 delas. A probabilidade de plágio/duplicação como razão para a retração foi mais de três vezes maior para o grupo "baixo CPP" (RR: 3,4; IC 95%: [1,9–6,2]), e resultados semelhantes foram observados para a análise de FI.

CONCLUSÃO: O estudo identificou maior incidência de plágio/duplicação nas retratações de países com menor impacto científico.

INTRODUCTION

The first recorded scientific retraction (withdrawal of a paper after its publication) apparently dates from 1756.[1] Although uncommon, increased frequency of such events has recently been observed.[2] Retractions are considered to be important events that deserve scientific investigation.[3] The reasons commonly mentioned for their occurrence are fraud, ethical issues in human research and issues relating to scientific communication (plagiarism, self-plagiarism and duplication).[3-6]

More recently, the association between retractions and scientometric factors such as research field, country and other characteristics of authors and journals has become a matter of interest and debate, with a view towards development of strategies for preventing misconduct.[3,5,7,8] For example, if retractions were mostly due to plagiarism, it would be important to focus on procedures such as the use of automatic detection software and journal guidelines for handling plagiarism cases.[9,10] On the other hand, for data fraud, more specific monitoring measures (for instance, introduction of data repositories, random audits and mandatory data sharing in an institution) would be appropriate.

OBJECTIVE

Given the recent increase in retractions, this study aimed to characterize cases and reasons for scientific retractions in the field of general and internal medicine, in a high-profile international indexed database.

METHODS

This study consisted of surveying the retraction notes in the Thomson-Reuters Web of Knowledge (WoK) indexing database,[11] with special interest in the country of origin of the article and the impact factor (IF) of the journal in which the retraction was made. Articles classified as "general and internal medicine" were searched using the keywords "retraction" and "retracted" in their title fields (field tag = TI). After this initial identification, duplicate records and non-pertinent records of retraction (i.e. cases in which "retraction" referred, for instance, to surgical retraction) were removed, and the following information was gathered: country of origin of the article (main author address as defined by the indexing database); IF; country and name of the journal in which the retraction was made; year of publication of the retraction and the alleged reason for this (see below); and, finally, the journal and year in which the original work was published (in cases of plagiarism or duplication). The search procedures ended in November 2014.

The reasons for retraction were ascertained independently by three of the present authors and were classified as plagiarism or duplication, fraud or suspected fraud, error and authorship problems. The IF for the journal was obtained from the Journal Citation Reports database[12] for the year closest to the retraction date. Additionally, the indicator "citations per paper" (CPP, i.e. the number of citations divided by the number of papers published over a specific period)[13] was also obtained from the WoK database for the countries studied, covering the period from 2001 to 2011.[14] When a CPP for a country was not available, its value was calculated directly from the WoK citation data with the aid of the "generate citation report" function, for the field of general and internal medicine.

The variables were aggregated as follows. The retraction reason was classified as "plagiarism/duplication" or "others"; the country of origin of the study was defined as high CPP or low CPP, dichotomized according to the median CPP value for the countries analyzed; and the IF was also dichotomized as high or low according to the median IF for the WoK-Web of Science subject area of general and internal medicine.[12] Since the objective of the present work was basically descriptive, no modeling (e.g. logistic regression) was attempted. Instead, data were analyzed by means of cross-tabulating the retraction reasons against the aggregated country and IF for the periods 1992-2002 and 2003-2014. The relative risk of plagiarism/duplication was determined firstly according to the CPP (the proportion of retractions due to plagiarism in low-CPP countries divided by the proportion of retractions due to plagiarism in high-CPP countries); and secondly according to the IF (the proportion of retractions due to plagiarism in low-IF journals divided by the proportion of retractions due to plagiarism in high-IF journals). Following this, 95% confidence intervals (CIs) were then estimated for all retractions from 1992 to 2014. The data processing was performed using the SPSS version 2.0 software.

RESULTS

Figure 1 shows the search strategy and number of retraction notes analyzed. After identification (through the title words "retraction of" and "retracted") and screening (elimination of duplicate records and non-pertinent uses of the word "retraction"), a total of 86 notes were gathered. Out of these, the reasons for retraction could not be determined in six cases, which were not included in the analysis. These six "missing" cases came from journals published in Japan, Pakistan, South Korea and England. The first low-CPP/low-IF retraction case was seen in 1992 (due to plagiarism/duplication), and the next retraction note for the low-CPP/low-IF groups appeared in 2004 (also due to plagiarism/duplication).

CPP values were obtained directly for all countries except Croatia, Iran, Malaysia, Pakistan, Saudi Arabia and Tunisia, for which the manually calculated CPPs were 7.72, 6.97, 6.62, 7.58, 8.18 and 7.61, respectively. These countries, together with Brazil, China, India, South Korea, Taiwan and Turkey represented the "low-CPP" countries, while Belgium, Canada, Finland, Germany,

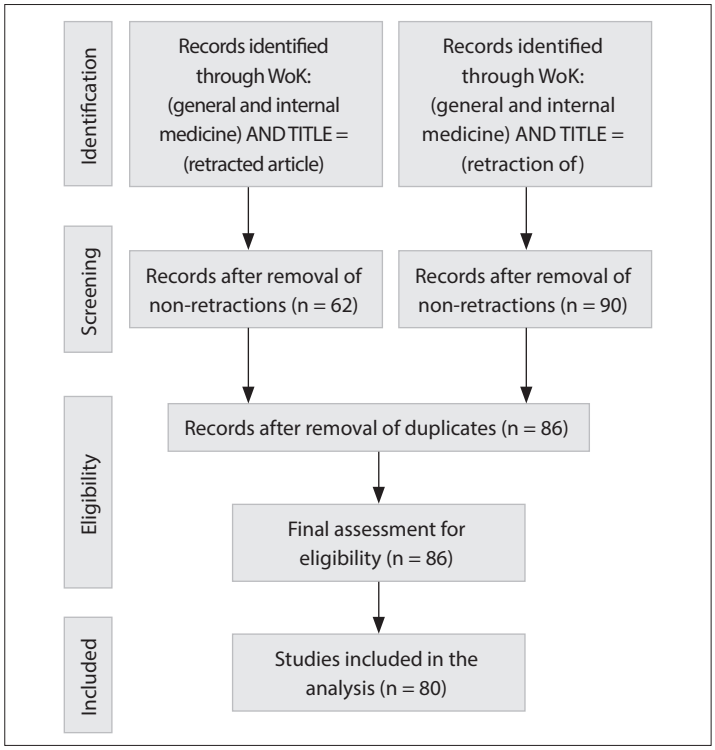

Figure 1. Search strategies and retraction notes identified, in relation to studies in the field of general and internal medicine, in the ISI Web of Knowledge (Wok) database.

Table 1. Retraction notes with identified reasons for retractions in the field of general and internal medicine, in the ISI Web of Knowledge database, aggregated according to countries of origin of the articles (high versus low, dichotomized according to the CPP median), impact factor (high versus low, dichotomized according to the IF median) and time period. The overall relative risk of plagiarism/duplication for the country group (reference group: high CPP), with 95% confidence interval, was 3.4 (1.9-6.2); for the IF group (reference: high IF), it was 3.9 (2.0-7.8). One case of mistaken duplication by an editor was classified as "error"

Period	Reason for retraction		
	Plagiarism/ duplication	Other	(Fraud + authorship + error)
1992-2002			
High CPP	2	10	(3 + 1 + 6)
Low CPP	1	0	
2003-2014			
High CPP	5	26	(13 + 2 + 11)
Low CPP	27	9	(2 + 5 + 2)
2003-2014			
High IF	7	28	(14 + 3 + 11)
Low IF	25	7	(1 + 2 + 4)

IF = impact factor; CPP = citations per paper.

Israel, Italy, Japan, Norway, Scotland, Switzerland, England and USA comprised the "high-CPP" group. **Table 1** indicates that in the high-CPP countries, 12 retractions took place in 1992-2002, while in the low-CPP group, only one retraction was seen (due to plagiarism/duplication). However, over the period 2003-2014, these numbers were, respectively, 31 (high CPP) and 36 (low CPP). Overall, nearly one in six retractions in the high-CPP group were due to plagiarism/duplication, while in the low-CPP group, this proportion was much higher, resulting in a relative risk for plagiarism/duplication (RRplag-dup) of 3.4 (CI: 1.9-6.2). Thus, retractions due to plagiarism/duplication were 3.4 times more likely among low-CPP countries than among high-CPP countries. Similar results were seen for the high/low IF analysis, with a relative risk (RRIF) of 3.9 (CI: 2.0-7.8). The IF results for 1992-2002 are coincident with the CPP analysis for this period (not shown in **Table 1**).

DISCUSSION

This study aimed to characterize retractions in the field of general and internal medicine, seen in a high-visibility indexing database, with a special interest in the reasons for retractions grouped according to the country of origin of the article country and the journal characteristics. Other studies (using broader databases such as the PubMed index)[5,7,8] have also identified greater incidence of plagiarism among lower-income countries. However, for the present study, it was decided to use an indicator of scientific output as an alternative. Scientific misconduct is highly dependent on the scientific tradition and culture of a research group and, for strong scientific communities to be developed, generations of researchers need to be trained.[15] Therefore, a well-known indicator of "scientific proficiency" was used: the number of citations per paper (CPP) of a country. This indicator is widely used for scientometric comparisons between countries[13,15-20] and provides a means of measuring the research impact and visibility of a country.

It should also be noted that there is disagreement in the literature on this topic with regard to how the reasons for retractions should be grouped. For instance, plagiarism is sometimes regarded as a type of error, while other researchers have preferred to classify it together with duplication.[3,5,6] In the present study, the latter option was adopted, given that: a) both of these types of misconduct involve inappropriate reporting and not flaws in experiments; b) the process of detecting them (e.g. using automatic detection software) is similar; and c) the measures for preventing them are similar. On the other hand, the lack of reporting on the reasons for retractions is a shortcoming that deserves attention from the scientific community, since, as mentioned earlier, precise characterization of the reasons that led to a retraction is a prerequisite for implementation of effective prevention strategies.

In the countries defined as low CPP, plagiarism/duplication accounted for a clear majority of the retraction cases, and a similar effect was seen in relation to the low-IF group (as expected, since most low-CPP cases were also low IF). Also in relation to the IF of the journal in which the retraction was made, some studies have pointed out that retractions are more common

among high-IF journals,[21] although this effect seemed to be leveling off in the more recent period analyzed here. One interpretation of these results is that, in countries with less tradition of research, procedures for ensuring academic integrity are also less widespread and, therefore, expansion of science in these countries leads to increases in the incidence of both retractions and plagiarism/duplication. In addition, detection of plagiarism has been made relatively easier by the internet and through the introduction of the aforementioned systems for automated detection.

Other results previously described in the literature could also be seen in the present study. For example, it is well established that retractions are a recent and increasing phenomenon,[2,6] and this effect is even clearer if the low-CPP countries analyzed here are considered. In fact, in the present study, apart from one case that occurred in 1992, the first low-CPP/low-IF retraction note only appeared in 2004. In journals based in high-CPP countries, retractions have been present since 1992, but it is clear that they have recently been increasing.

The following limitations of the present study should be noted: a) the time periods used for estimating IFs and CPPs did not precisely correspond to the retraction dates; and b) the reasons for six retractions could not be ascertained. Another limitation relates to classification of reasons for retractions, which is not always straightforward and sometimes requires a "reading" of the reported information. However, in the present study, the researchers were in agreement regarding all the cases analyzed.

CONCLUSION

It is well known that the frequency of scientific retractions has markedly increased over recent years. The present study documents the extent of this phenomenon among low-CPP countries in the field of general and internal medicine, using the WoK database. It found that plagiarism and duplication were the major cause of retractions among the countries involved, and similar results could be seen in relation to the low-IF journals in which the retractions were made. It is expected that studies such as the present one could lead to measures aimed towards international dissemination of best practices within research.

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Influence of type 2 diabetes mellitus on liver histology among morbidly obese individuals. A cross-sectional study

Influência do diabetes mellitus tipo 2 sobre a histologia hepática entre indivíduos com obesidade mórbida. Um estudo transversal

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Bariatric surgery.
Obesity.

PALAVRAS-CHAVE:
Fígado gorduroso.
Resistência à insulina.
Diabetes mellitus.
Cirurgia bariátrica.
Obesidade.

ABSTRACT

CONTEXT AND OBJECTIVE: Nonalcoholic fatty liver disease (NAFLD) has become a public health concern. It encompasses a wide spectrum of histological abnormalities and has close relationships with insulin resistance and type 2 diabetes mellitus (T2DM). This study sought to compare the histological alterations observed in morbidly obese individuals with and without T2DM who underwent Roux-en-Y gastric bypass.

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

METHODS: This was a cross-sectional study on 197 individuals who underwent gastric bypass surgery between 2011 and 2013. NAFLD was assessed through liver biopsies. T2DM was diagnosed through the International Diabetes Federation criteria.

RESULTS: Non-diabetics presented significantly more biopsies without any histological abnormalities, regarding steatosis (42.6% versus 25.5%; P = 0.0400), fibrosis (60.6% versus 36.2%; P = 0.0042) and steatohepatitis (27.3% versus 12.8%; P = 0.0495), while diabetics presented significantly higher frequency of moderate forms of steatosis (36.2% versus 20%; P = 0.0307) and fibrosis (23.4% versus 4%; P = 0.0002).

DISCUSSION: T2DM was associated with more advanced forms of NAFLD within the population studied. NAFLD has previously been correlated with severe forms of heart disease.

CONCLUSION: Screening for and early detecting of NAFLD in high-risk populations are important for avoiding further development of severe forms and the need for liver transplantation.

RESUMO

CONTEXTO E OBJETIVO: A doença gordurosa não alcoólica do fígado se tornou um problema de saúde pública. Ela compreende um amplo espectro de alterações histológicas e se relaciona intimamente com a resistência insulínica e o diabetes mellitus tipo 2. Este estudo tem por objetivo comparar as alterações histológicas observadas em obesos mórbidos com e sem diabetes submetidos ao *bypass* gástrico em Y de Roux.

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

MÉTODOS: Este é um estudo transversal que envolveu 197 indivíduos submetidos ao *bypass* gástrico entre 2011 e 2013. A doença gordurosa do fígado foi avaliada através de biópsia hepática. O diabetes mellitus tipo 2 foi diagnosticado através dos critérios da Federação Internacional de Diabetes.

RESULTADOS: Indivíduos não diabéticos apresentaram significativamente mais biópsias sem anormalidades histológicas, em relação a esteatose (42,6% *versus* 25,5%; P = 0.04), fibrose (60,6% *versus* 36,2%; P = 0.0042) e esteato-hepatite (27,3% *versus* 12,8%; P = 0.0495); os diabéticos apresentaram uma frequência significativamente mais alta de formas moderadas de esteatose (36,2% *versus* 20%; P = 0.0307) e fibrose (23,4% *versus* 4%; P = 0.0002).

DISCUSSÃO: O DM-2 associou-se a formas mais avançadas de doença gordurosa do fígado dentro da população estudada. A doença gordurosa não alcoólica do fígado foi associada previamente com formas graves de doença cardíaca.

CONCLUSÃO: A busca e detecção precoce da doença gordurosa em populações de alto risco são importantes para evitar o futuro desenvolvimento de formas graves e a necessidade de transplante hepático.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has been increasingly diagnosed worldwide and is now recognized as a source of public health concern. It encompasses a wide spectrum of histological features that range from simple steatosis to severe forms of fibrosis, steatohepatitis and even cirrhosis.[1-3] Its pathogenesis is not completely understood, but several abnormalities have been strongly linked to its onset, such as central obesity, insulin resistance, chronic inflammation, increased uptake of fatty acids by the liver and lipotoxicity.[4,5]

NAFLD has been considered to be a hepatic manifestation of metabolic syndrome (MetS) and, as such, is strongly related to type 2 diabetes mellitus (T2DM). Some studies have correlated the severity of insulin resistance with the development of severe forms of NAFLD. Moreover, NAFLD has been described as a reliable predictor of development of T2DM.[6-10]

Bariatric surgery has become the standard treatment for morbid obesity, and Roux-en-Y gastric bypass (RYGB) is the surgical technique most performed worldwide nowadays.[11] Among the morbidly obese individuals who undergo surgery, NAFLD presents high prevalence, and liver biopsy during surgery is considered mandatory in order to address the severity of NAFLD. Several studies have observed significant improvement in liver histology following RYGB, including complete reversal of liver abnormalities.[12-18]

OBJECTIVE

This study sought to assess the liver histology observed in a group of individuals who underwent Roux-en-Y gastric bypass, in order to identify possible differences regarding NAFLD, between diabetic and non-diabetic individuals.

METHODS

This was a cross-sectional study in which individuals who underwent open Roux-en-Y gastric bypass (RYGB) surgery at Hospital de Clínicas, Universidade Estadual de Campinas (Unicamp), between 2011 and 2013, were enrolled. This study was submitted to and was approved by the local Research Ethics Committee. RYGB was indicated in accordance with the American National Institutes of Health Consensus Statement criteria. Thus, surgery was indicated for individuals who had been obese for at least five years, with at least two unsuccessful attempts at conservative treatment, with a body mass index (BMI) greater than or equal to 40 kg/m^2, or greater than or equal to 35 kg/m^2 if this was associated with obesity-related comorbidities.[19] The sample size was estimated using a single-proportion formula with a 95% confidence interval. The precision was set at 5% and the sample size thus calculated was 169. The inclusion criteria were that the subjects needed to be between 18 and 65 years of age, and to have undergone RYGB. The exclusion criteria comprised membership of vulnerable groups (mentally ill, institutionalized or aged below 18 years); recent or previous abuse of alcohol; antecedents of acute or chronic viral hepatitis; serological abnormalities relating to the hepatitis B or C virus; previous biliary obstruction; and preoperative biochemical examination data not completely available.

Out of the 302 subjects considered, 197 were selected for this study. The reasons for exclusion were: incomplete preoperative biochemical examinations in the medical records (77 individuals), previous alcohol abuse (19), serological abnormalities relating to chronic viral hepatitis (8) and recently treated biliary obstruction caused by gallstones (1). The main characteristics regarding demographics and anthropometric parameters were assessed.

The presence of T2DM was assessed in accordance with the criteria defined by the International Diabetes Federation (IDF) guidelines. Thus, the presence of T2DM was defined by the presence of any of the following abnormalities: fasting plasma glucose ≥ 126 mg/dl; 75 g oral glucose tolerance test with two-hour plasma glucose ≥ 200 mg/dl; glycated hemoglobin (HbA1c) ≥ 6.5%; and random plasma glucose ≥ 200 mg/dl in the presence of classical diabetes symptoms.[20]

NAFLD was assessed through histological examination of liver biopsies carried out during the surgical procedure. Liver abnormalities were classified into three categories:

1. steatosis;
2. fibrosis; and
3. steatohepatitis.

Each category was divided according to the degree of severity:

1. absent;
2. mild;
3. moderate; and
4. severe.

Statistical analysis

The data were examined to ascertain whether the distribution was normal, in accordance with the Shapiro-Wilk test. The chi-square test and Fisher's exact test were used to compare proportions. The Mann-Whitney test was used to compare continuous measurements between independent groups. The significance level used was 5% (P-value < 0.05). The analysis was performed using the Statistical Analysis System (SAS) software for Windows, version 9.2.

RESULTS

Out of the 197 patients selected for this study, 155 (78.7%) were female and 42 (21.3%) were male. The mean age at the time of surgery was 38.4 years (range, 18-64). The main baseline characteristics of the subjects are summarized in **Table 1**.

The diabetes group comprised 47 individuals (23.8%). Diabetics presented significantly older age (44.8 years ± 9 versus

Table 1. Characteristics of subjects and comparison of diabetics versus non-diabetics

Variable		Overall (mean ± SD)		DM		Non-DM	P-value
Number of subjects		197		47 (23.8%)		150 (76.2%)	NA
Age (years)		38.4 ± 9.8 (range, 18 – 64)		44.8 ± 9		36.3 ± 9.1	**< 0.0001**
Gender		Male: 42 (21.3%) Female: 155 (78.7%)		Male: 12 (25.5%) Female: 35 (74.5%)		Male: 30 (20%) Female: 120 (80%)	0.4202
Weight (kg)		111.1 ± 15.5 (range, 71.8 – 161.4)		107 ± 13.1		112.1 ± 14.5	0.7234
BMI (kg/m^2)		40.6 ± 5.6 (range, 35 – 59.7)		38.6 ± 3.7		41.2 ± 5.9	**0.00714**
Liver histology	Steatosis	1) Absent: 76 (38.6%)	Steatosis	1) Absent: 12 (25.5%)	Steatosis	1) Absent: 64 (42.6%)	**0.0400**
		2) Mild: 73 (37%)		2) Mild: 18 (38.3%)		2) Mild: 55 (36.7%)	0.8637
		3) Moderate: 47 (23.9%)		3) Moderate: 17 (36.2%)		3) Moderate: 30 (20%) (23.9%)	**0.0307**
		4) Severe: 1 (0.5%)		4) Severe: 0		4) Severe: 1 (0.7%)	1.0
	Fibrosis	1) Absent: 108 (54.8%)	Fibrosis	1) Absent: 17 (36.2%)	Fibrosis	1) Absent: 91 (60.6%)	**0.0042**
		2) Mild: 70 (35.6%)		2) Mild: 18 (38.3%)		2) Mild: 52 (34.7%)	0.7274
		3) Moderate: 17 (8.6%)		3) Moderate: 11 (23.4%)		3) Moderate: 6 (4%)	**0.0002**
		4) Severe: 2 (1%)		4) Severe: 1 (2.1%)		4) Severe: 1 (0.7%)	0.4212
	Steatohepatitis	1) Absent: 47 (23.9%)	Steatohepatitis	1) Absent: 6 (12.8%)	Steatohepatitis	1) Absent: 41 (27.3%)	**0.0495**
		2) Mild: 143 (72.6%)		2) Mild: 38 (80.8%)		2) Mild: 105 (70%)	0.1897
		3) Moderate: 6 (3%)		3) Moderate: 3 (6.4%)		3) Moderate: 3 (2%)	0.1486
		4) Severe: 1 (0.5%)		4) Severe: 0		4) Severe: 1 (0.7%)	1.0

DM = diabetes mellitus; SD = standard deviation; BMI = body mass index; NA: not applicable.

36.3 ± 9.1 years; P < 0.0001) and lower body mass index (44.8 ± 9 kg/m^2 versus 36.3 ± 9.1 kg/m^2; P = 0.00714). Weight and gender distribution did not significantly differ between the groups (**Table 1**).

Non-diabetics presented significantly more biopsies without any abnormalities regarding steatosis (42.6% versus 25.5%; P = 0.0400), fibrosis (60.6% versus 36.2%; P = 0.0042) and steatohepatitis (27.3% versus 12.8%; P = 0.0495), while diabetics presented significantly higher frequency of moderate forms of steatosis (36.2% versus 20%; P = 0.0307) and fibrosis (23.4% versus 4%; P = 0.0002). The frequency of the mild forms did not differ in relation to any parameter in the groups. There is a detailed summary of the histological findings in **Table 1**.

DISCUSSION

T2DM is currently considered to be intrinsically linked to NAFLD. The exact pathophysiological pathways through which these conditions are interconnected are not completely understood, but several metabolic abnormalities are present in both of them, especially insulin resistance, defective glucose and lipid homeostasis and chronic inflammation.[6-10]

Since liver biopsies during bariatric surgery are considered mandatory, since they can be performed safely and provide useful information, significantly large numbers of subjects may be analyzed within this context regarding NAFLD.[21-23] On the other hand, in non-surgical settings, liver biopsies are not risk-free and therefore are not widely available. In these situations, noninvasive models that use simple laboratory examinations to assess NAFLD have been developed and validated, and may be of great usefulness for screening purposes. Of these, the NAFLD fibrosis score is the most widely known nowadays.[24-27]

This study showed that T2DM was significantly associated with the presence of NAFLD in a morbidly obese population. Furthermore, it was also associated with advanced forms of NAFLD, especially the presence of nonalcoholic steatohepatitis (NASH). The prevalence of NAFLD among obese adults with T2DM has been estimated to be greater than 70%. Alanine aminotransferase levels have been noted to be more than twice the normal levels in 20% of children with T2DM, and this is attributed to NAFLD in most cases.[28-30]

It is important to emphasize that the diabetic population of this study was significantly older than the non-diabetic population. Thus, these individuals may have been exposed to insulin resistance-related metabolic abnormalities for longer periods, possibly leading to liver disease of greater severity and to T2DM development from a previous MetS background.

The lower BMI of the diabetic population, compared with the non-diabetic population was also notable. This may have been due to the fact that surgery is indicated for obese individuals who are free of comorbidities when BMI is greater than or equal to 40 kg/m^2. However, the limitations of BMI alone as an index for obesity need to be borne in mind. Since insulin resistance and its main clinical conditions (MetS and T2DM) are more related to central/visceral obesity, BMI may not be so reliable for address the severity of obesity within this group, in comparison, for example, with waist circumference or waist-to-hip ratio.[20]

The interconnection between NAFLD and T2DM has been noted previously in the literature. Fukuda et al. observed that even among non-overweight individuals, NAFLD was an independent predictor of T2DM.[31] Yamazaki et al. followed up a cohort of 4,604 subjects and showed that, in a long-term evaluation of individuals with ultrasonographically assessed liver disease, that improvement of NAFLD leads to reduced incidence of T2DM.[32]

NAFLD in diabetic individuals has been linked to severe complications of heart disease. Targher et al. demonstrated that NAFLD was independently associated with cardiovascular events, and therefore suggested that NAFLD was not merely a marker of cardiovascular disease (CVD) but might also be involved in its pathogenesis. The possible molecular mediators linking NAFLD and CVD include proatherogenic mediators released from the liver, including C-reactive protein, fibrinogen and plasminogen activator inhibitor-1.[33] Mantovani et al. observed that NAFLD is independently associated with early left ventricular diastolic dysfunction in type 2 diabetic patients with preserved systolic function.[34]

Since bariatric surgery provides significant weight loss and high rates of resolution of metabolic comorbidities, it has also been associated with improvement of liver disease. It is now believed that this metabolic improvement is only partially linked to the weight loss itself. In fact, it begins very early following surgery, possibly due to structural changes in gastrointestinal transit, leading to increased incretin/adipokine activity and immunomodulation. Even individuals with severe forms may benefit from surgical outcomes. Considering the possible ominous risks of NAFLD/NASH, especially end-stage liver disease and liver cancer, this benefit is even more pronounced.[12-18,35-37]

This study has some limitations, especially its use of data collected from the medical records, which may provide data of poor quality and may lead to the impossibility of evaluating a considerable number of individuals, because of incomplete medical reports. In this study, incomplete medical records caused high loss of subjects who might have been suitable for analysis. Furthermore, there were only a few subjects with severe forms of NAFLD within the sample studied.

Since NAFLD is nowadays the third most common indication for liver transplantation in the USA, and it is expected to be the first by 2030,[38,39] screening and early detection of high-risk populations, such as diabetics, may have a major impact on its onset and further prognosis.

CONCLUSION

Liver disease occurred more frequently among diabetics in this study. T2DM was associated with more advanced forms of NAFLD.

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Mixed adenoneuroendocrine carcinoma of the gastric stump following Billroth II gastrectomy: case report and review of the literature

Adenocarcinoma neuroendócrino misto do coto gástrico após gastrectomia à Billroth II: relato de caso e revisão de literatura

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KEY WORDS:
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PALAVRAS-CHAVE:
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Coto gástrico.
Tumor misto maligno.
Adenocarcinoma.
Tumores neuroendócrinos.

ABSTRACT

CONTEXT: Gastric stump cancer after gastric resection is a well-known disease. It may be a newly developed cancer after resection due to benign disease, or recurrent or residual disease after oncological surgery. The predominant histological type is usually adenocarcinoma. This study aimed to report on a rare occurrence of a mixed adenoneuroendocrine carcinoma (MANEC) on the gastric stump.

CASE REPORT: The case of an 83-year-old female who presented a locally aggressive gastric stump MANEC, 35 years after Billroth II gastrectomy to treat a peptic ulcer, is reported. The patient underwent resection and adjuvant therapy. She has been followed up for one year without signs of recurrence.

CONCLUSION: MANEC is a rare type of gastrointestinal neoplasm. The classification, histopathology, clinical features, treatment issues and prognosis are discussed along with a brief review of the literature.

RESUMO

CONTEXTO: O câncer de coto gástrico após gastrectomia é uma condição extensamente documentada. Pode se tratar de doença desenvolvida após a ressecção por doença benigna, ou ainda doença recorrente ou residual após cirurgia oncológica. Geralmente, o tipo histológico predominante é o adenocarcinoma. Este estudo tem como propósito relatar a rara ocorrência de um adenocarcinoma neuroendócrino misto (MANEC) no coto gástrico.

RELATO DE CASO: É relatado o caso de uma mulher de 83 anos que apresentou um MANEC localmente agressivo 35 anos após uma gastrectomia à Billroth II devido a úlcera péptica. Foi submetida a ressecção e terapia adjuvante e foi seguida por 12 meses sem sinais de recorrência.

CONCLUSÃO: Os MANECs constituem raro tipo de neoplasia gastrointestinal. Sua classificação, histopatologia, aspectos clínicos, tratamento e prognóstico são discutidos junto com uma breve revisão de literatura.

INTRODUCTION

Occurrences of gastric stump cancer (GSC) after partial gastric resection, especially when Billroth II reconstruction is carried out, are a well-recognized problem.[1,2] GSC was classified into three categories by Kidokoro et al.:[3] cancer newly developed in the remnant stomach; recurrent cancer in the remnant stomach; and cancer remaining in the remnant stomach after the initial gastric surgery. The carcinogenesis of newly developed GSC is strongly associated with chronic duodenogastric reflux of bile and pancreatic juice, and hypochlorhydria secondary to denervation through vagotomy.[1,3,4]

Because a great number of younger patients underwent this procedure over the decades prior to the introduction of more effective drug therapies against peptic disease that have been developed lately, a significant number of individuals are exposed to higher risk of gastric cancer nowadays. It is generally reported that chronic degenerative changes to the gastric mucosa lead to development of adenocarcinoma with varying degrees of differentiation.[4] There are no previously reported cases of mixed adenoneuroendocrine carcinoma (MANEC) arising in the gastric stump subsequent to Billroth II gastrectomy.

CASE REPORT

An 83-year-old female sought assistance due to weight loss (10 kg), epigastric fullness and regurgitation of solid food over a three-month period. The patient presented mild hypertension that was under control by means of monotherapy (enalapril maleate) and had undergone partial gastric resection due to a peptic ulcer 35 years earlier.

On clinical examination, an epigastric mass was palpated. Rectal and vaginal examinations showed no alterations. From esophagogastroscopy, the following were observed: Billroth II gastrectomy and diffuse thickening and infiltrative appearance of the gastric stump mucosa, from the esophagogastric junction to the gastrojejunostomy site, suggestive of *linitis plastica*. Histopathological examination revealed poorly differentiated adenocarcinoma with signet ring cells. A computed tomography scan showed a thickening of the gastric stump from the cardia to the gastrojejunostomy site; there was apparent invasion of the transverse colon and pancreas tail. Colonoscopy confirmed the presence of transmural invasion of the colon.

The patient underwent open total gastrectomy along with D2 lymphadenectomy, segmental colectomy, distal pancreatectomy, splenectomy, cholecystectomy and Roux-en-Y reconstruction. The operation lasted four hours and the patient was then moved to the intensive care unit. During the postoperative period, the patient presented nosocomial pneumonia that required treated using broad-spectrum antibiotic therapy and developed deep venous thrombosis in her left leg that needed anticoagulation. Enteral nutrition through a jejunostomy was introduced on the fourth day after the operation and oral feeding was started on the tenth day. The patient was discharged from hospital 28 days after surgery, at the time when antibiotic therapy ended and anticoagulation with oral drugs had been achieved.

Histopathological examination on the surgical specimen revealed that it comprised a poorly differentiated, ulcerated adenocarcinoma with signet ring cells, which infiltrated the gastric wall and invaded the colon segment. Angiolymphatic and perineural invasion were present; the surgical margins were free; none of the lymph node presented metastases (0/15); the TNM classification was T4N0 (stage IIIA). Immunohistochemical analysis revealed diffuse positivity for AE1/AE3; 40% of the sample was positive for chromogranin A and synaptophysin, thus characterizing a differentiated neuroendocrine tumor (NET). Hence, the diagnosis of gastric stump intermediate-grade malignant mixed adenoneuroendocrine carcinoma (MANEC) was confirmed, with predominance of the exocrine phenotype.

Adjuvant therapy was used based on the most common tumor cell type, and the most aggressive type (adenocarcinoma) was taken into consideration. We used postoperative bolus-based chemotherapy consisting of a combination of 5-fluorouracil (5-FU) plus leucovorin (LEU), along with sandwiched chemoradiation therapy of a bolus of 5-FU plus LEU as a radiosensitizer.[5]

The patient presented mild symptoms during the first two courses of chemotherapy, such as abdominal pain, nausea and vomiting, but no dose reduction was applied. The third course was administered with concomitant locoregional radiotherapy. After ten days, the patient presented significant gastrointestinal symptoms comprising diarrhea, nausea, vomiting and abdominal pain, and the radiation therapy was suspended. The treatment continued with chemotherapy alone until five cycles had been completed, with mild gastrointestinal symptoms. The patient has been followed up for one year since the surgery, and the last CT scan did not show any signs of recurrence.

DISCUSSION

MANECs of the gastrointestinal tract are rare tumors.[6] A wide spectrum of possible combinations of exocrine and neuroendocrine components has been recognized, ranging from adenomas or carcinomas with interspersed neuroendocrine cells to typical NET with a focal exocrine component.[6,7] Both the exocrine and the neuroendocrine components may present different morphological characteristics. For the former, these range from adenomas to adenocarcinomas with varying degrees of differentiation, while for the latter, these range from well to poorly differentiated NET.[7] A tumor is considered to be of mixed exocrine and neuroendocrine type when at least 30% of the lesion is represented by one of the components.[8]

A review of the literature was conducted through an online search for the MeSH terms gastric stump and stomach neoplasms in Medline (via PubMed); and for the MeSH/DeCS terms gastric stump and stomach neoplasms in Lilacs (via Bireme) (**Table 1**). There were no cases in which the histopathological findings were similar to those reported in this study.

Mixed exocrine-neuroendocrine neoplasms can be grouped into different prognostic categories according to the grade of malignancy of each component.[6,7] They are classified as follows: 1) high-grade malignant MANEC: combination of an adenomatous or carcinomatous component with a poorly differentiated (small, intermediate or large cell type) neuroendocrine carcinoma (NEC); 2) intermediate-grade malignant MANEC: this group includes mixed adenocarcinoma-neuroendocrine tumors (adenocarcinoma/carcinoma that may show different degrees of differentiation, combined with a differentiated NET) and amphicrine carcinoma (a peculiar form of tumor in which the same neoplastic cells coexpress both endocrine and exocrine features, with varying grades of differentiation); 3) low-grade malignant mixed adenoneuroendocrine tumor: neoplasms composed of well-differentiated neuroendocrine and exocrine cells that generally have indolent behavior.[6]

Mixed adenocarcinoma-neuroendocrine tumors, which are in the intermediate-grade category, are formed by areas of tubular, papillary or mucinous adenocarcinoma and areas of grade 1 or 2 NET.[6,7] Unlike high grade MANECs, the exocrine component is usually more aggressive than the neuroendocrine component. There are approximately 60 reported cases in the literature, throughout the gastrointestinal tract. They are more prevalent in men in their fifth to sixth decades of life. In the stomach, their distribution is equal in the antrum and in the body.[6] This group also includes poorly cohesive neuroendocrine carcinoma, in which there are noncohesive signet ring cells mixed with neuroendocrine cells. This subtype often involves the whole stomach with a pattern of *linitis plastica*.[6,9,10]

There is no optimal management strategy to date, because of the rarity of this pathological condition.[6] The most aggressive component should be taken into account when treatment options are considered.[11-13] Tumors with a poorly differentiated neuroendocrine carcinoma component must be treated as neuroendocrine carcinomas; tumors composed of an adenocarcinoma along with well-differentiated NET must be treated as adenocarcinoma.[6,11] Surgical resection is mostly indicated and must be followed by adjuvant therapy. Early diagnosis is an important factor for avoiding extensive resection like in the case reported in this study.[14]

The prognosis for patients with MANECs is not well-defined.[15,16] The data available suggest that high grade MANECs appear to lead to better overall survival than do pure neuroendocrine carcinomas.

Table 1. Database search results for mixed adenoneuroendocrine tumor of the gastric stump on July 15, 2014

Electronic databases	Search strategies	Results
Medline (PubMed)	(Gastric Stump) AND (Stomach neoplasms)	67 case reports (no mixed adenoneuroendocrine carcinoma)
Lilacs (Bireme)	((Gastric Stump) OR (Muñón Gástrico) OR (Coto Gástrico)) AND ((Stomach neoplasms) OR (Neoplasias gástricas))	110 case reports (no mixed adenoneuroendocrine carcinoma)

Intermediate-grade MANECs do not yet have any defined overall prognosis.[6,17,18] Specifically, when the mixed poorly cohesive neuroendocrine carcinoma is presented in *linitis plastica* form, this leads to a poor prognosis, such that most patients die within 10 months of the surgery.[18] The case reported in the present paper, which was of this subtype, had an unusual outcome, probably due to nonoccurrence of lymph node involvement or distant metastasis, despite the locally aggressive pattern observed. In classical cases of newly developed adenocarcinoma of the gastric stump, the overall survival rate is very similar to what is observed in cases of primary gastric cancer. Conversely, for patients whose prior resection was due to malignant disease, the prognosis is even more somber.[1,19]

The specific carcinogenetic pathways that lead to mixed exocrine-neuroendocrine lesions are largely unknown.[14-16] Whether these can be correlated with the classical mechanisms described for gastric stump cancer development remains to be better understood. The case reported here was a rare malignant neoplasm that developed with a somewhat unusual presentation. Because of the scarcity of data on these specific issues, further study is needed in order to determine issues regarding pathophysiology, treatment options and prognosis, with better accuracy.

CONCLUSION

Gastric MANECs are rare tumors and this study presents the even more unusual occurrence of MANEC in the gastric stump following Billroth II gastrectomy. Because of the scarcity of such cases, further research is needed in order to determine novel diagnostic and therapeutic approaches.

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Detection of human papillomavirus in dental biofilm and the uterine cervix of a pregnant adolescent

Detecção do papilomavírus humano em biofilme dental e no colo uterino de uma adolescente grávida

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KEY WORDS:
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PALAVRAS-CHAVE
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Placa dentária.
Gengivite.
Periodontite.
Gravidez.

ABSTRACT

CONTEXT: Adolescence and pregnancy are considered to be risk factors for human papillomavirus (HPV) infection. The relationship between this infection in the uterine cervix and oral HPV infection is controversial.

CASE REPORT: This report describes a case of a pregnant 16-year-old adolescent who presented HPV infection in the uterine cervix and the mouth. Smears were collected from the cervix and the tongue/palate. Dental biofilm samples were also collected. The microarray technique was used to detect HPV. The HPV 56 subtype was observed in the cervical smear and HPV 6 in dental biofilm.

CONCLUSION: In this pregnant adolescent, HPV infection was present in both the cervix and the mouth, but the HPV subtypes infecting these two areas were different.

RESUMO

CONTEXTO: A adolescência e a gestação são consideradas fatores de risco para a infecção pelo papilomavírus humano (HPV). A relação entre essa infecção no colo do útero e na boca num mesmo paciente é controversa.

RELATO DE CASO: Descrever o caso de uma adolescente grávida de 16 anos que apresentou a infecção pelo HPV no colo do útero e na boca. Esfregaços foram realizados no colo do útero e em língua/palato. Amostras de biofilme dental também foram coletadas. Para detectar o HPV, foi utilizada a técnica do microarranjo. O HPV 56 foi o subtipo encontrado no esfregaço cervical e o tipo HPV 6 no biofilme dental.

CONCLUSÕES: Observamos, nessa adolescente grávida, a presença do HPV na boca e no colo do útero, mas os subtipos virais que infectavam essas duas regiões eram distintos.

INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted disease (STD). The reported risk factors for HPV infection are multiple partners, oral contraceptive and an early start to sexual activity.[1] The hormonal alterations that occur during pregnancy and puberty may predispose towards immunosuppression and result in persistence of HPV infection and progression of lesions.[2,3]

In order to promote the health of both mother and child, pregnant women need to adhere to primary healthcare measures. Cervical screening and health education strategies are powerful tools for gaining knowledge about HPV. The treatment for the induced lesions ranges from home-based therapy to surgical therapy. The present case report describes a 16-year-old patient who was diagnosed with cervical and oral HPV infection.

CASE REPORT

A 16-year-old pregnant adolescent attended a routine prenatal consultation at the Maternity School of the Federal University of Rio de Janeiro (Universidade Federal do Rio de Janeiro, UFRJ). According to her medical records, she had a history of syphilis and bacterial vaginosis that had been adequately treated at the same health clinic. In the clinical examination performed during the first trimester of pregnancy, she presented cervical lesions diagnosed as HPV-induced lesions in the cytopathological evaluation. The patient received guidance regarding her HPV infection and for periodic monitoring of the cervical lesions. Moreover, aspects of STD prevention, including oral sex, and family planning issues were addressed.

At the time of the clinical appointment, she was 31 weeks pregnant with her first child. She had been using an oral contraceptive method, which failed due to incorrect use, and resulted in an unwanted pregnancy. When interviewed, she reported that her active sex life started when she was 13 years old and that she had had 10 sexual partners since her first sexual intercourse, but that at that moment, she had only one sexual partner. During the interview, she also reported having vaginal intercourse and oral sex at weekly frequency. The last vaginal and oral intercourse had been on the previous day and four days earlier, respectively. She stated that she had never used alcohol, marijuana or cocaine.

In the genital examination, white stained areas were identified in the uterine cervix, after applying acetic acid. Local smears for cytopathological analysis were collected from these areas. The slides were sent to the laboratory at the same clinic. An oral examination was performed, including a complete periodontal examination. The patient did not present any oral lesions and her teeth were healthy. The gingival bleeding index, dental plaque index and the mean probing depth of the gingival sulcus were recorded. The patient presented bleeding in 9% of the gingival sites and dental biofilm in 65% of the tooth sites. The mean probing depth was 2.24 mm, with no attachment loss.

The slides sent to the laboratory were processed using the Papanicolaou (Pap) test. The cytological data were evaluated by means of the Bethesda criteria and the cells were found to present koilocytosis, nuclear enlargement, nuclear hyperchromasia, irregular nuclear outlines and perinuclear halos (**Figure 1**).

Swab samples for HPV identification were collected from the cervix and the mouth (dorsum of the tongue and the area of the soft and hard palate). Samples of dental biofilm were also collected using a sterile periodontal curette, from the teeth with deeper sulci. The samples collected were subjected to DNA purification (QIAamp DNA Mini Kit, Qiagen) and the microarray reaction for DNA HPV genotyping (Papillocheck, Greiner-Bio-One).

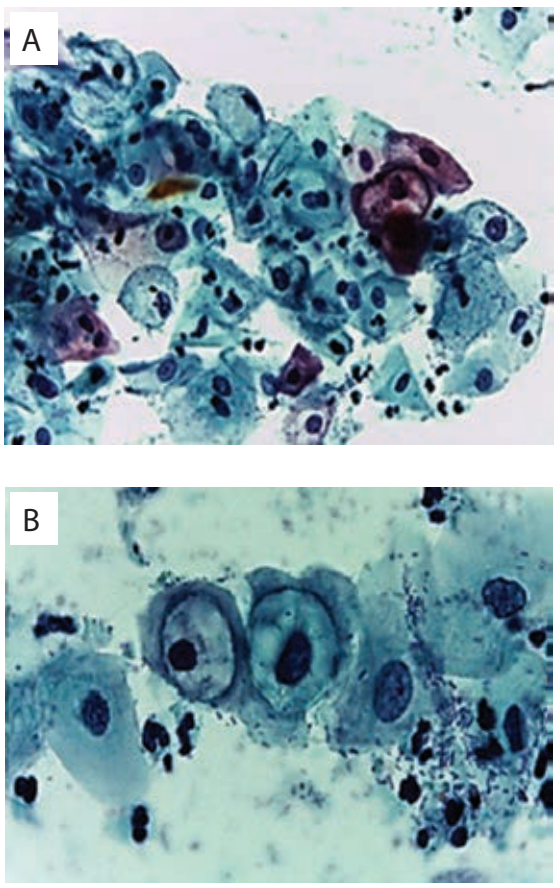

Figure 1. Micrograph showing a low-grade squamous intraepithelial lesion (LSIL, CIN1): (A) cells exhibiting vacuoles, atypical mitosis and different sizes of nucleus, with Pap staining, 400 X; (B) koilocytosis halo image, with Pap staining, 1,000 X.

The cervical smear showed the presence of DNA from HPV56, which is a high-risk subtype. No HPV DNA was detected in the tongue/palate smear. DNA from HPV 6 was detected in one of the four samples of dental biofilm. HPV was present in the periodontal sulcus of the lower left canine. The depth of the gingival sulcus at this site was 4 mm, and it did not present bleeding on probing.

Preventive measures were reaffirmed and a clinical monitoring approach was implemented in relation to the cervix HPV-induced lesions, which consisted of cervical screening every 12 months. The lesions presented a self-healing course within the first year of observation.

DISCUSSION

The presence of HPV-infected lesions is sometimes only shown through screening techniques.[4,5] In this case report, a patient presented asymptomatic cervical lesions that were suggestive of HPV infection, which were identified through white staining after acetic acid application, and were diagnosed by means of cytopathological examination as low-grade intraepithelial lesions. Identification of high-risk HPV56 in the cervical lesions showed the importance of using molecular techniques for identifying the subtype of the virus.

The HPV56 viral subtype detected in this pregnant adolescent is among the high-risk oncogenic subtypes that might be found in adolescents.[6] It is also frequently found in populations of adult women in countries such as Kuwait, Germany, Philippines, United States and Brazil.[7]

The protocol for monitoring low-grade squamous intraepithelial lesions in adolescents (≤ 20 years) consists of performing cytological tests every 12 months, for a period of two years.[6] These lesions do not require treatment, because of their transient and self-healing course.[6] Thus, the clinical monitoring approach was used for the patient in this case report. In fact, the lesions in this patient self-healed during the first year of the follow up.

Presence of HPV DNA has been observed under some pathological conditions that affect the mouth. This virus has been identified in abscesses of endodontic origin; in gingivitis and periodontitis; and in malignant tumors, such as oral squamous cell carcinoma.[8] HPV may play a role in facilitating periodontal disease.[9] Periodontitis is an inflammatory disease induced by specific infectious bacteria, which causes destruction of the supporting dental tissues with consequent tooth loss. The clinical characteristics of periodontitis include tissue inflammation, which results in loss of clinical attachment and alveolar bone and development of periodontal sulci. Chronic periodontitis is the most common type of periodontal disease, and it is more prevalent in adults; however, it may affect individuals at any age.

Some human viruses have been implicated in facilitating establishment of periodontal pathogenic bacteria in the gingival sulcus. HPV may infect deeper layers and reach the basal cell layer without necessarily causing any type of lesion, because the junctional epithelium connects the gingival sulcus with the connective tissue through a gap in the epithelial barrier.[10] Therefore, gingival tissues could act as a reservoir for the virus and release pro-inflammatory cytokines, thereby causing instability of the cell defense mechanisms and contributing towards development of periodontitis.

Even though the patient reported a recent history of oral sex, she did not present HPV in the cells collected from the mouth smears. The oral site from which HPV DNA was observed in this pregnant adolescent was in dental biofilm from a periodontal sulcus of an anterior tooth that did not present any clinical signs of inflammation or deep sulci. Detection of HPV at this site may suggest that the anterior sites of the mouth were exposed to HPV during oral intercourse. Other authors did not believe that periodontal tissues were able to act as a reservoir for HPV, because they were unable to observe the virus in any sample of gingivitis, periodontitis or healthy gingival tissue in their study.[9]

Little is known about the prevalence of this infection in the mouth. The practice of oral sex is currently suggested to be a risk factor for HPV infection in the mouth.[1,11] Other forms of HPV transmission have been described, such as kissing, contact through hands due to sexual practices like masturbation, maternal-fetal transmission and, rarely, by means of self-inoculation and fomites.[5]

Some studies have attempted to find evidence of an association and/or relationship between HPV infection in the mouth and genitalia of pregnant women.[4,12] The studies that have reported HPV infection in the mouth and genitalia in pregnant women are listed in **Table 1**. These studies observed presence of HPV at both of these anatomical sites. The mouth is a region of many anatomical peculiarities that comprises both hard and soft tissues. The latter has both keratinized and non-keratinized components. These features may prevent the HPV infection in the mouth. However, they found no evidence of any association between subtypes.[4,12]

CONCLUSIONS

In this pregnant adolescent, there were different subtypes of HPV infection affecting the uterine cervix and the mouth. Further clinical studies with data on individual characteristics and behavior are needed, in order to determine the real risk factors for HPV infection in the mouth.

Table 1. Database search results for the relationship between HPV infections in the mouth and genitalia among pregnant women. Search performed on April 8, 2014

Database	Search strategy (descriptors)	Papers found	Papers used
Medline (PubMed)	(Pregnancy) AND (Oral Cavity) AND (Genital) AND (HPV)	13	2
	(Pregnancy) AND (Oral Cavity) AND (Genital) AND (HPV) AND (Adolescence)	4	0
Lilacs (Bireme)	(Pregnancy) AND (Oral Cavity) AND (Genital) AND (HPV)	0	-
	((Pregnancy) OR (Gravidez)) AND (Oral Cavity) AND (Genital) AND ((Papillomavírus Humano 6) OR (Papillomavírus Humano 11) OR (Papillomavírus Humano 16) OR (Papillomavírus Humano 18) OR (Papillomavírus Humano 31)) AND ((Adolescence) OR (Adolescente))	0	-
Scopus (Elsevier)	(Pregnancy) AND (Oral Cavity) AND (Genital) AND (HPV)	7	1*
	(Pregnancy) AND (Oral Cavity) AND (Genital) AND (HPV) AND (Adolescence)	0	-

*One of two studies also found in PubMed database.

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Preventing occupational stress in healthcare workers

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Jani H. Ruotsalainen, Jos H. Verbeek, Albert Mariné, Consol Serra

The independent commentary was written by João Silvestre Silva-Junior

ABSTRACT

BACKGROUND: Healthcare workers can suffer from occupational stress which may lead to serious mental and physical health problems.

OBJECTIVES: To evaluate the effectiveness of work and person-directed interventions in preventing stress at work in healthcare workers.

METHODS:

Search methods: We searched the Cochrane Depression Anxiety and Neurosis Group trials Specialised Register, MEDLINE, PsychInfo and Cochrane Occupational Health Field database.

Selection criteria: Randomised controlled clinical trials (RCT) of interventions aimed at preventing psychological stress in healthcare workers. For work-directed interventions interrupted time series and prospective cohort were also eligible.

Data collection and analysis: Two authors independently extracted data and assessed trial quality. Meta-analysis and qualitative synthesis were performed where appropriate.

MAIN RESULTS: We identified 14 RCTs, three cluster-randomised trials and two crossover trials, including a total of 1,564 participants in intervention groups and 1,248 controls. Two trials were of high quality. Interventions were grouped into 1) person-directed: cognitive-behavioural, relaxation, music-making, therapeutic massage and multicomponent; and 2) work-directed: attitude change and communication, support from colleagues and participatory problem solving and decision-making, and changes in work organisation. There is limited evidence that person-directed interventions can reduce stress (standardised mean difference or SMD -0.85; 95% CI -1.21, -0.49); burnout: Emotional Exhaustion (weighted mean difference or WMD -5.82; 95% CI -11.02, -0.63) and lack of Personal Accomplishment (WMD -3.61; 95% CI -4.65, -2.58); and anxiety: state anxiety (WMD -9.42; 95% CI -16.92, -1.93) and trait anxiety (WMD -6.91; 95% CI -12.80, -1.01). One trial showed that stress remained low a month after intervention (WMD -6.10; 95% CI -8.44, -3.76). Another trial showed a reduction in Emotional Exhaustion (Mean Difference or MD -2.69; 95% CI -4.20, -1.17) and in lack of Personal Accomplishment (MD -2.41; 95% CI -3.83, -0.99) maintained up to two years when the intervention was boosted with refresher sessions. Two studies showed a reduction that was maintained up to a month in state anxiety (WMD -8.31; 95% CI -11.49, -5.13) and trait anxiety (WMD -4.09; 95% CI -7.60, -0.58). There is limited evidence that work-directed interventions can reduce stress symptoms (Mean Difference or MD -0.34; 95% CI -0.62, -0.06); Depersonalization (MD -1.14; 95% CI -2.18, -0.10), and general symptoms (MD -2.90; 95% CI -5.16, -0.64). One study showed that the difference in stress symptom level was nonsignificant at six months (MD -0.19; 95% CI -0.49, 0.11).

AUTHORS' CONCLUSIONS: Limited evidence is available for the effectiveness of interventions to reduce stress levels in healthcare workers. Larger and better quality trials are needed.

The full text of this review is available free of charge from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002892.pub5/epdf

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COMMENTS

Occupational stress has been shown to be an important social determinant of health through its negative impact among healthcare workers.[1] Adverse conditions within the context and content of work are risk factors for problems such as decreased work ability,[2] which may affect the quality and safety of healthcare services. Because of the socioeconomic impact of occupational stress,[3] studies on interventions for minimizing its effects are necessary.

The Cochrane Occupational Safety and Health Review Group indicates in this review that the results relating to reduction of the effects of occupational stress through interventions at the individual level (such as cognitive-behavioral therapy or mental and physical relaxation) or at the organizational level (such as changes to work schedules) have been of limited extent. The authors indicate that further studies with greater representation of workers and validated methodologies are required, in order to advance the proposition of effective actions on this issue.

Despite the results from this review, it is recommended that professionals responsible for promotion of overall health and prevention of disease among workers should undertake assessment and mitigation of this occupational hazard within the healthcare sector. After all, these missions are basic assumptions within Occupational Medicine and Occupational Health.

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Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers

This is the abstract of a Cochrane Review published in the Cochrane Database of Systematic Reviews (CDSR) 2013, issue 6, art. nº CD007760. DOI: 10.1002/14651858.CD007760.pub2. For full text and details about the authors, see reference 1.

Barbara Gomes, Natalia Calanzani, Vito Curiale, Paul McCrone P, Irene J. Higginson, Maja de Brito

The independent commentary was written by Mauricio de Miranda Ventura

ABSTRACT

BACKGROUND: Extensive evidence shows that well over 50% of people prefer to be cared for and to die at home provided circumstances allow choice. Despite best efforts and policies, one-third or less of all deaths take place at home in many countries of the world.

OBJECTIVES: 1. to quantify the effect of home palliative care services for adult patients with advanced illness and their family caregivers on patients' odds of dying at home; 2. to examine the clinical effectiveness of home palliative care services on other outcomes for patients and their caregivers such as symptom control, quality of life, caregiver distress and satisfaction with care; 3. to compare the resource use and costs associated with these services; 4. to critically appraise and summarize the current evidence on cost-effectiveness.

METHODS:

Search methods: We searched 12 electronic databases up to November 2012. We checked the reference lists of all included studies, 49 relevant systematic reviews, four key textbooks and recent conference abstracts. We contacted 17 experts and researchers for unpublished data.

Selection criteria: We included randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs) and interrupted time series (ITSs) evaluating the impact of home palliative care services on outcomes for adults with advanced illness or their family caregivers, or both.

Data collection and analysis: One review author assessed the identified titles and abstracts. Two independent reviewers performed assessment of all potentially relevant studies, data extraction and assessment of methodological quality. We carried out meta-analysis where appropriate and calculated numbers needed to treat to benefit (NNTBs) for the primary outcome (death at home).

MAIN RESULTS: We identified 23 studies (16 RCTs, 6 of high quality), including 37,561 participants and 4042 family caregivers, largely with advanced cancer but also congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), HIV/AIDS and multiple sclerosis (MS), among other conditions. Meta-analysis showed increased odds of dying at home (odds ratio (OR) 2.21, 95% CI 1.31 to 3.71; Z = 2.98, P value = 0.003; Chi2 = 20.57, degrees of freedom (df) = 6, P value = 0.002; I2 = 71%; NNTB 5, 95% CI 3 to 14 (seven trials with 1222 participants, three of high quality)). In addition, narrative synthesis showed evidence of small but statistically significant beneficial effects of home palliative care services compared to usual care on reducing symptom burden for patients (three trials, two of high quality, and one CBA with 2107 participants) and of no effect on caregiver grief (three RCTs, two of high quality, and one CBA with 2113 caregivers). Evidence on cost-effectiveness (six studies) is inconclusive.

AUTHORS' CONCLUSIONS: The results provide clear and reliable evidence that home palliative care increases the chance of dying at home and reduces symptom burden in particular for patients with cancer, without impacting on caregiver grief. This justifies providing home palliative care for patients who wish to die at home. More work is needed to study cost-effectiveness especially for people with non-malignant conditions, assessing place of death and appropriate outcomes that are sensitive to change and valid in these populations, and to compare different models of home palliative care, in powered studies.

The full text of this review is available free of charge from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007760.pub2/abstract

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1. Gomes B, Calanzani N, Curiale V, et al. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev. 2013;(6):CD007760.

COMMENTS

The relevance of this study stems from the fact that aging of populations gives rise to living with irreversible, progressive and life-threatening diseases. Therefore, the main question is what such patients' wishes are: how do they want to be cared for at the end of their lives? This question relates to guidelines for anticipating wishes, as regulated by the Brazilian Federal Medical Council in its ordinance 1995/2012.[1] To assist in responding to such needs and provide supporting guidance, healthcare teams require studies of this nature, in order to guide the choice of where care can be provided, so as to enable comfort and a dignified death for individuals with advanced disease, and ensure that this provision always depends on their needs. It is well-known that hospital environments may be impersonal, cold and grim, with risks that are inherent to them, such as infections and even implementation of unnecessary procedures.

The four objectives listed by the authors seem to me to be fundamental. In short, the issue is whether a home-based palliative care service is able to provide symptom control, avoid unpleasant procedures and reduce caregiver stress, with a cost/benefit advantage.

It seems clear that it can. A well-structured home-based palliative care service increases the chance that patients will suffer fewer unpleasant symptoms before death. It is disappointing that no decrease in caregiver stress or favorable cost/benefit relationship was shown. However, it should be noted that the diseases evaluated in the study were primarily cancer and, to a lesser extent, heart failure and chronic obstructive pulmonary disease. Degenerative diseases of the central nervous system such as Alzheimer's disease, Parkinson's disease and stroke sequelae, which are responsible for the death of a significant portion of this population, were not present in this study. In my opinion, this may have led to significant bias, given that the particular characteristics inherent to these clinical conditions might imply results differing from those obtained.

In conclusion, given the possibility that well-structured home-based palliative care services can be established, it seems feasible to offer this possibility to patients with advanced disease, if they desire this.

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Indexing and scope

The São Paulo Medical Journal/Evidence for Health Care was founded in 1932. Its articles are indexed in Medline, Lilacs, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Published bimonthly by the Associação Paulista de Medicina, the journal accepts articles in the fields of clinical health science (internal medicine, gynecology and obstetrics, mental health, surgery, pediatrics and public health). Articles will be accepted in the form of original articles (clinical trials, cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies and systematic reviews with or without meta-analysis), narrative reviews of the literature, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

The Journal's policy and procedures

After receipt of the article by the Scientific Publications Sector, the authors will be provided with a protocol number. This number serves to maintain good understanding between the authors and the Scientific Publications Sector. Following this, the article will be read by the Editor, who will verify whether it is consonant with the journal's policy and interests, i.e. whether the research or review is within the fields of health or public health.

Next, the Scientific Publications Sector will verify whether the text complies with the journal's Instructions for Authors. If the text is incomplete or if it is not organized as required, the authors will be asked to resubmit their text after resolving such problems. When its format is acceptable, the Scientific Publications Sector will submit the manuscript to closed peer review, in which the reviewers will not sign their verdict and will not know the names of the authors. Each paper will be reviewed by at least three reviewers: one expert in the field, one associate editor (who will evaluate the article from the reader's perspective) and one *ad hoc* editorial advisor (who will assess methodological aspects of the study).

The authors will then receive the reviewers' evaluation and will be asked to resolve all the problems that have been pointed out. Once the Scientific Publications Sector receives the manuscript again, the text will be sent to the scientific editor and the proofreader, who will point out problems with sentence construction, spelling, grammar, bibliographical references and other matters. The authors should then provide all further information and corrections requested and should mark in the text all the points at which modifications have been made, using different colors or electronic text marking systems, so that these modifications are easy to see.

When the text is considered acceptable for publication, and only then, it will enter the queue for publication and the author will receive a letter of acceptance of the article. The Scientific Publications Sector will provide a proof, including any tables and figures, for the authors to approve. No article is published without this last procedure.

Instructions for authors

General guidelines: for all types of articles

Texts must be submitted exclusively through the Internet, using the 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 must be submitted in English. Nonetheless, it must also include a summary and five key words both in Portuguese and in English. The key words must be selected from the DeCS and MeSH lists only, as explained in detail below (no other key words will be accepted).

Papers submitted must be original and therefore all the authors need to declare that the text has not been and will not be submitted for publication in any other journal. Papers involving human beings (individually or collectively, directly or indirectly, totally or partially, including the management of information and materials) must be accompanied by a copy of the authorization from the Research Ethics Committee of the institution in which the experiment was performed.

All articles submitted must comply with the editorial standards established in the Vancouver Convention (Uniform Requirements for Manuscripts Submitted to Biomedical Journals)[1] and the specific quality guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE)[5,6] and accuracy studies on diagnostic tests (STARD).[7,8]

The style known as the "Vancouver Style" is to be used not only for the format of the references, but also for the whole text. The Editors recommend that authors should familiarize themselves with this style by accessing http://www.icmje.org.

Abbreviations must not be used, even those in common use. Drugs or medications must be referred to using their generic names, avoiding unnecessary mention of commercial or brand names, and should be followed by the dosage and posology. 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.

Grants, bursaries and any other financial support for studies must be mentioned separately after the references, in a section named "Acknowledgements", along with any other acknowledgements to individuals or professionals who have helped in producing the study but whose contribution does not constitute authorship (we recommend that the item "Authorship" at http://www.icmje.org should be read to obtain clarifications regarding the criteria for authorship).

For any type of study, all statements in the text that are not results from the study presented for publication in the São Paulo Medical Journal/Evidence for Health Care, but are data from other studies already published elsewhere must be accompanied by citations of the pertinent literature. Thus, statements about the incidence or prevalence of diseases, costs, frequency of use of certain therapies

and epidemiological data in general should be followed by the references for the surveys that generated this information, even if the data come from government institutions or databases, given that these are data from other studies.

Format

First page (cover page)

The first page must contain:

1) the type of paper (original article, review or updating article, short communication or letter to the editor);
2) the title of the paper in English and Portuguese, which must be short but informative;
3) the full name of each author (the editorial policy of the São Paulo Medical Journal is that abbreviations for authors' names must not be used; thus, names should either be sent complete or with middle names omitted, for example: an author whose full name is John Richard Smith can be presented as John Smith or John Richard Smith, but not as John R. Smith; likewise, use Christopher Smith and not Chris Smith, or William Smith and not Bill Smith, and so on)), his/her academic titles (abbreviated in English), in the order obtained (for example: MD for medical doctor, MSc for holders of a master's title, PhD for holders of a doctorate or BSc for bachelor of science, such as in biology), and the positions currently held (for example, Doctoral Student, Attending Physician, Adjunct Professor, Associate Professor, Head of Department, etc.), in the department and institution where he/she works, and the city and country;
4) the place where the work was developed;
5) the complete address (name of street or avenue, building number, city) of the corresponding author, telephone and e-mail that can be published together with the article.
6) the date and place of the event at which the paper was presented, if applicable, such as congresses or dissertation or thesis presentations;
7) sources of support in the forms of finance for the project, study bursaries or funding for purchasing equipment or drugs. The protocol number for the funding must be presented;
8) description of any conflicts of interest held by the authors. We recommend 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.

Second page: abstract (English and Portuguese) and key words

The second page must include the title and an abstract (English and Portuguese, maximum of 250 words each),[9] structured in five items:

1) context and objective;
2) design (type of study) and setting (place where the study was developed);
3) methods (described in detail);
4) results; and
5) conclusions.

The abstract (both in English and in Portuguese) should contain five key words. The English terms must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which are available on the internet (http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh).[10] The Portuguese terms must be chosen from the *Descritores em Ciências da Saúde* (DeCS), developed by Bireme, which are available on the internet (http://decs.bvs.br/).[11]

References

The list of references (in the "Vancouver style", as indicated by the International Committee of Medical Journal Editors, ICMJE) should be laid out in the final part of the article, after the conclusions and before the tables and figures. In the text, the references must be numbered according to the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences (see examples in the preceding section), and must be in superscript form (without using parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references cited 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 their computer internet browsers, the journal's readers will be taken to the exact document cited, and not to a general website. The following are some examples of the most common types of references:

Article in journal

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

Chapter of book

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

Text on the internet

- Centers for Disease Control and Prevention. Children's food environment State Indicator Report, 2011. Available from: http://www.cdc.gov/obesity/downloads/ChildrensFoodEnvironment.pdf. Accessed in 2012 (Mar 7).

Figures and tables

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

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

All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The legend or title sentence should be short but comprehensible without depending on reading the article.

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

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

Original articles

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Short communications, case reports or case series

Short communications and case reports must be limited to 3,000 words (from the introduction to the end of the conclusion). Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured thus: Introduction, Objective, Methods, Results, Discussion and Conclusion, like in original articles.

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

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

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

Narrative reviews

Narrative reviews may be accepted by the São Paulo Medical Journal/Evidence for Health Care and should be structured with: Introduction, Objectives, Methods, Results, Discussion and Conclusions. The abstract must be structured with: Context and objective, Design and setting, Methods, Results and Conclusions, like in original articles. The manuscript must comply with the norms of the Vancouver style[1] and must include a systematic search in the main databases: Medline, Embase, Lilacs and Cochrane Library. The search strategy for each database and the number of articles obtained from each database should be presented in a table. The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be use for Medline, LILACS and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, search strategy must be performed, at the same time, with English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, AND NOT).

Letters to the editor

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

Documents cited

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XIV Congresso Paulista de Medicina do Sono

13 e 14 de maio de 2016

TEMAS PRINCIPAIS

- Métodos diagnósticos em sono
- Distúrbios respiratórios do sono
- Insônia
- Sono e psiquiatria
- Tratamento da SAOS
- Distúrbios do movimento
- Ciclo de conferências
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WEBTRANSMISSÃO

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- Fundamentos de genética;
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- Adrenoleucodistrofia;
- Doenças neurogenéticas tratáveis;
- Genética e Epilepsias;
- Atualização no tratamento da distrofia muscular de Duchene;
- Genética e Distúrbios do Movimento;
- Ataxias recessivas;
- ELA de causa genética;
- Neuro-oftalmologia e genética;
- Abordagem prática para o neurologista clínico;
- Paraparesias espásticas hereditárias;
- Expandindo o diagnóstico genético das neuropatias hereditárias;
- Atualização no tratamento das ataxias hereditárias;
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