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SUMMARY

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SECTIONS

ORIGINAL ARTICLES

REVIEW ARTICLES

Special Dossier: "Scientific Evidence for Homeopathy"

Dossiê Especial: "Evidências Científicas em Homeopatia"

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In July 2017, to demystify the fallacy – or post-truth – asserting "there are no scientific evidence for homeopathy", the Technical Chamber for Homeopathy, Regional Medical Council of the State of São Paulo (Cremesp, Brazil) published the Dossiê Especial: "Evidências Científicas em Homeopatia",[1] available online and in printed editions of the scientific journal of the São Paulo Homeopathic Medical Association (APH), *Revista de Homeopatia*.[2,3]

After this publication, in view of the request of homeopathic physicians and institutions from other countries, the Technical Chamber for Homeopathy (TC-Homeopathy, Cremesp) produced an English edition of the dossier (Special Dossier: "Scientific Evidence for Homeopathy"), which is also available online at the *Revista de Homeopatia* webpage.[4]

Encompassing nine reviews on several lines of homeopathic research (and two randomized clinical trials developed by members of the TC-Homeopathy), containing hundreds of scientific articles published in various journals, this dossier highlights, to the scientific and medical class, as well as to the general public, the state of the art of homeopathic research.

Content of the Portuguese edition

http://aph.org.br/revista/index.php/aph/issue/view/41/showToc

- "Editorial: Aos que clamam pelas evidências científicas em homeopatia" (http://aph.org.br/revista/index.php/aph/article/view/402).
- "Homeopatia: um breve panorama desta especialidade médica" (http://aph.org.br/revista/index.php/aph/article/view/393).
- "Panorama mundial da educação médica em terapêuticas não convencionais" (http://aph.org.br/revista/index.php/aph/article/view/392).
- "Fundamentação científica do princípio de cura homeopático na farmacologia moderna" (http://aph.org.br/revista/index.php/aph/article/view/391).
- "A solidez da pesquisa básica em homeopatia" (http://aph.org.br/revista/index.php/aph/article/view/394).
- "Efeito de ultradiluições homeopáticas em modelos *in vitro*: revisão da literatura" (http://aph.org.br/revista/index.php/aph/article/view/396).
- "Efeito de ultradiluições homeopáticas em plantas: revisão da literatura" (http://aph.org.br/revista/index.php/aph/article/view/386).
- "Pesquisa clínica em homeopatia: revisões sistemáticas e ensaios clínicos randomizados controlados" (http://aph.org.br/revista/index.php/aph/article/view/397).
- "Estrogênio potencializado no tratamento homeopático da dor pélvica associada à endometriose: Um estudo de 24 semanas, randomizado, duplo-cego e placebo-controlado" (http://aph.org.br/revista/index.php/aph/article/view/390).
- "Estudo clínico, duplo-cego, randomizado, em crianças com amigdalites recorrentes submetidas a tratamento homeopático" (http://aph.org.br/revista/index.php/aph/article/view/398).
- "O medicamento homeopático provoca efeitos adversos ou agravações medicamento-dependentes?" (http://aph.org.br/revista/index.php/aph/article/view/401).
- "O medicamento homeopático provoca sintomas em voluntários aparentemente sadios? A contribuição

brasileira ao debate sobre os ensaios patogenéticos homeopáticos" (http://aph.org.br/revista/index.php/aph/article/view/404).

Content of the English edition

http://aph.org.br/revista/index.php/aph/issue/view/42/showToc

- "Editorial: To those who demand scientific evidence for homeopathy" (https://aph.org.br/revista/index.php/aph/article/view/405).
- "Homeopathy: a brief description of this medical specialty" (http://aph.org.br/revista/index.php/aph/article/view/406).
- "Medical education in non-conventional therapeutics in the world (homeopathy and acupuncture)" (http://aph.org.br/revista/index.php/aph/article/view/407).
- "Scientific basis of the homeopathic healing principle in modern pharmacology" (http://aph.org.br/revista/index.php/aph/article/view/408).
- "The soundness of homeopathic fundamental research" (http://aph.org.br/revista/index.php/aph/article/view/409).
- "Effects of homeopathic high dilutions on *in vitro* models: literature review" (http://aph.org.br/revista/index.php/aph/article/view/410).
- "Effects of homeopathic high dilutions on plants: literature review" (http://aph.org.br/revista/index.php/aph/article/view/411).
- "Clinical research in homeopathy: systematic reviews and randomized clinical trials" (http://aph.org.br/revista/index.php/aph/article/view/412).
- "Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study" (http://aph.org.br/revista/index.php/aph/article/view/414).
- "Randomized, double-blind trial on the efficacy of homeopathic treatment in children with recurrent tonsillitis" (http://aph.org.br/revista/index.php/aph/article/view/413).
- "Do homeopathic medicines cause drug-dependent adverse effects or aggravations?" (http://aph.org.br/revista/index.php/aph/article/view/416).
- "Do homeopathic medicines induce symptoms in apparently healthy volunteers? The Brazilian contribution to the debate on homeopathic pathogenetic trials" (http://aph.org.br/revista/index.php/aph/article/view/417).

Despite the ongoing difficulties and limitations opposing the development of research in homeopathy – partly due to methodological aspects, and partly to lack of institutional and financial support –, the experimental and clinical studies described in this dossier, which ground the homeopathic assumptions and confirm the efficacy and safety of this approach to therapeutics, provide unquestionable proof for the availability of scientific evidence for homeopathy, against the false and prejudiced opinion that is widely divulgated.

With the publishing of the present dossier, prepared with the support of Technical Chamber for Homeopathy, Cremesp, we hope to dispel doubts and sensitize our colleagues as to the validity and relevance of homeopathy as adjuvant treatment complementary to all other medical specialties according to ethical and safe principles. Our overall goals are to broaden the understanding of human disease, increase the therapeutic resources, contribute to the definition and effectiveness of medicine in chronic diseases, minimize the adverse effects of modern drugs and strengthen the patient-doctor relationship, among other aspects. In this way, we will be able to work together, since "The physician's high and only mission is to restore the sick to health, to cure, as it is termed" (Samuel Hahnemann, *Organon of medicine,* § 1).

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Asthma and occupation: Diagnosis using serial peak flow measurements

Asma e trabalho: diagnóstico por medida seriada do *peak flow*

Authorship: Brazilian Association of Occupational Medicine (ANAMT)

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Evidence collection method

This guideline followed the standard of a systematic review with evidence retrieval based on evidence-based medicine (EBM), so that clinical experience is integrated with the ability to critically analyze and apply scientific information rationally, thus improving the quality of medical care.

We used the structured mode of formulating questions synthesized by the acronym PICO, where P stands for patients with occupational asthma, I for indicator i.e. serial peak flow measurement, and O stands for the outcome of diagnosis.

By raising a relevant question related to the proposed topic, we identified, based on the structured question, the keywords that formed the basis of the search for evidence in the databases: Medline-Pubmed, Lilacs, Labordoc and Cochrane Library. The studies had their abstracts reviewed and after applying the eligibility criteria (inclusion and exclusion), 33 articles were selected in order to answer the clinical doubt (Annex I).

Clinical question

Is there repercussion on clinical outcomes when applying serial peak flow measurements to diagnose work-related asthma among workers with respiratory symptoms?

Grades of recommendation and levels of evidence

- **A:** Experimental or observational studies of higher consistency.
- **B:** Experimental or observational studies of lower consistency.
- **C:** Case reports / non-controlled studies.
- **D:** Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Objective

This Guideline aims to present and discuss the best scientific evidence currently available regarding the clinical outcomes of work-related asthma diagnosis using a serial peak-flow measure for workers with respiratory symptoms.

Introduction

Occupational asthma (OA) is a form of work-related asthma (WRA) characterized by reversible airflow obstruction, bronchial hyperreactivity and airway inflammation, and may be mediated by immunological or non-immunological reactions, resulting from conditions attributable to a certain etiological factor in the work environment. According to population-based studies, OA is estimated to account for about 10 to 25 percent of adult asthma.[1-3]

In this context, OA is characterized as asthma beginning after exposure to an etiologic factor in the work environment, but there is also another form of WRA that is characterized by pre-existing asthma aggravated or exacerbated as a result of an agent present in the work environment called work aggravated asthma (WAA).

Part of the problem that involves WRA comes from the analysis of observational studies which, in comparing the incidence of this pneumopathy with the records of notifications in several countries, objectively verified its underdiagnosis.[4-9]

Thus, WRA underdiagnosis generates impacts on workers' health, with impairment of quality of life and work capacity, and on economic indicators such as workplace absenteeism and consumption of health resources.[10,11]

In any case, for an adequate diagnosis of WRA, it is essential that the relation between signs and symptoms in an individual with occupational exposure is well established as early as possible. Diagnostic methods for WRA include serial peak flow measurement that is intended to monitor airflow limitation in the presence (period worked) and absence (non-working time) of possible risk factors in the work environment.

In the technical analysis of a diagnostic test, there are some requirements that need to be met for incorporation into medical practice. They include adequate sensitivity (percentage of positive results in a group presenting the disease) and specificity (percentage of negative results in a healthy group). In addition, the diagnostic test should contribute to adequate treatment in order to promote objective modification in the natural history of the disease.[12]

Therefore, given the magnitude, underdiagnosis and impact of WRA in the clinical practice of the occupational physician, this guideline is intended to present and discuss the best available scientific evidence on the effectiveness of WRA diagnosis using serial peak flow measurement for workers with respiratory symptoms.

Data extraction

Is there repercussion on clinical outcomes when applying serial peak flow measurements to diagnose work-related asthma among workers with respiratory symptoms?

The selected articles were reviewed in order to calculate the sensitivity and specificity for WRA diagnosis. We found a sensitivity of 82% (95CI 76-90%) and a specificity of 88% (95CI 80-95%).[13-40] (**B**)

The gold standard used in the diagnostic test studies was broncoprovocation with specific agents and forced expiratory volume measurement in the first second (FEV1). FEV1 was more sensitive to assess asthma alterations than peak flow; however, respiratory maneuvers for FEV1 were considered less reliable when not personally supervised by a health professional and thus less reproducible in cases of serial measurements at work and outside work. In contrast, serial peak flow measurements were more reliable and more reproducible in the unsupervised diagnostic format.[41] (**A**)

For adequate assessment, in an individual with suspected WRA, serial peak flow measurements should be indicated at the onset of the pulmonary condition and should monitor airflow limitation during the work period compared to periods away from work. A wide variety of specific protocols have been described for satisfactory measurement, including peak flow measurements at least four times a day over two weeks at the workplace, presumably due to respiratory symptoms, and for two weeks in settings away from the work environment.[42] (**A**)

The rate of return of serial peak flow measurements was adequate containing 61% of measures returned for analysis with interpretable and acceptable data for WRA diagnosis.[41] (**A**)

The rate of return of serial measurements can be improved when the employee receives face-to-face instructions rather than only written instructions. In addition, the result can be further optimized when the employee uses a registration card to point out measurement frequencies and periods.[41] (**A**)

Data interpretation can be performed with visual analysis of the information by a trained specialist. However, software-based interpretation improves data analysis.[41] (**A**) One of the softwares available for analysis of serial peak flow measurements is Oasys.

Limitations of the application of serial peak flow measurements include: the need for worker collaboration to obtain satisfactory records, the presence of functional illiteracy rendering it impossible to record the information, and the non-applicability of the method to severe episodes of asthma while in the work environment.[41,43,44] (**A**)

However, when these potential sources of error are understood, serial peak flow measurement is a viable, useful and low-cost method for diagnosing WRA, mainly due to adequate specificity, sensitivity, rate of return of the measurements, possibility to analyze other differential diagnoses and possibility of associating labor activity with the presence of respiratory symptoms.[45] (**A**)

Diagnosis of WRA is largely important for both primary prevention and tertiary prevention in the workplace. Regarding primary prevention, even the diagnostic elucidation of a single case of WRA in a group of workers sharing similar occupational exposures offers the possibility

of reassessing occupational hazards in the workplace, thereby offering individual and/or collective protective measures to prevent the incidence of new cases. As for tertiary prevention, the diagnostic elucidation of WRA in a specific case subsidizes the occupational physician with technical information to guarantee the control of presumed factors in the work environment that might be generating disease, exacerbation or aggravation and, thus, allow decision-making, in the sense of avoiding the presumed exposure with professional rehabilitation or readaptation of specific cases in a different work location.[42] (**A**)

Recommendation

The analysis of the selected articles indicates that there is sufficient scientific evidence to strongly recommend the application of serial peak flow measurements with a moderate impact on the diagnosis of work-related asthma. Serial peak flow measurement should be applied in the presence of suspected work-related asthma, i.e. when there are respiratory symptoms. Thus, our recommendation is to use the method in a diagnostic format, which does not apply to asymptomatic populations in the screening format.

Conflict of interest

No conflict of interest was stated by the participants who developed this guideline.

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Annex I

Structured question

The clinical question was structured based on the PICO components: P (patient), I (intervention), C (comparison), O (outcome).

- **P –** Occupational asthma
- **I** – Serial peak flow measurements
- **C –**
- **O –** Diagnosis

Search strategy

The scientific databases consulted were:

PubMed-Medline

- (Occupational Asthma) AND (Peak Expiratory Flow OR Peak Flow) AND (Diagnosis)

Cochrane

- (Occupational Asthma) AND (Peak Expiratory Flow OR Peak Flow) AND (Diagnosis)

Lilacs

- Asma Ocupacional AND Peak Expiratory Flow AND Diagnosis

Labordoc

- (Occupational Asthma) AND (Peak Expiratory Flow) AND Diagnosis

Articles retrieved

A total of 1,011 articles were retrieved by 3/12/2017 (Table 1); 433 articles were retrieved from Medline; 522 articles were retrieved from Labordoc; 54 articles were retrieved from Cochrane; two articles were retrieved from Lilacs. Seven articles were found in duplicate in the Medline and Labordoc databases.

TABLE 1 Absolute and relative distribution of the search results of references according to database.

Database	Nº of studies retrieved	Nº of studies selected
PubMed/Medline	433	19
Labordoc	522	16
Cochrane	54	0
Lilacs	2	0
Verification of reference lists	---	5
Repeated	---	7
Total	1,011	33

After the evidence retrieval process, the results were independently classified by two researchers who decided whether the title and abstract of the study covered the scope proposed for this guideline. The studies that did not reach agreement of both evaluators were read by a third evaluator in order to define for inclusion or exclusion of the study in the review.

After reading the full articles, the studies were selected according to inclusion and exclusion criteria. To complement the search strategy, we analyzed the reference lists of the selected articles and included five more articles. After completing this stage, 33 articles were selected, of which 28 were diagnostic test articles and other five were articles based on the systematic literature review model.

Inclusion criteria for selected studies

In order to be included in the evidence analysis step, the retrieved studies were required to be in line with the clinical question raised for this study.

Study design

Narrative reviews, case reports and studies presenting preliminary results only were excluded from selection.

Language

We included studies available in Portuguese and/or English.

According to publication

Only full-text studies were considered for critical assessment. There was no time limit for retrieval of articles.

Evidence selected based on critical assessment

The quality of the scientific evidence was analyzed after applying the inclusion and exclusion criteria. The selected articles were defined as systematic reviews of the literature and diagnostic test studies. All evidence selected under the methodological format of a systematic review of the literature were submitted to an appropriate critical evaluation checklist, allowing the classification of the study according to the AGREE II score (Table 2).[46] Diagnostic test studies were critically analyzed for quality of evidence based on QUADAS 2 (Table 3).[47]

Exposure of the results

In order to present the results, we evaluated the selected scientific evidence by specifically considering the nuances of the population, intervention and outcomes, including the presence or absence of benefit and/or harm and the controversies related to the application of that specific intervention.

Exposure of the recommendations

In order to present the recommendations, we adopted the suggested clinical conduct of the authors of the technical guideline, considering the characteristics of the synthesis of the evidence, later submitted to validation by all the authors participating in the Working Group.

The grade of recommendation stems directly from the available strength of included studies, according to the Oxford scale[48] and the GRADE system.[49]

TABLE 2 Articles that were selected under the systematic review format and included critical analysis based on AGREE II.

Author	Year	Type of study	Quality
Jolly et al.[43]	2015	Systematic review	6
Baur et al.[45]	2012	Systematic review	6
Moore et al.[41]	2009	Systematic review	6
Tarlo et al.[42]	2008	Systematic review	6
Nicholson et al.[44]	2005	Systematic review	5

Remark 1: AGREE II is a quality analysis method that classifies studies from 1 to 7 based on 23 items for evaluation.
Remark 2: the five studies analyzed were included in the critical analysis.

TABLE 3 Articles that were selected under the diagnostic test format and included critical analysis based on QUADAS 2.

Author	Year	Type of study	Quality
Moore et al.[13]	2010	Diagnostic test	2+
Burger et al.[14]	2009	Diagnostic test	1+
Moore et al. I[15]	2009	Diagnostic test	2+
Moore et al. II[16]	2009	Diagnostic test	1+
Moore et al. III[17]	2009	Diagnostic test	1-
Park et al.[18]	2009	Diagnostic test	2+
Sauni et al.[19]	2009	Diagnostic test	1+
Hayati et al.[20]	2008	Diagnostic test	1+
Bolen et al.[21]	2007	Diagnostic test	1+
Chiry et al.[22]	2007	Diagnostic test	2+
Hannu et al.[23]	2007	Diagnostic test	1+
Minov et al.[24]	2007	Diagnostic test	1+
Robertson et al.[25]	2007	Diagnostic test	1+
Hayati et al.[26]	2006	Diagnostic test	1+
Medina-Ramón et al.[27]	2006	Diagnostic test	1+
Eifan et al.[28]	2005	Diagnostic test	1+
Huggins et al.[29]	2005	Diagnostic test	1+
Anees et al.[30]	2004	Diagnostic test	2+
Hollander et al.[31]	1998	Diagnostic test	1+
Leroyer et al.[32]	1998	Diagnostic test	2+
Gannon et al.[33]	1996	Diagnostic test	2+
Malo et al.[34]	1995	Diagnostic test	1+
Quirce et al.[35]	1995	Diagnostic test	1+
Cote et al.[36]	1993	Diagnostic test	2+
Malo et al.[37]	1993	Diagnostic test	2+
Liss et al.[38]	1991	Diagnostic test	2+
Cote et al.[39]	1990	Diagnostic test	2+
Revsbech et al.[40]	1989	Diagnostic test	1+

Remark 1: QUADAS 2 is a quality analysis method that classifies diagnostic test studies. The general methodological evaluation of the studies uses the following quality criteria: high (2+) (most of the criteria met), acceptable (1+) (most of the criteria were met), low (1-), and unacceptable (most of the unmet criteria).
Remark 2: the 28 studies analyzed were included in the critical analysis.

The ORBITA trial: A point of view

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Summary

Treatment of stable coronary artery disease (CAD) relies on improved prognosis and relief of symptoms. National and international guidelines on CAD support the indication for revascularization in patients with limiting symptoms and refractory to drug treatment. Previous studies attested the efficacy of angioplasty to improve angina as well as the functional capacity of patients with symptomatic stable CAD. The ORBITA trial, recently published in an international journal, showed no benefit in terms of exercise tolerance compared to a placebo procedure in a population of single-vessel patients undergoing contemporary percutaneous coronary intervention. In this point of view article, the authors discuss the ORBITA trial regarding methodological issues, limitations and clinical applicability.

Keywords: Coronary Artery Disease. Percutaneous Coronary Intervention. Stents. Stable Angina.

Treatment of stable coronary artery disease (CAD) relies on improved prognosis and relief of symptoms. National and international guidelines on CAD support the indication for revascularization in patients with limiting symptoms and refractory to drug treatment.[1-3]

In this scenario, percutaneous coronary intervention (PCI) is often performed, especially in single- or multivessel patients with a disease of lesser angiographic complexity (SYNTAX Score ≤ 22).[2] It is estimated that more than 500,000 angioplasties are performed annually in Europe and the USA, most of which not clearly indicated.[4]

One of the first studies evaluating the role of PCI in symptomatic relief was the Angioplasty Compared to Medicine (ACME) trial in 1992. It showed a lower prevalence of angina and greater tolerance to exercise in patients undergoing angioplasty compared to those who remained under exclusive drug treatment.[5] Similarly, the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial, composed predominantly of oligosymptomatic and multivessel patients, also revealed symptomatic relief in the group undergoing PCI with conventional stenting after 30 days, but this benefit was not sustained after three years of follow-up.[6] Recently, the publication of three-year follow-up data from the FAME 2 study reported less angina in the PCI group compared to the group undergoing drug therapy.[7]

There was no clinical trial assessing the possible "placebo effect" of angioplasty. Based on this, a group of UK researchers designed a specific study to compare PCI versus a "placebo procedure." That is the ORBITA trial, a multicenter, randomized, double-blind clinical trial, including patients 18-85 years of age, single-vessels, with preserved left ventricular systolic function, without unprotected left main lesion and who presented with symptoms (angina according to the Canadian Cardiovascular Society classification I-III, or anginal equivalent).[8] The results were recently published in *The Lancet*.[4]

It is important to emphasize that this is a low-risk single-vessel population, with a small number of diabetics (18%) and without left ventricular dysfunction. Although all patients in the study had symptoms, only a minority (39%) suffered from limiting angina (CCS III). The primary endpoint analyzed was the difference between the increases in exercise time in both groups. Secondary endpoints were change in peak VO2; change in time for ST segment decline of 1 mm; improvement of angina according to the CCS classification; questionnaires of angina and quality of life (Seattle Angina Questionnaire and EQ-5D-5L, respectively); Duke score for exercise testing, and change in echocardiogram with dobutamine stress.

The study consisted of two follow-up phases. First, the patients were followed for six weeks in a period of

clinical optimization, with titration of anti-anginal medications by telephone consultations. After this time interval, 200 patients remained symptomatic and were included for analysis of the results. They all underwent coronary angiograms, with randomization performed during the procedure. A total of 105 subjects were randomized to angioplasty and the remaining 95 were maintained in the placebo group.

Measurements of fractional flow reserve (FFR) and immediate wave-free ratio (IFR) were taken from all patients. All angioplasty procedures were performed using second-generation drug-eluting stents. The median angiographic epicardial stenosis among study participants was 85.7% (77.4-93.0). Median FFR, in turn, was 0.72 (0.57-0.81). Fifty-seven (57) patients (29%) had an FFR value greater than 0.80, and 64 of them (32%) had IFR greater than 0.89. We must keep in mind that FFR > 0.82 or iFR > 0.92 was found in 25% of patients in the PCI group, which indicates lesions with no functional impairment and no formal recommendation for revascularization. After PCI, there was improvement in the median values of FFR and IFR (0.90 and 0.94, respectively). A total of four patients in the placebo group (4.2%) required angioplasty due to complications associated with the coronary angiogram.

Study blinding was very well done, which was a merit of the researchers. The exams (exercise test, echocardiogram and catheterization) were performed by professionals who were not part of the research group. Neither patients nor researchers knew the group to which each individual belonged. During catheterization, patients were sedated and remained with headphones throughout the procedure. This fact ensures that the placebo effect has in fact been eliminated from the analysis of the results.

Patients were followed for six weeks after the procedure (angioplasty or placebo). The exams and questionnaires analyzed in the outcomes were performed before the catheterization procedure and after the follow-up period. There was no statistically significant difference in any of the outcomes analyzed, except for echocardiography with pharmacological stress, favoring angioplasty (p=0.0011).

Although it was a very well-designed study, with enviable methodology and blinding, some criticism should be considered. First, this was a low-risk population (single-vessel disease, without ventricular dysfunction), which prevents the extrapolation of study results to the other spectra of the disease. It is also important to note that patients were poorly symptomatic with CCS I-II angina in most cases, and that approximately one-third of the patients did not even have a functionally significant obstruction based on FFR and IFR measures. In addition, the DEFER (Deferral Versus Performance of PTCA [percutaneous transluminal coronary angioplasty] in Patients Without Documented Ischemia) trial, a prospective and randomized study, clearly demonstrated that the long-term prognosis of patients with FFR > 0.75 and intermediate lesions not treated with angioplasty is excellent (risk of cardiac death or myocardial infarction < 1%).[9] It is noteworthy that the follow-up time in the ORBITA trial was short, and difficulties regarding drug adherence in the long-term could be considered. Once in this trial there was an average of approximately three anti-anginal drugs, a longer follow-up time would be necessary for a better comparison between treatment strategies.

It is a fact that the ORBITA is not the first study to reveal the ineffectiveness of angioplasty in promoting symptomatic improvement or improvement of exercise tolerance in specific subpopulations in the context of stable CAD. A subanalysis of the BARI-2D trial evaluated the health status and symptoms of patients randomized to revascularization or drug treatment.[10] In the study, patients treated with surgical revascularization showed improvement of symptoms, which did not occur among those who underwent angioplasty in a long-term follow-up. Another clinical trial conducted by Hambrecht et al. compared ICP with physical rehabilitation and showed better tolerance to exercise in the group treated with physical rehabilitation alone.[11] Finally, a meta-analysis published in 2013 including a total of 4,064 patients with objective documentation of ischemia failed to demonstrate improved angina among patients undergoing PCI compared with those on drug therapy.[12]

While evaluating the body of available evidence, it must be kept in mind that angina is a symptom with complex and multifactorial pathophysiology, so the reduction of coronary flow caused by stenosis in the epicardial artery is not the only factor involved with the pain (Figure 1). The regulation of this flow also depends on the preservation of endothelial function and microvasculature. Furthermore, nonvascular factors such as myocardial hypertrophy can compromise blood flow to a given territory. Angina is often a difficult symptom to characterize, being greatly influenced by subjective factors. Also, thoracic pain of diverse etiologies may occur concomitantly, reducing the beneficial effect of revascularization.

A possible conclusion is that the ORBITA trial was daring to test the concept of the placebo effect of PCI; however, we must be careful about its results. PCI adequately fulfilled its role of resolving epicardial vessel obstruction, which is clear with improved FFR/IFR values

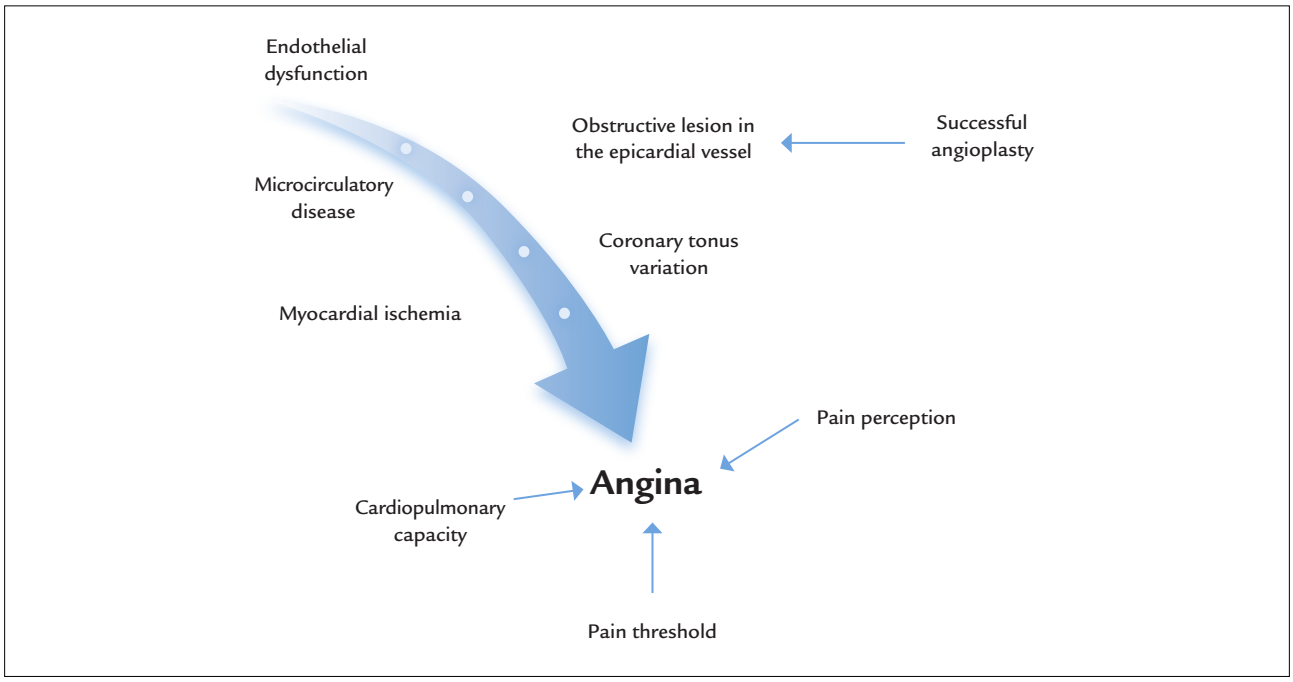

FIGURE 1 Complexity of the processes that culminate in the occurrence of angina accompanied by factors that modulate its intensity. Note that successful angioplasty suppresses only one of the steps in this process.

and stress echocardiography. Nevertheless, revascularization of the epicardial artery did not necessarily translate into an improvement in angina, much less a better tolerance to exercise, which is understandable given the multifactorial nature of these variables.

Much is debated whether the ORBITA trial will impact the guidelines for management of stable CAD. Considering the limitations mentioned, as well as the profile of patients included in the ORBITA, we believe that little will change in clinical practice, since the current guidelines would not even suggest revascularization for many patients included in the study. In any case, the study leads the medical community to reflect on the indication of intervention in the population with chronic CAD, always pondering the real benefits, risks and expectations of both the patient and the physician indicating the procedure. Understanding the pathophysiology of the disease and adequately interpreting the clinical evidence are fundamental steps in this process.

Conflict of interest

The authors declare no conflicts of interest.

Resumo

Estudo ORBITA: um ponto de vista

O tratamento da doença arterial coronariana (DAC) estável se baseia na melhora do prognóstico e alívio de sintomas. Diretrizes nacionais e internacionais sobre a DAC respaldam a indicação de revascularização em pacientes com sintomas limitantes e refratários ao tratamento medicamentoso. Estudos prévios atestavam a eficácia da angioplastia na melhora da angina, bem como na capacidade funcional de pacientes com DAC estável sintomática. O estudo ORBITA, publicado recentemente em revista internacional, mostrou em população de uniarteriais submetidos a angioplastia com *stent* farmacológico ausência de benefício na tolerância ao exercício quando comparado a procedimento placebo. No presente ponto de vista, os autores discutem o trabalho em questão quanto a método, limitações e aplicabilidade clínica.

Palavras-chave: Doença Arterial Coronariana. Angioplastia. Stents. Angina Estável.

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Heat-not-burn and electronic cigarettes: Truths and untruths about harm reduction

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The Editorial by the Brazilian Medical Association (AMB)[1] warning physicians and the society against the use of electronic (EC) and heat-not-burn (HNB) cigarettes is very timely, given the powerful lobby for their approval in Brazil. ECs heat liquids containing nicotine, flavorings and propylene glycol, and/or glycerin into aerosols for inhalation. Since they do not mimic tobacco cigarettes' taste and flavor, they do not satisfy many smokers. Manufacturers' allegations that ECs are "safe" are questionable, and studies on the adversity of EC vapors to respiratory airways yielded conflicting results.

Recently, tobacco companies bet their chips on HNB cigarettes that they claim to be a "new wave of a harm reduction revolution." HNB tobacco is breaking into markets around the world, and a study suggested that consumption of this new type of nicotine delivery product is poised for explosive growth over the coming years.[2] Unlike conventional cigarettes, HNB products heat the tobacco (350°C) instead of burning it at higher temperatures (around 800°C). While HNB devices aerosolize nicotine and deliver it efficiently to the bloodstream and brain, and give users a tobacco-flavored vapor, they do not produce carbon monoxide (CO) or generate carcinogens and pyrolysis-derived compounds that play a major role in the cigarette smoke toxicity.[3] Thus, although it is plausible to think that replacing traditional cigarettes with HNB tobacco products would lower the risks of smoking-related diseases such as chronic obstructive pulmonary disease (COPD), lung cancer and some other conditions, this notion requires confirmation by epidemiological data. HNB tobacco, however, is not harmless. No matter whether nicotine is absorbed from tobacco vapor or from the smoke of cigarettes, it is one of the most addictive drugs. Nicotine addiction is a chronic and relapsing illness characterized by compulsive drug seeking and use despite user awareness about health risks and desire to quit. In other words, nicotine addiction per se is a major health hazard. Moreover, pharmacological and toxicological studies as well as some epidemiological investigations suggested that nicotine, in addition to CO and other smoke chemicals, contributes to cardiovascular events in smokers with underlying cardiovascular disease, and some authors believe that it accelerates formation of atheromatous lesions in arterial walls.[4]

Harm reduction policies and practices aim to minimize the harms associated with psychoactive drug consumption in people who are unable or unwilling to quit. That is, harm reduction focuses on the prevention of harms in people who continue to use drugs. In this line, as far as smoking is concerned, a distinction should be made between harm reduction at the individual patient and collective levels.

As pointed out by the AMB, "... there is no scientific evidence that the use of e-cigarettes is effective in reducing traditional cigarette smoking or in stopping smoking."[1] Actually, a systematic review of randomized controlled trials (RCT) on the use of ECs for smoking cessation found two RCTs indicating that ECs (compared to placebo) aided smokers to quit smoking, and one trial showing no difference between ECs and nicotine patches.[5] The authors, however, rated the confidence on the review conclusions as "low" (GRADE standards), owing to the small number of trials, low event rates and

wide confidence intervals around the mean estimates.[5] In other words, it remains unclear whether ECs are effective and, if so, whether they are more effective (and safe) than nicotine patches as smoking cessation treatments. The use of ECs to reduce harm in smokers at risk of, or with COPD, on the other hand, was unsupported by an observational study.[6] A large prospective cohort study revealed that ECs were associated with worse pulmonary-related health outcomes, but not with cessation of smoking.[6]

Contrasting with ECs, which do not find full acceptance among tobacco smokers, HNB products provide smokers not only quickly absorbable nicotine but also typical tobacco flavor. Obviously, replacing HNB tobacco with traditional cigarettes does not reduce smokers' dependence on nicotine and so it is unlikely that they contribute for achieving abstinence. The use of HNB tobacco reduces exposure to toxic substances contained in tobacco smoke, which is expected to translate into lower risks of tobacco-associated chronic diseases. Epidemiology studies and/or RCTs, however, fail to substantiate the conjecture that long-term use of HNB tobacco is safer than smoking traditional cigarettes. At any rate, for patients addicted to nicotine who failed previous treatments with conventional smoking cessation medications, or are unwilling to quit smoking, HNB cigarettes may become a valid alternative for harm reduction.

A possible health benefit for a particular group of smokers, however, does not justify approval of HNB tobacco products for (unrestricted) sales. The tobacco industry's allegations that approval of HNB products for marketing would improve public health by reducing tobacco-associated deaths and diseases is at best an untested and self-serving hypothesis.

Were HNB products (and ECs) in fact less harmful than conventional cigarettes, they would still have the potential to cause addiction to nicotine (a major health hazard) and other adverse health effects. Moreover, marketed as supposedly healthier alternatives, HNB tobacco products would not only promote smoking appeal and initiation among young people, but also discourage older health-conscious smokers to seek treatment for their addiction to nicotine. Finally, if HNB tobacco products and traditional cigarettes coexist on the market, smokers can switch easily from one product to the other depending on a number of factors. In summary, it is foreseeable that unrestricted access to HNB cigarettes would make the quest for the first tobacco-free generation of Brazilians a distant or even unattainable public health goal. Approval of HNB products for use under medical supervision (prescription only) with advertising restrictions is a regulatory decision that would reconcile the needs of a group of nicotine-dependent patients and the collective goals in public health.

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Yellow fever

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Summary

The yellow fever (YF) virus is a *Flavivirus*, transmitted by *Haemagogus*, *Sabethes* or *Aedes aegypti* mosquitoes. The disease is endemic in forest areas in Africa and Latin America leading to epizootics in monkeys that constitute the reservoir of the disease. There are two forms of YF: sylvatic, transmitted accidentally when approaching the forests, and urban, which can be perpetuated by *Aedes aegypti*. In Brazil, the last case of urban YF occurred in 1942. Since then, there has been an expansion of transmission areas from the North and Midwest regions to the South and Southeast. In 2017, the country faced an important outbreak of the disease mainly in the states of Minas Gerais, Espírito Santo and Rio de Janeiro. In 2018, its reach extended from Minas Gerais toward São Paulo. Yellow fever has an incubation period of 3 to 6 days and sudden onset of symptoms with high fever, myalgia, headache, nausea/vomiting and increased transaminases. The disease ranges from asymptomatic to severe forms. The most serious forms occur in around 15% of those infected, with high lethality rates. These forms lead to renal, hepatic and neurological impairment, and bleeding episodes. Treatment of mild and moderate forms is symptomatic, while severe and malignant forms depend on intensive care. Prevention is achieved by administering the vaccine, which is an effective (immunogenicity at 90-98%) and safe (0.4 severe events per 100,000 doses) measure. In 2018, the first transplants in the world due to YF were performed. There is also an attempt to evaluate the use of active drugs against the virus in order to reduce disease severity.

Keywords: Yellow Fever. Epidemiology, Brazil. Clinical Aspects. Treatment Perspectives. Vaccine.

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Introduction

Yellow fever is a non-contagious infectious disease caused by an arbovirus (arthropod-borne virus) belonging to the *Flaviviridae* family. The disease is endemic only in the tropical forests of the African continent and Latin America, with the possibility of determining urban cycles (Figures 1 and 2). The vectors of the sylvatic form in Brazil are *Haemagogus* or *Sabethes* mosquitoes that live and feed on the treetops. Urban YF is associated with the participation of the vector *Aedes aegypti*, present in several Brazilian cities.[1]

According to the World Health Organization (WHO), the estimated number of severe cases in both continents is 84,000-170,000, with approximately 29,000-60,000 deaths annually.[2]

Yellow fever was an unknown disease until the discovery of the Americas. It probably originated in Africa and was possibly introduced to the American continent by ships carrying slaves and the vector *Aedes aegypti*. The first epidemic was reported in the American continent, where it is possible to characterize with greater certainty the infection by yellow fever, occurred in the Yucatán peninsula in 1648.[3,4]

In the US, an epidemic in Philadelphia in 1793 decimated about 10% of the population.[2] In 1881, Cuban epidemiologist Carlos Finlay associated the transmission of the disease with mosquito bites. In 1900, physician Walter Reed proved this association and carried out effective measures to control the transmission by mosquitoes in the American territory.

In Brazil, the descriptions of epidemics of yellow fever date back to the 17th century; since then, we have found several reports of seasonal activity of the disease in many localities throughout the country. Yellow fever, which was

FIGURE 1 Yellow fever vaccine recommendations in the Americas.[1]

[1]Current as of September 2016. This map, which aligns with recommendations also published by the World Health Organization (WHO), is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever.

[2]Yellow fever (YF) vaccination is generally not recommended in areas where there is low potential for YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler's risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g., age, immune status).

FIGURE 2 Yellow fever vaccine recommendations in Africa.[1]

[1]Current as of September 2016. This map, which aligns with recommendations also published by the World Health Organization (WHO), is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever.

[2]Yellow fever (YF) vaccination is generally not recommended in areas where there is low potential for YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler's risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g., age, immune status).

considered an important public health problem in Rio de Janeiro, was a challenge tackled by Oswaldo Cruz, who in 1903 was the general director of Public Health and adopted measures similar to those of the Cuban model in the fight against *Aedes aegypti*, known at the time as *Stegomia fasciata*. In 1907, after great efforts, the endemic in the city of Rio de Janeiro was considered controlled.[5]

The last cases of urban yellow fever in Brazil occurred in the city of Sena Madureira, state of Acre, in 1942. Since then, all reported cases are due to the accidental infection of humans when entering or approaching forest areas where the virus circulates (wild cycle). In cycles of approximately 5 to 10 years, it is possible to observe the intensification of cases in primates (epizootics) leading to a greater chance of human infection. Over the years, epizootic areas have spread to the mid-south of the country and more recently to the southeast, near densely populated areas, which increases the risk of urban reintroduction of the disease.

Recent epidemics such as those reported in Angola and the Democratic Republic of Congo between 2015 and 2016 remind us of the significant risk of local outbreaks progressing when control measures are not readily taken.

Etiological agent

The yellow fever virus is an RNA virus of the genus *Flavivirus* and family *Flaviviridae*. The virus was isolated in 1927 by Adrian Stokes of a patient from Ghana, known as Asibi. Other viruses from the same family that affect humans include: Dengue, West Nile virus, Rocio and St. Louis encephalitis. There are genotype differences among strains found on the African and South American continent.[4]

Epidemiology

Yellow fever is a disease with compulsory notification, even on simple suspicion of the disease. About 80% of the cases are in males, predominantly in the age group of 15-35 years, which reflects a higher degree of exposure to forests.

The most common period of the disease occurs between the months of December and May, characterized by higher rainfall volume in Brazil. Currently, transmission to humans is linked to the wild cycle, which has monkeys as reservoir and mosquitoes of the genera *Haemagogus* (*Haemagogus janthinomys* and *Haemagogus leucocelaenus*) and *Sabethes* (*Sabethes chloropterus* and *Sabethes albiprivus*) as vectors. The most susceptible animals are howler monkeys, capuchin monkeys and the common marmoset. Transmission to humans is incidental, occuring most of times when people enter a forest area for extraction or recreation activities. Epizootics occur cyclically and periods of epidemiological silence probably coincide with a decrease in the number of susceptible primates.

The urban cycle involves infected humans and the *Aedes aegypti* vector. There have been no urban cases in the Americas since 1954, but it is still very common in African countries. An intermediate cycle was described in areas of transition to forest in Africa (savannah), with participation of monkeys, vector *Aedes* spp and humans.

In Brazil, after the eradication of the *Aedes aegypti* mosquito in 1954, the sylvatic transmission area of the virus predominantly covered the legal Amazon region (Figure 3). Over the years, the transition area has also moved to the Midwest and Southeastern states such as São Paulo, Minas Gerais and Rio de Janeiro, as well as the southern states of Paraná, Santa Catarina and Rio Grande do Sul.

In December 2016, the Brazilian Ministry of Health reported cases of sylvatic yellow fever in the state of Minas Gerais, with rapid expansion in the first six months of the outbreak to the states of Espírito Santo, São Paulo, Bahia and Rio de Janeiro. In the first half of 2017, there were 3,564 suspected cases of sylvatic yellow fever. Of these, 777 (21.8%) were confirmed, 2,270 (63.7%) ruled out, 213 (6.0%) were still being investigated, and 304 (8.5%) were considered inconclusive.

After the Brazilian Ministry of Health declared the end of the transmission of new cases on September 6th, 2017 new autochthonous cases began to be notified as of epidemiological week number 38/2017 in the state of São Paulo (Figures 3, 4 and 5).

According to official CVE-SP (Center for Surveillance and Epidemiology – São Paulo) data, from January 2017 to February 14th, 2018 there have been 183 confirmed autochthonous cases, with 64 deaths, resulting in a mortality rate of 35%. The majority of cases occur in males (83.1%) and the median age is 43 years (2-89 years). Many cases are still being investigated.[6] New cases have also been confirmed in Minas Gerais (77) and Rio de Janeiro (27).

Incubation period

The mean time between being bitten by the infected mosquito and the onset of the first symptoms is 3-6 days[2,7,8] and may reach 10-15 days.[8]

Clinical manifestation

Half of those infected are estimated to be asymptomatic.[8]

Yellow fever is described as a biphasic disease:[7]

- Viremic phase: high fever, with a mean duration of three days,[9] myalgia, headache, lack of appetite and nausea. Mostly, these symptoms subside within 2 to 4 days, characterizing mild and moderate cases, which are estimated to account for 20-30% of infected patients.[8]
- Toxemic phase: takes place in approximately 15% of patients[2,7,10] and begins after a period of clinical improve-

FIGURE 3 Distribution of autochthonous yellow fever cases by municipality (origin of infection). State of São Paulo, 2017-2018.

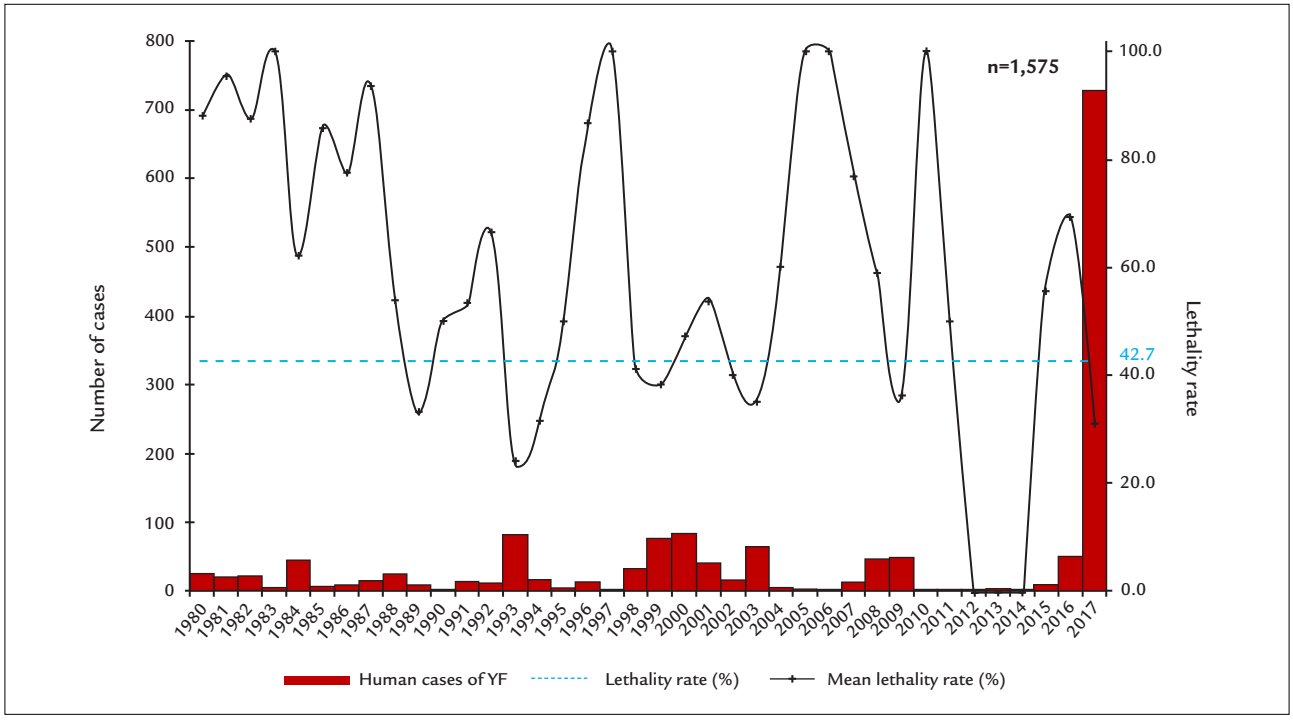

FIGURE 4 Historical series of the number of confirmed human cases of YF and lethality according to the year of onset of symptoms, Brazil, from 1980 to June 2017.

Source: Sinan; GT-Arbo/UVTV/CGDT/DEVIT/SVS/MS

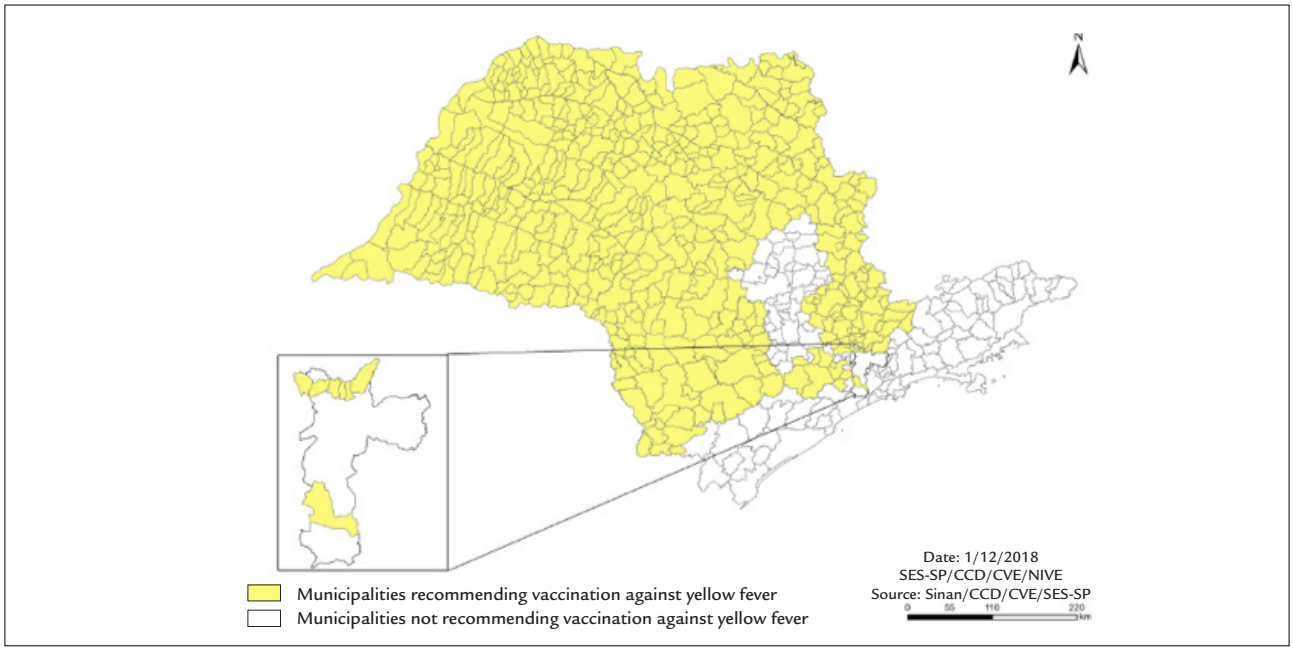

FIGURE 5 Municipalities in the state of São Paulo and Administrative Districts of the capital currently recommending vaccination against yellow fever. State of São Paulo, 2018.

ment that follows the first phase, lasting 24 hours on average.[9] It is characterized by recrudescence of high fever, chills, worsening of headache and myalgia, and involvement of various organs and systems. It is in this second phase that, later on, icteric discoloration of the skin that characterizes the disease develops. There may be bleeding, kidney dysfunction with oliguria,[11] as well as cardiovascular dysfunction and neurological impairment with seizures.[7,8,10] Often, the unusual pairing of fever with bradycardia (Faget sign) is observed.[8-10] Up to half of these patients progress to death in 10 to 14 days, and the rest recover without significant sequelae.[7,8]

During the outbreak in São Paulo, some patients who progressed to severe disease (mainly elderly) did not develop fever at any time (personal observation of the authors).

It should be noted that the notification must be made on suspicion, as it is COMPULSORY and IMMEDIATE, and must be informed by telephone, fax or e-mail to the local responsible agency.[8]

Laboratory changes

The main changes are listed below.

Leukopenia is characteristic (leukocytes between 1,500 and 2,500 cells/mL, plus relative neutropenia[9]) both in the early and late phases; however, leukocytosis is sometimes seen in a later period.[10] C-reactive protein is generally low, even in patients who progress to death. Hyperbilirubinemia usually occurs more intensely at the end of the first week, and appears after an increase in transaminases. The observed levels of AST and ALT in severe cases are often above 5,000 IU/L, sometimes reaching more than 20,000 IU/L, levels rarely seen in other causes of hepatitis. AST values are usually higher than ALT values. Both creatinine and urea levels rise frequently and their worsening correlates with deterioration of the patient's condition.

Classification

The clinical picture can be classified as mild, moderate, severe or malignant.[8] In mild and moderate forms, the symptoms and laboratory changes are less intense, with mild thrombocytopenia and moderate increase in transaminases. In this form, there is usually no increase in bilirubin. Severe disease, on the other hand, leads to intense thrombocytopenia and increased transaminases, in addition to increased creatinine. Malignant yellow fever is that in which disseminated intravascular coagulation is observed with fibrinogen consumption and accumulation of D-dimer, in addition to the previous alterations.[8]

Treatment

To date, there is no specific antiviral against yellow fever.

In mild cases (Table 1), outpatient follow-up with daily visits can be implemented, provided that there is quick access to health services and someone at home who can observe the patient. It is important to alert patients

with suspected yellow fever that there may be a rapid worsening of the condition. In such cases, only symptomatic medications with no potential action on the liver, such as dipyrone (avoiding NSAIDs and paracetamol, due to the risk of hepatotoxicity), and adequate hydration (60 mL/kg/day) are recommended.[8]

Other patients (moderately severe and severe cases) should be hospitalized. For patients hospitalized in infirmary wards, the following is recommended: thorough control of diuresis, with an ideal flow of > 1mL/kg/h, with clinical reassessments at least every 4 hours; and daily laboratory tests or if there is any sign of clinical worsening.[4] In this case, it is important to keep the patient euvolemic. If there is any sign of dehydration, it is recommended to initiate intravenous fluid replacement with 0.9% saline boluses of 10 mL/kg in the first hour, with subsequent reassessment of vital signs and diuresis and, if necessary, maintenance with 30 mL/kg/day or a sufficient volume of fluids to maintain adequate diuresis.[8]

Patients with the malignant form may progress with a need for endotracheal intubation and protective mechanical ventilation due to upper gastrointestinal bleeding, lowered level of consciousness or respiratory failure. Dialysis is often necessary. Use of routine gastric protectors and transfusion of fresh frozen plasma (10 mg/kg) in cases of bleeding or intense coagulopathy is also recommended.[8]

Diagnosis

Clinically, it is difficult to differentiate it from other viral diseases in the initial phase, and yellow fever should be considered in all cases with compatible clinical manifestations, even if mild, and positive epidemiology (having visited a risk area within 15 days prior to the onset of symptoms without being previously vaccinated, or having been vaccinated within less than 30 days[8]).

Yet, in patients who evolve more severely, some clinical and laboratory characteristics lead us to suspect more readily of yellow fever, such as a rapid increase (in a matter of 2-3 days) of the transaminases to very high levels, with a predominance of AST compared to ALT,[8,11] which is the opposite of that seen in classical viral hepatitis, perhaps reflecting skeletal and myocardial muscle cell involvement.[11] As observed in the São Paulo outbreak, laboratory worsening tends to precede clinical worsening.

Confirmation of the diagnosis is made using a method of molecular amplification of the virus in the blood (highly sensitive and specific method, which may even allow to differentiate the sylvatic virus from the vaccine strain[11]), which classically occurs up to the fifth day of the disease.[8] It should be noted, however, that, in some patients, viremia seems to persist longer, sometimes until after the 10th day.

As of day 5, serology (detection of IgM and IgG, specific for yellow fever) is recommended.[8] Serology, how-

TABLE 1 Classification table according to clinical picture, expected laboratory changes and treatment for cases of suspected or confirmed yellow fever.

Classification	Symptoms	Laboratory changes	Treatment
Mild	Fever	Leukopenia	Dipyrone
	Myalgia	AST and ALT < 2x the normal limit	Oral fluid therapy (ORT) 60 mL/kg/day
	Headache	Normal platelets	Daily outpatient visits
	Lack of appetite		
	Bradycardia		
Moderate	The previous ones, plus:	Leukopenia	Admission into infirmary ward
	Abdominal pain	Mild low platelet count	Control of diuresis
	Vomit	AST and ALT < 10x	IV fluids, if necessary
	Mild jaundice	Bilirubin < 5x	Clinical reassessment each 4 h
			Daily laboratory analyses
Severe/malignant	The above, plus:	Leukopenia	ICU admission
	Intense abdominal pain	Severely low platelet count	Hydration and euvolemia
	Frequent vomiting	AST and ALT > 10x	Hemodialysis
	Jaundice	Increased bilirubin	Endotracheal intubation
	Bleeding	Increased PT/aPTT	Transfusion of blood products, if necessary
	Organ and system failure (oliguria, AKF, lowered level of consciousness)	Depressed fibrinogen levels	
		Increased D-dimer	
		Increased urea and creatinine	
		Hypoglycemia	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; aPTT: activated partial thromboplastin time; ICU: intensive care unit; IV: intravenous.

ever, can cross-react with other flaviviruses, such as dengue virus[10,11] or simply indicate a response to recent vaccination for yellow fever. In case of death, the diagnosis can be confirmed in several tissues in up to 24 hours;[8] or by immunohistochemistry.[8,10]

Treatment perspectives

This year at Hospital das Clínicas da FMUSP, the first YF-related liver transplant was performed, followed by four more in patients with malignant yellow fever who progressed to complete liver failure. At this point, the role of liver transplantation in treating severe forms of yellow fever, or the correct timing for this, has not yet been established. Criteria such as hepatic encephalopathy and factor V < 20 or 30% (if the patient is younger or older than 30 years, respectively) for indication of transplantation is currently being discussed.

Clinical and laboratory research is underway for antiviral testing against yellow fever virus, such as sofosbuvir (now used for treatment of hepatitis C).[12]

Differential diagnosis

Leptospirosis (of all, the disease most similar to yellow fever[9]), malaria, dengue, mononucleosis, influenza, viral hepatitis, rickettsiosis, Zika (in mild early phases), chikungunya, sepsis and typhoid fever.[1]

Follow-up

The Brazilian Ministry of Health recommends hospital discharge based on the following criteria: patient afebrile for > 24 hours with at least 10 days of illness or afebrile for > 3 days, regardless of disease duration, in both cases with progressive improvement of transaminases and platelets.[8] Convalescence, with prolonged asthenia, may last up to 8 weeks, with transaminase oscillations (ALT prevailing at this stage) and even transient increases in bilirubin. There is no need for future vaccination, as the patient is considered protected.[8]

Yellow fever vaccine

Prevention is based on the use of attenuated live virus vaccine from strain 17D, developed in 1937 by Max Theiler, a virologist who received the Nobel Prize in Medicine in 1951. The vaccine is considered safe (1,255 severe adverse events for 333 million doses applied[13]) and highly effective (immunogenicity between 90% and 98% after day 10[8]). Since 2013, the WHO has reviewed the need to repeat additional doses every 10 years.[14] Currently, only a single dose is indicated throughout life. In immunocompromised populations such as people living with HIV/AIDS, women vaccinated while pregnant and children under 5 years of age, there may be changes in the recommendations in the near future. However, the main contraindication is related to the use of immunosuppressive drugs at the time of vaccination or weeks before receiving the vaccine (Table 2).

During the 2015 and 2016 epidemic in Angola and the Federative Republic of Congo, the fractional dose of the vaccine was chosen to protect large numbers of people, with a good response to restrain the epidemic.[15]

This strategy was also adopted in 2018 for the vaccination of part of the population in the states of São Paulo, Rio de Janeiro and Bahia. Studies suggest that the use of fractionated doses (1/5 of the usual dose) leads to the production of neutralizing antibodies at levels equivalent to that of the conventional dose.[15] The durability of this pro-

TABLE 2 Vaccine recommendation by the Brazilian Ministry of Health.[8]

Recommended	Contraindicated	With caution***
People residing or traveling to areas with vaccine recommendation*	Cancer patients on chemotherapy or radiotherapy	Those aged > 60 years who have never been vaccinated
	Immunosuppressive or immunomodulating drugs	Pregnant or lactating women with infants < 6 months
	Steroids, depending on dose and length of use**	Breastfeeding women should stop breastfeeding for 10 days after vaccination
AND	Patients who underwent bone marrow or solid organ transplantation < 2 years	HIV+ patients with CD4 > 350 cells/mm^3 (require more attention if CD4 between 200 and 350 cells/mm^3)
Age > 9 months and < 60 years	Previous thymus disease (myasthenia gravis, thymoma)	Autoimmune diseases
	Systemic lupus erythematosus	Hematologic diseases
AND	Rheumatoid arthritis	Patients who underwent bone marrow transplantation > 2 years, stable, with no graft versus host disease (GVHD)
	Primary immunodeficiencies	
No contraindications	Advanced HIV infection (CD4 < 200 cells/mm^3)	
	Infants under 6 months of age	
	Individuals with a history of anaphylactic reaction related to substances present in the vaccine	

*List of Brazilian municipalities with vaccine recommendation: <http://portalarquivos2.saude.gov.br/images/listavacinacaofa.pdf>.
**Equivalent to 20 mg or more of prednisone for > 14 days; or pulse therapy.
***Cases where the administration of the vaccine is conditional on individual medical risk-benefit assessment.

tection is not certain. In a Bio-Manguinhos/Fiocruz study, the fractional dose vaccine continued to provide protection after 8 years. Those vaccinated with the fractionated dose do not receive an international yellow fever vaccination certificate and, therefore, if a certificate is necessary, they must request the standard dose.

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Use of illicit drugs by adolescents and young adults of an urban settlement in Brazil

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Summary

Objective: To estimate the prevalence and factors associated with illicit drug use by adolescents and young adults of a formal urban settlement.
Method: Cross-sectional study including adolescents and young adults 12-24 years of an urban settlement in the Midwest Region of Brazil. Data were collected using a structured questionnaire and analyzed using Stata, version 12.0. We used Poisson regression model to estimate the factors associated with illicit drug use.
Results: Of the total participants (n=105), 27.6% (95CI 20.0-36.9%) had used illicit drugs such as marijuana, cocaine, crack, LSD and inhalants. The consumption of these substances was associated with male gender, use of body piercing and/or tattoos, licit drug use and self-report of signs and/or symptoms of sexually transmitted infections.
Conclusion: High prevalence of illicit drug use was found in the individuals investigated, ratifying the presence of risk factors to the vulnerability of the settlers to use these substances in the urban settlement population.

Keywords: Street Drugs. Adolescent. Young Adult. Urban Area.

Introduction

The consumption of illicit drugs represents an important public health problem worldwide, and especially in developing countries such as Brazil.[1] The use of these substances is associated with multiple consequences, including violence, traffic accidents, impaired psychosocial development, infectious diseases, mental disorder and suicide, particularly in the young population.[2,3] A total of 246 million people aged 15-64 are estimated to have used illicit drugs in 2013 around the world.[1]

The prevalence of illicit drug use among adolescents and young people is high, and these groups are considered to be highly vulnerable to substance abuse.[4] Multiple factors are associated with the use of drugs in these populations, including sociodemographic characteristics, risk behaviors, exposure to situations of violence and use of licit substances, namely alcohol and tobacco.[4-7] Also, studies indicate the use of illicit drugs as a predictor of sexually transmitted infections (STIs), including human immunodeficiency virus (HIV).[8]

In Brazil, there are still no investigations into the use of illicit drugs in individuals from urban settlements, who are potentially vulnerable to these substances. In addition, there are no studies on the potential risk factors for illicit drug use in the population of urban settlements in the country. Some studies show that people living in urban settlements have a high prevalence of illicit drug use,[9,10] and that may contribute to the increase of morbidity and mortality due to diseases associated with the use of these substances. Thus, the objective of our study was to estimate the prevalence and factors associated with the use of illicit drugs by adolescents and young adults in a formal urban settlement.

Method

This is a cross-sectional cohort study of adolescents and young adults from a formal urban settlement in the city of Goiânia, Midwestern Brazil, previously described. The inclusion criteria were: (i) to be between 12 and 24 years old and (ii) to have been living in the settlement for at least 12 months. Data were collected between June and July 2014.

Participants were recruited at the institution of education of the settlement or by indication of their peers (friends or relatives). After the consent of the individuals and/or their legal guardians, all the participants were

interviewed in person in the premises of the educational institution or local basic health unit, using a structured questionnaire on sociodemographic and behavioral data as well as consumption of legal and illegal drugs.

Study variables

- Outcome variable: Self-reported use of illicit drugs (marijuana, crack, cocaine, LSD and inhalants) in the past 12 months.
- Predictor variable: Sociodemographic characteristics (gender [male versus female], age [12-18 versus 19-24 years], education [≤ 6 versus > 6 years of formal education], marital status of the parents [married/common law partner versus single/separated/widowed], formal or informal employment [no versus yes]), behavioral characteristics (use of body piercing and/or tattoos [no versus yes], use of licit drugs [no versus yes], criminal records [no versus yes], signs or symptoms of STI [no versus yes] and access to a Basic Health Unit [UBS, public health care] [yes versus no]. The categorization of age between 12-18 years and 19-24 years was based on the Brazilian Statute of the Child and the Adolescent.[11] Licit drug use was defined as the use of alcohol and/or tobacco in the past 30 days. Signs or symptoms of STI were considered positive in the presence of self-reported genital discharge and/or genital ulcer at any time in life.[12]

Statistical analysis

Data analysis was performed using Stata software version 12.0. Prevalences of illicit drug use were calculated with a confidence interval of 95% (95CI). Initially, a bivariate analysis was performed between the outcome and potential associated factors. Variables with $p<0.10$ were entered into the Poisson regression model with robust variance.[13] Potential confounders were adjusted for the multivariate model. p values < 0.05 were considered statistically significant.

Ethical aspects

Our study was approved by the Research Ethics Committee of the Federal University of Goiás, protocol no. 365/2011. All individuals aged 18 years or older or parents/guardians of individuals under the age of 18 signed a consent form.

Results

A total of 105 participants were included in the study, 58.1% were male. Means for age, education and time living in the settlement were 16.2 years (SD ± 3.32), 7.76 years (SD ± 1.75; min.: 3; max.: 12) and 2.73 years (SD ± 0.94; min.:1, max.: 5), respectively.

The prevalence of use of illicit drugs in the past 12 months was 27.6% (95CI 20.0-36.9%). In addition, use of marijuana, cocaine, crack, LSD and inhalants was reported by 24.8% (95CI 17.5-33.8%), 6.7% (95CI 3.3-13.1%), 2.9% (95CI 1.0-8.1%), 1.9% (95CI 0.5-6.7%) and 1.0% (95CI 0.2-5.2%) of the participants, respectively (Figure 1).

In our study, gender, age, employment, criminal records, use of body piercing and/or tattoos, and consumption of licit drugs were associated with the outcome in the bivariate analysis ($p<0.05$). These variables, as well as the presence of signs and/or symptoms of STI, were entered into the multivariate model. After controlling for the confounding variables, male gender (adjusted prevalence ratio [APR]: 2.6; 95CI 1.3-5.2), use of body piercing and/or tattoo (APR: 2.6; 95CI 1.2-5.6), consumption of licit drugs (APR: 3.4; 95CI 1.1-11.6) and presence of signs and/or symptoms of STI (APR: 1.7; 95CI 1.1 -2.8) were statistically associated with consumption of illicit drugs (Table 1).

Discussion

Estimating prevalence and assessing factors associated with illicit drug use among adolescents and young adults, especially in vulnerable groups such as urban settlement areas, contributes to the formulation of public health policies aimed at preventing and controling the use of these substances, which have a strong negative impact on adult life. Our study presents the first data on the epidemiology of illicit drug use in individuals living in urban settlements in Brazil.

The prevalence of illicit drug use found by us (27.6%; 95CI 20.0-36.9%) was nine times higher than that estimated in adolescents from a population-based study in Brazil (2.8%; 95CI 2.3-4.8%),[14] ratifying the vulnerability of these individuals to the consumption of these substances. Consumption of cocaine and crack is associated with a series of consequences for the health condition and social relations of a person, including mental disorders, STIs and violence.[15-17] Brazil's Midwest concentrates the highest rates of cocaine and crack consumption due to its proximity to other drug-producing countries and is considered a key region for the circulation of these substances to other areas in the country.[18] We observed high rates of cocaine and crack consumption, indicating a need for the implementation of public policies to prevent drug abuse among dwellers of urban settlements.

Male individuals showed a prevalence 2.6 (95CI 1.3-5.2) times higher for use of illicit drugs compared with women, corroborating the findings of other studies that included adolescents and young adults.[6,14] Differences between the sexes are present in the multiple phases of drug abuse

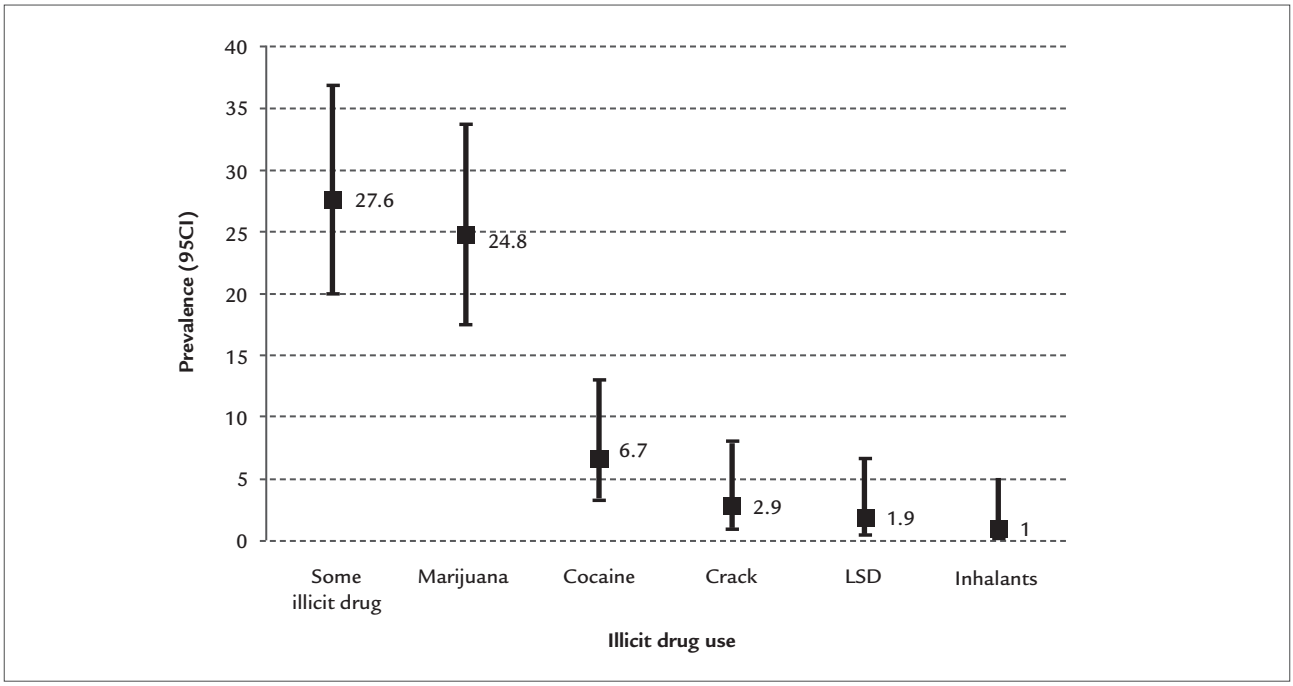

FIGURE 1 Prevalence of illicit drug use by adolescents and young adults in an urban settlement. Goiânia, State of Goiás, Brazil, 2013.

TABLE 1 Factors associated with illicit drug use by adolescents and young adults in an urban settlement. State of Goiás, Brazil, 2013.

Variables	Illicit drug use		PR†, crude (95CI)‡	p	PR†, adjusted§ (95CI)‡	p
	n/Total*	%				
Sex						
Female	7/44	15.9	1.0		1.0	
Male	22/61	36.1	2.3 (1.1-4.9)	0.04	2.6 (1.3-5.2)	<0.01
Age (years)						
12-18	16/77	20.8	1.0		1.0	
19-24	13/28	46.4	2.2 (1.2-4.0)	<0.01	1.1 (0.7-1.8)	0.62
Education (years)						
≤ 6	8/27	29.6	1.0		-	
> 6	21/78	26.9	0.90 (0.45-1.81)	0.78	-	-
Marital status of the parents						
Married/Common law partners	9/44	20.4	1.0		-	
Single/separated/widowed	20/61	32.9	1.60 (0.80-3.18)	0.18	-	-
Formal or informal employment						
No	13/70	20.0	1.0		1.0	
Yes	15/35	42.9	2.2 (1.2-4.1)	<0.01	1.1 (0.7-1.7)	0.80
Criminal records‖						
No	24/97	24.7	1.0		1.0	
Yes	5/8	62.5	2.5 (1.3-4.8)	<0.01	1.9 (1.0-3.6)	0.06
Use of body piercing/tattoos						
No	7/54	13.0	1.0		1.0	
Yes	22/51	43.1	3.3 (1.6-7.1)	<0.01	2.6 (1.2-5.6)	0.01

(*continues*)

TABLE 1 (Cont.) Factors associated with illicit drug use by adolescents and young adults in an urban settlement. State of Goiás, Brazil, 2013.

Variables	Illicit drug use		PR†, crude (95CI)‡	p	PR†, adjusted§ (95CI)‡	p
	n/Total*	%				
Licit drug use‖						
No	3/46	6.5	1.0		1.0	
Yes	26/59	44.1	6.8 (2.2-21.0)	<0.01	3.4 (1.1-11.6)	0.04
Signs and/or symptoms of STI‖						
No	19/81	23.9	1.0		1.0	
Yes	9/21	42.9	1.8 (1.0-3.4)	0.06	1.7 (1.1-2.8)	0.03
User of UBS (public health service)						
Yes	20/68	29.4	1.0		-	
No	9/37	24.3	0.82 (0.41-1.63)	0.58	-	-

*Number of valid responses; †Prevalence ratio; ‡95% Confidence interval; §Adjusted by sex, age, use of body piercing/tattoo, licit drug use, and signs/symptoms of STI; ‖Throughout life; UBS: Basic Health Unit; STI: sexually transmitted infections.

(initiation, increased use and dependence) and should be considered in planning health promotion actions in adolescents and young adults.[19]

Use of body piercing and/or tattoos, practices increasingly common in adolescence and youth, has remained associated with the use of illicit drugs (APR: 2.6; 95CI 1.2-5.6). Studies[20,21] have demonstrated that changes in the body are associated with risk behaviors, such as alcohol consumption and use of illicit drugs. Considering the relation between body piercing and/or tattoo and risk behaviors, changes in the body should be markers evaluated by health professionals while assisting the populations of adolescents and young adults, with a view to screening the use of illicit drugs and health problems arising from abuse of these substances.

Polydrug use is associated with multiple health consequences, including mental disorders and infectious diseases.[22] In young adults, it is related with progression to drug abuse and increased risk of chemical dependence.[22] In this study, we found a positive association between licit (APR: 2.4; 95CI 1.1-11.6) and illicit drug use, corroborating the findings described in the domestic and international literature.

Individuals who reported signs and/or symptoms of STI had a prevalence 1.7 (95CI 1.1-2.8) greater of use of illicit drugs compared to those who did not present this clinical picture. Illicit drug use corresponds to an important predictor of STI vulnerability, since they increase the chances of exposure to risk behaviors/attitudes.[23] Using these drugs increases the disinhibition factor, decreases the perception of risk and negotiation capacity for condom use,[24] also increases the individual's vulnerability to STIs. In addition, the presence of discharge and/or genital ulcers is associated with HIV infection and increases up to 10 times the chance of viral acquisition and transmission, contributing to increase the burden of this infection in adolescents and young adults.[8]

Our research has some limitations due to the design of cross-sectional studies, which do not allow the establishment of temporality between exposure and outcome. In addition, the data are self-reported, liable to memory bias and underestimation due to questions sensitive to morals. In an attempt to minimize bias, the interviews were conducted individually in a private setting.

Conclusion

We found a high prevalence of illicit drug use in this population. The use of drugs was associated with the male gender, use of body piercing and/or tattoos, consumption of licit drugs and reporting of signs and/or symptoms of STIs. In this context, implementing interventional actions and public health policies to prevent illicit drug use and its consequences is a pressing issue, considering the associated factors and peculiarities of this emerging social group.

Resumo

Uso de drogas ilícitas por adolescentes e adultos jovens de um assentamento urbano no Brasil

Objetivo: Estimar a prevalência e fatores associados ao consumo de drogas ilícitas por adolescentes e adultos jovens de um assentamento urbano formal.
Método: Estudo de corte transversal conduzido em adolescentes e adultos jovens de 12 a 24 anos de um assentamento urbano da região Centro-oeste do Brasil. Os dados foram coletados por meio de um questionário estruturado e analisados no programa Stata, versão 12.0. Utilizou-

-se modelo de regressão de Poisson com variância robusta para estimar os fatores associados ao uso de drogas ilícitas. **Resultados:** Do total de participantes (n = 105), 27,6% (IC95% 20,0-36,9%) reportaram uso de drogas ilícitas, como maconha, cocaína, *crack*, LSD e inalantes nos últimos 30 dias. O consumo dessas substâncias foi associado a sexo masculino, uso de *body piercing* e/ou tatuagem, consumo de drogas lícitas (álcool e/ou tabaco) e autorrelato de sinais e/ou sintomas de infecções sexualmente transmissíveis. **Conclusão:** Verificou-se alta prevalência de consumo de drogas ilícitas nos indivíduos investigados, ratificando a presença de fatores de risco para uso dessas substâncias na população de assentamento urbano.

Palavras-chave: Drogas Ilícitas. Adolescente. Adulto Jovem. Área Urbana.

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Individualized threshold for tumor segmentation in ^{18}F-FDG PET/CT imaging: The key for response evaluation of neoadjuvant chemoradiation therapy in patients with rectal cancer?

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Summary

Introduction: The standard treatment for locally advanced rectal cancer (RC) consists of neoadjuvant chemoradiation followed by radical surgery. Regardless the extensive use of SUV_{max} in ^{18}F-FDG PET tumor uptake as representation of tumor glycolytic consumption, there is a trend to apply metabolic volume instead. Thus, the aim of the present study was to evaluate a noninvasive method for tumor segmentation using the ^{18}F-FDG PET imaging in order to predict response to neoadjuvant chemoradiation therapy in patients with rectal cancer.
Method: The sample consisted of stage II and III rectal cancer patients undergoing ^{18}F-FDG PET/CT examination before and eight weeks after neoadjuvant therapy. An individualized tumor segmentation methodology was applied to generate tumor volumes (SUV_{2SD}) and compare with standard SUVmax and fixed threshold ($SUV_{40\%}$, $SUV_{50\%}$ and $SUV_{60\%}$) pre- and post-therapy. Therapeutic response was assessed in the resected specimens using Dworak's protocol recommendations. Several variables were generated and compared with the histopathological results.
Results: Seventeen (17) patients were included and analyzed. Significant differences were observed between responders (Dworak 3 and 4) and non-responders for $SUV_{max\text{-}2}$ ($p<0.01$), $SUV_{2SD\text{-}2}$ ($p<0.05$), $SUV_{40\%\text{-}2}$ ($p<0.05$), $SUV5_{0\%\text{-}2}$ ($p<0.05$) and $SUV_{60\%\text{-}2}$ ($p<0.05$). ROC analyses showed significant areas under the curve ($p<0.01$) for the proposed methodology with sensitivity and specificity varying from 60% to 83% and 73% to 82%, respectively.
Conclusion: The present study confirmed the predictive power of the variables using a noninvasive individualized methodology for tumor segmentation based on ^{18}F-FDG PET/CT imaging for response evaluation in patients with rectal cancer after neoadjuvant chemoradiation therapy.

Keywords: Rectal Neoplasms. Neoadjuvant Therapy. Fluorodeoxyglucose F18. Positron-Emission Tomography.

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Introduction

Colorectal cancer corresponds to the third more incident (9.7%) and the fourth deadlier (8.5%) cancer of all cancers in the world.[1] In Brazil, it is the third more incident cancer.[2] Clinical T3/T4 or node-positive rectal cancer (locally advanced rectal cancer) patients are usually assigned to preoperative or postoperative chemoradiotherapy. Previous published studies have shown that preoperative chemoradiotherapy significantly improves disease-free survival and local control compared with postoperative chemoradiotherapy.[3,4]

In spite of different neoadjuvant chemoradiation therapy regimens available for treatment of rectal cancer (RC), down staging can be observed only in 20% of patients,[5] and

response to therapy is usually done with the analysis of the surgical specimens, known as the gold standard. Tumor regression grade is mostly associated with prognosis and is of great interest due to survival.[5] Complete and partial regression have improved long-term outcome in patients with rectal carcinoma after preoperative chemoradiation.[3-6]

The ability to predict responders to preoperative chemoradiation in RC using conventional imaging methods (CT, US, MRI) alone or in combination is a difficult task, with non-reliable data.[7,8] Accurate restaging before operation is important to determine the best surgical strategy. Surgical extension and aggressiveness, and sphincter preservation should be considered in light of the response to neoadjuvant treatment, ideally through a noninvasive test.[9]

Fluorine-18-labeled fluorodeoxyglucose-positron emission tomography studies (^{18}F-FDG) have been used to evaluate response to therapy in different cancer types.[10-13] In rectal cancer, previously published data have shown promising use of ^{18}F-FDG PET/CT as an important tool to discriminate responders from non-responders.[7-9,14-19] ^{18}F-FDG PET/CT is a test capable of providing metabolic information of viable cancer cells based on radiotracer retention in the compartment of interest, mediated by an enzyme-substrate reaction. However, there is no consensus on how the quantitative analysis should be used to predict response to therapy using ^{18}F-FDG PET/CT.

^{18}F-FDG-PET images have some limitations regarding the provision of accurate information on external and internal contours of the tumor because of the limited spatial resolution associated with this imaging modality. Despite the extensive use of the most intense ^{18}F-FDG tumor uptake value (known as SUV_{max}) to represent tumor glycolytic consumption using PET images, there is a trend to apply metabolic volume instead.

Due to the inherited heterogeneous behavior of cancer cells, expressing the glucose metabolism of the entire tumor in a single voxel might not be the best manner. Tumor metabolism using volume based on PET images seems a more precise representation than SUV_{max}. Thus, several approaches have been used for tumor segmentation with ^{18}F- FDG-PET images[20-26] for the evaluation of the metabolic pattern of the entire tumor. However, these results are still undergoing evaluation due to large variability depending on the choice of the threshold employed, and none of them were used as a non-subjective way to generate PET tumor volumes.[20-26]

Thus, the aim of our study was to evaluate a noninvasive and non-subjective method for tumor segmentation using ^{18}F-FDG PET/CT imaging to predict response to therapy in patients with rectal cancer that underwent neoadjuvant chemoradiation therapy. To date and to our knowledge, this is the first study to use this methodology to evaluate response to therapy in rectal cancer patients.

Method

The study retrospectively evaluated 17 patients with histopathological confirmation of adenocarcinoma of rectum whom underwent ^{18}F-FDG PET/CT before and eight weeks after neoadjuvant chemoradiation at our institution. Staging was done according to the TNM system[27] presented in the 7th edition of the American Joint Committee on Cancer (AJCC) and included colonoscopy, high-resolution magnetic resonance imaging (MRI) and abdominal and chest computerized tomography (CT) scans. Patients with baseline metastatic disease were excluded. All patients underwent standard neoadjuvant long-course chemoradiation as previously described.[4] Briefly, the regimen consisted of 50.4 Gy delivered on weekdays to the pelvis and a 9 Gy boost to the primary tumor. Concomitantly, chemotherapy (5-fluorouracil and leucovorin) was delivered on the 1st and 5th week of radiation therapy. Surgical resection of the rectum was performed after the second PET scan for all patients. The study was approved by the human research ethics committee, and all of the study's participants signed an informed consent form aware that their privacy rights would be observed.

^{18}F-FDG PET/CT scans were performed according to our research protocol for oncological patients using a Discovery 690 PET/CT scanner (GE, Milwaukee, WI, USA). Patients fasted for at least six hours before the intravenous administration of 3.7 MBq/kg (mean 251.6 ± 62.9 MBq and 244.2 ± 66.6 MBq, before and after therapy, respectively) body weight of ^{18}F-FDG. Blood glucose levels was checked before tracer administration (mean 95.2 ± 9.1 mg/dL and 95.8 ± 9.3 mg/dL, before and after therapy, respectively) and patients with glucose levels higher than 190 mg/dL were excluded from the study. CT scans were performed from the top of the head to mid thigh approximately 60 minutes (mean 95.8 ± 9.3 minutes and 91.1 ± 11.4 minutes, before and after therapy, respectively) after intravenous injection of ^{18}F-FDG using a low-dose protocol (120 kV, smart mA) for attenuation map without diagnostic purpose and without oral or intravenous contrast media. Then, PET images were acquired with 2 minutes per bed position for the same region. All PET images were reconstructed using OSEM-like reconstruction algorithm with 2 interations and 24 subsets.

The ^{18}F-FDG PET/CT images were evaluated independently by two board certified nuclear physicians

blinded to all imaging studies and clinical and pathological results. In case of discrepancy, the interpretation was made by consensus between the investigators. All lesions were analyzed semiquantitatively based on the maximum standardized uptake value (SUV_{max}) in the transaxial plane method normalized by lean body mass and were considered pre- and post-therapy (SUV_{max1} and SUV_{max2}, respectively).

In order to evaluate volumetric tumor glucose consumption, an algorithm for tumor segmentation using PET images was applied, which was initially validated in esophageal cancer patients.[28,29] This methodology uses the ^{18}F-FDG uptake in the liver as a control to individualize threshold for tumor segmentation. Briefly, a region-of-interest comprising the entire organ on a transaxial slice was drawn in the liver and mean and standard deviation of the uptake value of ^{18}F-FDG (L_{mean} and L_{SD}, respectively) were calculated. Meanwhile, the highest tumor uptake value in a voxel (T_{max}) was also calculated. Then, to individualize the threshold for tumor segmentation, a lower SUV value (T_{2SD}) was generated as a result of the following formula: $T_{2SD} = T_{max} - (L_{mean} + 2xL_{SD})$.[28] Figure 1 shows the segmentation methods applied.

Using a region-growing methodology, volumes of interest from a seed point (voxel with highest uptake of ^{18}F-FDG in the tumor: T_{max}) with an specific threshold (T_{2SD}) recognizes all surrounding areas to capture up voxels with the difference of initial value based on the segmentation algorithm. For that, a dedicated workstation was used (Advantage Windows Workstation, GE, Milwaukee, WI, USA).

After generating the target lesion volume (Vol_{2SD}), the program calculates the average SUV volume (SUV_{2SD}), and the product of Vol_{2SD} with SUV_{2SD} determines the total lesion glycolysis (TLG_{2SD}). Fixed thresholds (40%, 50% and 60%) were also applied to generate PET-volumes ($Vol_{40\%}$, $Vol_{50\%}$ and $Vol_{60\%}$, respectively), averaged SUVs ($SUV_{40\%}$, $SUV_{50\%}$ and $SUV_{60\%}$, respectively) and the total lesion glycolysis ($TLG_{40\%}$, $TLG_{50\%}$, and $TLG_{60\%}$, respectively). All variables were calculated for each patient before and after neoadjuvant therapy. In addition, percentage of differences between pre- and post-therapy analyses was also calculated for each parameter as follows: $\%\Delta SUV=[(SUV_1-SUV_2)/SUV_1]x100$, $\%\Delta Vol=[(Vol_1-Vol_2)/Vol_1]x100\%$ and $\%\Delta TLG=[(TLG_1-TLG_2)/TLG_1]$ x100.

Response was assessed using the protocol recommendations by Dworak et al.[30] Resected specimens were analyzed by the same pathologist with particular expertise in gastrointestinal diseases. Tumor response to neoadjuvant therapy was scored using the semiquantitative evaluation of histological regression according to the tumor regression grade (TRG) scale:[30] TRG 0, no response; TRG 1, residual cancer cells outgrowing fibrosis; TRG 2, fibrosis outgrowing residual cancer cells; TRG 3, presence of residual cancer cells; TRG 4, complete histopathological response, i.e. no viable cancer cells in the resected specimen. Applying this rating method, tumors were classified as either non-responders (TRG 0-2) or responders (TRG 3 or 4).

Statistical analysis was performed using MedCalc version 14.8.1 (MedCalc Software, Ostend, Belgium). Numerical variables were analyzed by Mann-Whitney test, and correlation test was applied to generate Pearson's coefficient. Differences were considered statistically significant for $p<0.05$. ROC analysis was performed to determine the metabolic parameters in predicting response to treatment.

Results

From March 2012 to November 2013, 17 patients were eligible and underwent ^{18}F-FDG PET/CT examination to assess therapeutic response after neoadjuvant chemoradiation. All tumors were adenocarcinoma of rectum. Eight men and nine women were included in the study. Patient age varied between 26 to 73 years with mean of 49.5 years. There were seven (41.2%) patients with rectal cancer stage II and ten (57.8%) patients with stage III. In terms of response to therapy, there were 11 (64.7%) non-responders (Dworak 0-2) and six (35.3%) responders (Dworak 3 and 4).

Table 1 shows various quantitative metabolic measurements using ^{18}F-FDG PET/CT images pre- and post-neoadjuvant therapy using different methodologies. All variables revealed significant reduction after chemoradiation therapy ($p<0.01$ for all). Table 2 shows the percentage changes among the variables evaluated in the present study.

Among all variables calculated using ^{18}F-FDG PET/CT images (Table 1), there were significant differences between responders (Dworak 3 or 4) vs. non- responders (Dworak 0-2) for SUV_{max-2} (5.8 ± 2.4 vs. 10.5 ± 3.0, $p<0.01$), SUV_{2SD-2} (3.3 ± 0.4 vs. 4.5 ± 1.2, $p<0.05$), $SUV_{40\%-2}$ (3.5 ± 0.9 vs. 6.2 ± 1.9, $p<0.05$), $SUV_{50\%-2}$ (4.1 ± 1.0 vs. 7.1 ± 2.1, $p<0.05$) and $SUV_{60\%-2}$ (4.7 ± 1.1 vs. 8.1 ± 2.4, $p<0.05$). However, there was no significant difference between responders and non-responders for all of percentage change variables presented in Table 2.

In order to determine the best cutoff values to differentiate responders from non-responders, ROC analyses were performed for all variables. Table 3 summarizes the variables with significant areas under the curve ($p<0.05$, except for the SUV_{2SD-1}). However, the variable SUV_{2SD-1} did not reach statistical significance ($p=0.055$) with the studied sample, the proposed methodology (SUV_{2SD-2}) was able to

TABLE 1 Metabolic measurements of ^{18}F-FDG PET/CT pre- and post-neoadjuvant therapy.

	2SD			40%			50%			60%		
Pre-therapy												
	SUV_{max-1}	Vol_{2SD-1}	SUV_{2SD-1}	TLG_{2SD-1}	$Vol_{40\%-1}$	$SUV_{40\%-1}$	$TLG_{40\%-1}$	$Vol_{50\%-1}$	$SUV_{50\%-1}$	$TLG_{50\%-1}$	$Vol_{60\%-1}$	$SUV_{60\%-1}$	$TLG_{60\%-1}$
Mean	24.0	81.5	7.3	681.7	23.4	12.7	344.3	13.7	15.1	232.5	7.1	16.9	133.2
Median	23.7	62.1	7.0	376.3	15.7	10.3	146.0	10.1	15.5	125.6	5.0	16.8	66.1
SD	8.9	72.5	2.3	797.8	21.7	5.6	430.0	13.4	5.6	284.9	7.6	6.2	165.2
Post-therapy													
	SUV_{max-2}	Vol_{2SD-2}	SUV_{2SD-2}	TLG_{2SD-2}	$Vol_{40\%-2}$	$SUV_{40\%-2}$	$TLG_{40\%-2}$	$Vol_{50\%-2}$	$SUV_{50\%-2}$	$TLG_{50\%-2}$	$Vol_{60\%-2}$	$SUV_{60\%-2}$	$TLG_{60\%-2}$
Mean	8.9	14.3	4.1	63.8	7.7	5.3	41.9	4.4	6.1	28.3	2.4	7.0	17.4
Median	8.1	9.6	3.7	39.5	4.9	4.5	23.0	2.6	5.1	13.5	1.2	5.8	7.1
SD	3.6	15.2	1.1	85.2	6.8	2.1	52.5	4.5	2.3	40.8	2.8	2.6	27.7

SUV: standardized uptake value; 2SD: individualized algorithm for tumor segmentation; 40%, 50% and 60%: fixed thresholds for tumor segmentation; Vol: tumor volume; TLG: total lesion glycolysis.

TABLE 2 Percentage change for metabolic measurements of ^{18}F-FDG PET/CT prior surgical resection.

Patient	$\%\Delta SUV_{max}$	2SD			40%			50%			60%		
		$\%\Delta VOl_{2SD}$	$\%\Delta SUV_{2SD}$	$\%\Delta TLG_{2SD}$	$\%\Delta Vol_{40\%}$	$\%\Delta SUV_{40\%}$	$\%\Delta TLG_{40\%}$	$\%\Delta Vol_{50\%}$	$\%\Delta SUV_{50\%}$	$\%\Delta TLG_{50\%}$	$\%\Delta Vol_{60\%}$	$\%\Delta SUV_{60\%}$	$\%\Delta TLG_{60\%}$
Mean	61.3	78.0	44.4	85.6	52.6	44.6	72.1	55.7	60.6	79.2	54.3	59.7	77.8
Median	63.3	82.9	40.3	93.3	59.6	60.7	88.5	72.1	56.8	91.7	70.2	56.8	90.7
SD	14.5	19.9	22.7	14.5	43.7	75.3	35.9	41.6	17.7	22.8	47.6	17.7	26.5

SUV: standardized uptake value; 2SD: individualized algorithm for tumor segmentation; 40%, 50% and 60%: fixed thresholds for tumor segmentation; %ΔSUVmax: percentage change in SUVmax; %ΔVol: percentage change in tumor volume; %ΔTLG: percentage change in total lesion glycolysis.

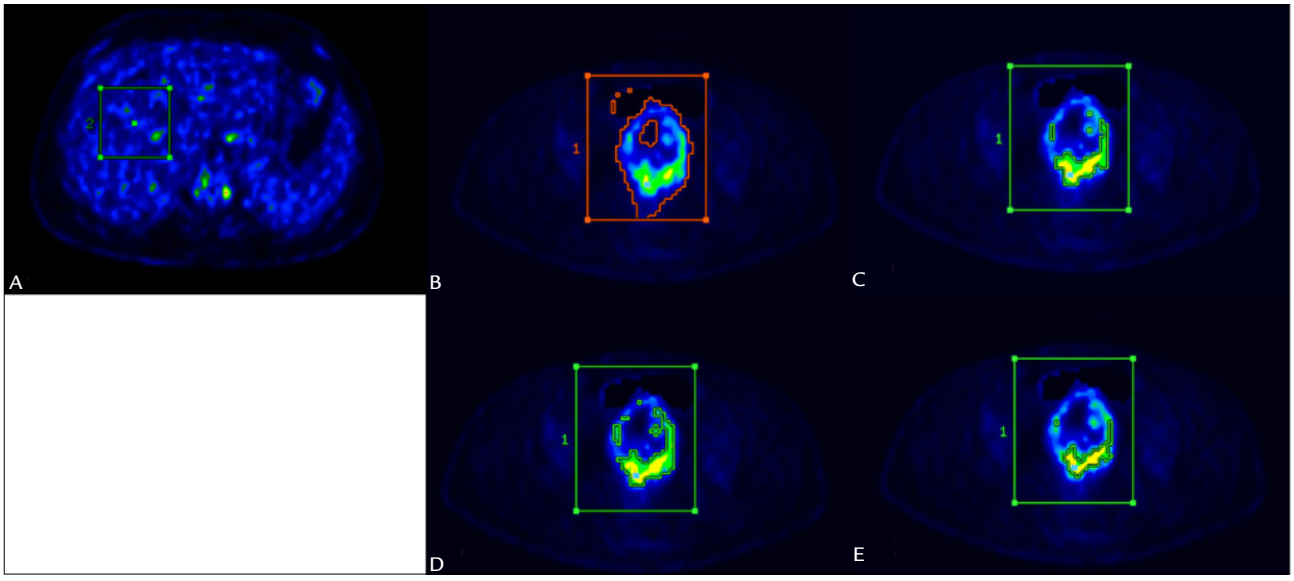

FIGURE 1 ^{18}F-FDG PET/CT tumor image segmentation methods. A. Region of interest (ROI) placed on a transaxial slice in liver. B. Tumor segmentation generated using 2SD individualized algorithm. C. Tumor segmentation generated using 40% threshold. D. Tumor segmentation generated using 50% threshold. E. Tumor segmentation generated using 60% threshold.

differentiate responders from non-responders with 60% and 82% of sensitivity and specificity, respectively. The proposed methodology showed lower sensitivity but higher specificity to discriminate responders from non-responders compared to fixed thresholds (Table 3). Figure 2 shows the significant ROC analyses for the thresholds applied. Figure 3 shows a typical example of ^{18}F-FDG PET/CT imaging tumor segmentation using 2SD individualized algorithm.

Discussion

There is an undeniable interest in assessing response to neoadjuvant chemoradiation in rectal cancer noninvasively with ^{18}F-FDG PET/CT. Tumor metabolic changes using volumetric analyses with PET images seem to be a more precise representation than SUV_{max}. However, there is no consensus about the threshold used for tumor segmentation in this matter. As far as we know, our study is the first in which the proposed methodology of using individualized threshold to segment tumor using ^{18}F-FDG PET/CT images in rectal cancer patients is addressed. This methodology has been applied in esophageal cancer patients[29] with promising results to predict response to neoadjuvant therapy and patient outcome. By using this methodology, SUV_{2SD-1} enabled the discrimination of responders from non-responders with reasonable sensitivity and specificity (83.3% and 72.7%, respectively), while the SUV_{2SD-2} showed approximate values (60.0% and 81.8%, respectively). SUV_{2SD-1} takes into account tumor heterogeneity and, therefore, could be used to predict patients with better outcome before the beginning of neoadjuvant therapy.

Accurate therapeutic response evaluation is crucial because it can guide optimization of the surgical approach (i.e. sphincter-sparing surgery in low rectal tumors), or less aggressive treatment in minimally-advanced tumors. Conventional imaging modalities cannot differentiate fibrosis from viable tumor cells in residual masses after neoadjuvant chemoradiation therapy, therefore being of limited impact on the prediction of pathological response.[7,8] On the other hand, ^{18}F-FDG PET/CT has been proven to be able to predict therapeutical response accurately.

Tumor response varies considerably and, in addition, not all patients benefit equally from treatment. Thus, assessment of potential predictors of histological response using ^{18}F-FDG PET/CT in patients undergoing preoperative treatment could help develop tailored therapy strategies. Our study showed that among the 35.3% of responders (Dworak 3 and 4), some analyzed variables were able to discriminate them from non-responders (SUV_{max-2}, SUV_{2SD-2}, $SUV_{40\%-2}$, $SUV_{50\%-2}$ and $SUV_{60\%-2}$) and the effectiveness of neoadjuvant therapy was in accordance with a previous study.[31]

Guerra et al.[32] showed that SUV_{max} after therapy was the best predictor of pathologic complete response (pCR). The values found were 3.6 ± 1.4 for responders and 6.6 ± 2.1 (p=0.0009) for non-responders.[32] Our study showed similar results for SUV_{max-2} with slightly higher values (5.3 ± 2.2 and 10.4 ± 2.9, respectively) compared to the findings of Guerra et al.[32] These differences could be related to the methodologies applied: 1. SUV correction for the patients' body weight rather than lean body mass, and 2. scan time after chemoradiation, twelve weeks instead of eight weeks applied in our study, respectively.

A study by Kim et al.[33] conducted univariate and multivariate analyses and found post-chemoradiation SUV_{max} as an independent predictor of complete pathological response (pCR). The predictive values of SUV_{max} post-chemoradiation proved to be a value for pCR with a sensitivity of 73.7%, specificity of 63.7% and accuracy of 64.9% for a cutoff value of 3.55. In our study, the cutoff value for SUV_{max-2} of 7.9 showed sensitivity of 83.3% and specificity of 72.7% to discriminate responders (Dworak 3 and 4) from non-responders (Dworak 0-2), a slightly different approach due to the same sample evaluated. Thus, both studies found that the predictive values of post- chemoradiation SUV_{max-2}

TABLE 3 ROC analyses results (only significant values are shown).

Variable	AUC	p-value	Cutoff value	Sensitivity (%)	Specificity (%)
SUV_{max-2}	0.894	0.0001	<7.9	83.3	72.7
SUV_{2SD-1}	0.750	0.055	<6.2	83.3	72.7
SUV_{2SD-2}	0.818	0.0034	<3.3	60.0	81.8
$SUV_{40\%-2}$	0.855	0.001	<4.5	100.0	63.6
$SUV_{50\%-2}$	0.864	0.0004	<5.2	100.0	63.6
$SUV_{60\%-2}$	0.864	0.0004	<6.0	100.0	63.6
$\%\Delta SUV_{40\%}$	0.758	0.037	>68.8%	66.7	81.8
$\%\Delta SUV_{50\%}$	0.758	0.037	>67.4%	66.7	81.8

AUC: area under the curve.

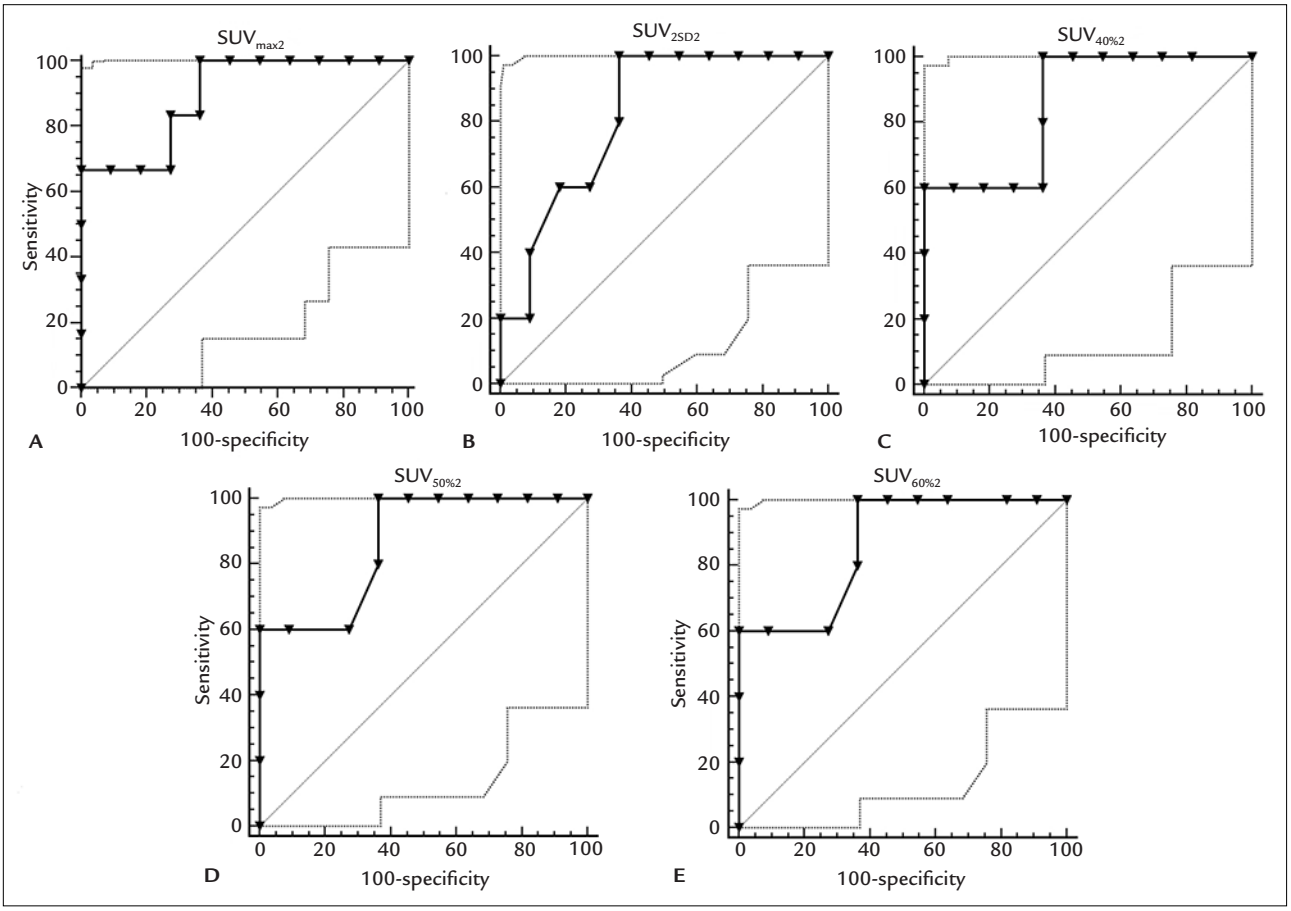

FIGURE 2 ROC analyses.

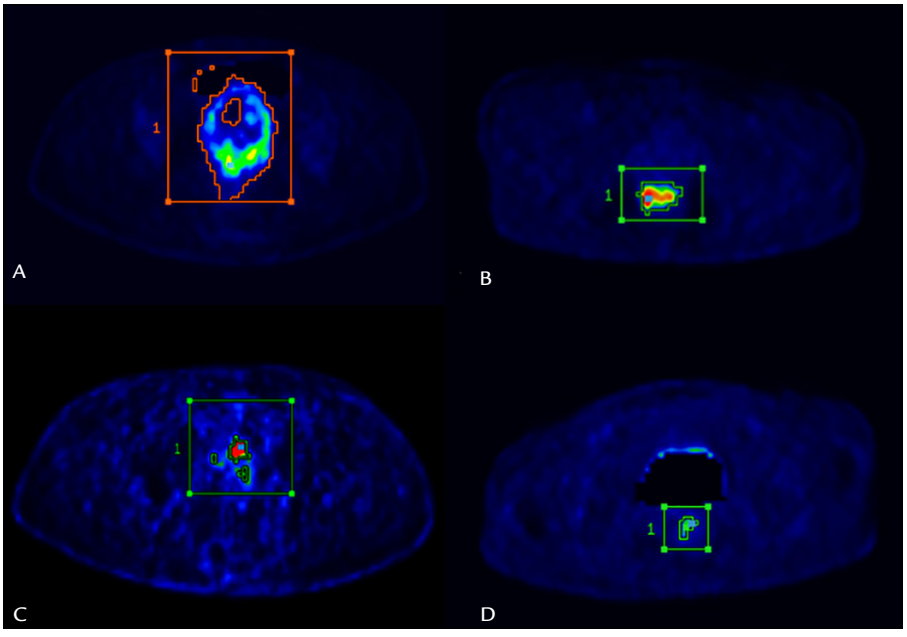

FIGURE 3 Typical example of ^{18}F-FDG PET/CT image tumor segmentation using 2SD individualized algorithm. A. Tumor segmentation pre-therapy in non-responder. B. Tumor segmentation post-therapy in non-responder. C. Tumor segmentation pre-therapy in responder. D. Tumor segmentation post-therapy in responder.

present low sensitivity and specificity to motivate a change in the treatment plan for locally advanced rectal cancer.

In the meta-analysis with the largest number of patients (n=1,527), Li et al.[34] found SUV_{max2} and Δ%TRP to determine pCR alone. The results of subgroup analysis showed that Δ%SUV_{max} before and after therapy had higher specificity to predict the degree of tumor regression than pCR alone. Unfortunately, Δ%SUV_{max} in our study was not strong enough to separate responders from non-responders due probably to the small sample size, which constitutes a limitation. The other potential issue related to the weakness of this variable might be related to inflammation after radiotherapy. Inflammatory cells can take ^{18}F-FDG up, mimicking viable cancer cells and limiting the use of this methodology for response evaluation.

The other variables $SUV_{40\%-2}$, $SUV_{50\%-2}$ and $SUV_{60\%-2}$ should be used with caution, since tumor segmentation using PET images with these thresholds has significant interference depending on the heterogeneity of the tumor. Thus, underestimation could be the main issue of this methodology to evaluate tumor response with unreliable results.

Conclusion

Our study confirmed the predictive power of the variables using a noninvasive individualized methodology for tumor segmentation based on ^{18}F-FDG PET/CT imaging for response evaluation in patients with rectal cancer after neoadjuvant chemoradiation therapy. The reliability of these results should be applied to a larger number of patients and cannot exempt responders from radical surgery. It is also worth noting that there is a need to standardize the methodology of the tests using ^{18}F- FDG PET/CT imaging so that the results can be compared. Although additional work remains to be done, the methodology presented in our study is of general interest, as it introduces a new perspective for the use of this imaging modality on the evaluation of chemoradiation therapy response, with potential clinical impact due to the personalized-type analysis for therapeutic response evaluation in rectal cancer patients.

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Resumo

Individualização na segmentação tumoral de imagens de ^{18}F-FDG PET/CT: a chave para avaliação de resposta terapêutica neoadjuvante em pacientes com câncer retal?

Introdução: O câncer retal (RC) é uma doença de importância global, e o tratamento padrão para o câncer retal localmente avançado compreende quimiorradiação neoadjuvante seguida de cirurgia radical. Independentemente do uso extensivo da captação tumoral mais intensa do ^{18}F-FDG (conhecida como SUV_{max}) como representativo do consumo glicolítico do tumor nas imagens de PET, há uma tendência para aplicar volume metabólico. Dessa forma, o objetivo do presente estudo foi avaliar um método não invasivo de segmentação tumoral utilizando a ^{18}F-FDG PET para predizer a resposta à quimiorradioterapia neoadjuvante em pacientes com câncer de reto.
Método: A amostra consistiu em pacientes com câncer retal em estádios II e III submetidos ao exame de ^{18}F-FDG PET/CT antes e oito semanas após a terapia neoadjuvante. Foi aplicada uma metodologia de segmentação tumoral individualizada para gerar volumes tumorais (SUV_{2SD}). A resposta terapêutica foi avaliada nos espécimes ressecados utilizando as recomendações do protocolo de Dworak. Várias variáveis foram geradas e comparadas com os resultados histopatológicos.
Resultados: Dezessete (17) pacientes foram incluídos e analisados. Foram observadas diferenças significativas entre os respondedores (Dworak 3 e 4) e não respondedores para SUV_{max-2} ($p<0,01$), SUV_{2SD-2} ($p<0,05$), $SUV_{40\%-2}$ ($p<0,05$), $SUV_{50\%-2}$ ($p<0,05$) e $SUV_{60\%-2}$ ($p< 0,05$). As análises ROC mostraram áreas significativas sob a curva ($p<0,01$) para a metodologia proposta, com sensibilidade e especificidade variando de 60% a 83% e 73% a 82%, respectivamente.
Conclusão: O presente estudo confirmou o poder preditivo das variáveis utilizando uma metodologia não invasiva individualizada para segmentação tumoral baseada em imagens ^{18}F-FDG PET/CT para avaliação da resposta em pacientes com câncer retal após tratamento com quimiorradiação neoadjuvante.

Palavras-chave: Neoplasias Retais. Terapia Neoadjuvante. Fluorodesoxiglucose F18. Tomografia por Emissão de Pósitrons.

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Combination of topical agents and oxybutynin as a therapeutic modality for patients with both osmidrosis and hyperhidrosis

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Summary

Introduction: The association of osmidrosis and hyperhidrosis often causes emotional and social problems that may impair the patients' quality of life. The purpose of our study was to analyze the therapeutic results of oxybutynin and topical agents in 89 patients with both osmidrosis and hyperhidrosis.
Method: We conducted an observational study at two specialized centers of hyperhidrosis between April 2007 and August 2013. Eighty-nine (89) patients with both osmidrosis and hyperhidrosis were treated with oxybutynin and topical agents. Patients were evaluated before treatment and at 3 and 6 weeks after treatment started, by using the Quality of Life Questionnaire and the Sweating Evolution Scale.
Results: Before treatment, 98% of the patients presented with poor or very poor quality of life. After six weeks of treatment, 70% stated their quality of life as being slightly better or much better ($p<0.001$) and nearly 70% of the patients experienced a moderate or great improvement in sweating and malodor. Improvement in osmidrosis was significantly greater when the axillary region was the first most disturbing site of hyperhidrosis.
Conclusion: There was a significant improvement in quality of life and a reduction in sweating and malodor after six weeks of treatment with topical agents and oxybutynin in patients with both hyperhidrosis and osmidrosis. Therefore, clinical treatment should be considered before invasive techniques.

Keywords: Hyperhidrosis. Apocrine Glands. Muscarinic Antagonists. Sweat Gland Diseases.

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Introduction

Osmidrosis (OH) is a disease caused by excessive secretion of the apocrine glands, resulting in malodor, mainly in the axillary and genital areas. It often causes emotional and social problems that may impair the patients' quality of life (QoL). Some patients with OH also have hyperhidrosis (HH), which is characterized by the overproduction of sweat by eccrine glands covering the body's surface, predominantly in the palmar, plantar, axillary and craniofacial regions. When OH and HH occur together, the problem becomes even more distressing for patients.[1]

In our institution, many patients present with both HH and OH. In such cases, treatment includes oxybutynin and topical agents. Oxybutynin is an anticholinergic drug that has been shown to decrease sweating and improve QoL with few side effects in more than 70% of the patients.[2-4] If this treatment fails, sympathectomy may be the first surgical choice for palmar HH and can be considered as a surgical alternative for axillary and facial HH because it is a definitive therapeutic option.[5,6] The topical agents used in our service are Sastid® (Stiefel, a GSK company, Middlesex, United Kingdom), which is a soap containing salicylic acid and sulfur that has fungicidal and keratolytic action, and Clinagel® (Stiefel, a GSK company, Middlesex, United Kingdom), which is a clindamycin 10 mg/g (1%) gel.

To the best of our knowledge, no study has demonstrated the therapeutic results of the combination of oxybutynin and topical agents in patients with both OH and HH. This study aimed to analyze the therapeutic results of oxybutynin and topical agents in 89 patients with both OH and HH.

Method

This was a retrospective study with a review of the patients' data at two specialized centers of HH (Hospital Israelita Albert Einstein and Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) between April 2007 and August 2013. Our study was conducted in accordance with the standards of the Ethics Committee for Analysis of Research Projects on Human Experimentation (Approval numbers at Plataforma Brasil: CAAE01582112.6.1001.0071 and CAAE01582112.2.3001.0068); all subjects gave informed consent. A total of 89 patients with both OH and HH in the axillary region and in other sites were treated with oxybutynin and topical agents. Follow-up was conducted 3 and 6 weeks after treatment started. Patients with compensatory HH were not included.

The group comprised 74 women (83%) and 15 men (17%), aged 5 to 57 years, with a median age of 27 years. The patients' body mass index (BMI) ranged from 15.7 to 33.2 kg/m^2, with a median of 23 kg/m^2.

At the first visit, oxybutynin and both topical agents (Sastid® and Clinagel®) were introduced. The soap and the gel were used once a day, daily.

Oxybutynin was prescribed for six weeks, in progressively increasing doses throughout treatment. At the first visit, patients were given 2.5 mg of oxybutynin to be taken once a day in the evening, for one week; they were then instructed to increase the dose to 2.5 mg twice a day from the 8th to the 21st day, after which a second visit was scheduled (three weeks of treatment). After this period of time, the dose was increased to 5 mg twice a day from the 22nd to the 42nd day, after which a third visit was scheduled (six weeks of treatment).

The patients were evaluated three times: at the first visit (before medications) and after the 3rd and 6th weeks, using the QoL questionnaire[7] and the Sweating Evolution Scale.

Patients answered the QoL questionnaire at the first visit and after six weeks of treatment. The QoL questionnaire consists of 20 specific questions about HH/OH, divided in five domains. Each domain or group contains five degrees of answers and the patient indicated only one, with scores ranging from 20 to 100. According to the scoring system, a higher score reflects a poorer QoL. QoL before treatment was considered very poor if the sum of points was greater than 83; poor if the sum was from 68 to 83; good if the sum was 52 to 67; very good if the sum was 36 to 51; and excellent if the sum was 20 to 35.

At the 6th week of treatment, QoL was classified as much worse when the total score was greater than 83; slightly worse when the total score was between 68 and 83; the same when the total score was between 52 and 67; slightly better when the total score was between 36 and 51; and much better when the total score was between 20 and 35.

The Sweating Evolution Scale is based on the patient's subjective perception of improvement in HH/OH after treatment. It was used at the second and third visits for all study participants. The scale ranges from 0 to 10, with 0 representing no improvement and 10 representing absence of HH. If the score was between 1 and 4, the improvement was considered slight; if the score was between 5 and 7, the improvement was considered moderate; and if the score was between 8 and 10, the improvement was considered great.

We analyzed the number and sites with HH symptoms in addition to axillary OH (HH sites associated with OH); the distribution of patients according to site of complaint; the association between OH and HH (sites of HH and the most disturbing complaints of the patients); the number of patients who mentioned OH as the first, second, third, or fourth complaint; the impact of OH on QoL before treatment; the effect of treatment on QoL; and the improvement in malodor and sweating after treatment.

The numerical variables were expressed by using mean and standard deviation, with normality being verified with the Shapiro-Wilk test. When normality could not be assumed, the variables were described as median and interquartile range. Categorical variables were described by using absolute and relative frequencies.

The Wilcoxon rank-sum test was used to analyze the self-reported improvement in malodor and sweating over the consecutive medical visits and to compare the therapeutic results between OH and HH. The same test was used to compare the impairment in QoL throughout the treatment. McNemar's test was used to compare categorical levels of malodor improvement.

The results were presented using p values. The significance level for all tests was p=0.05.

Results

All the patients with both OH and HH had axillary HH associated, wherein 80% of the patients reported axillary HH as the first most disturbing complaint. OH was never the first most disturbing complaint. In more than half of the patients (51 out of 89), OH was reported as the

second most disturbing complaint. Figure 1 shows the most disturbing sites of complaint by patients.

The number of body sites affected by HH and their locations are presented in Table 1. Most patients (86%) had HH in one, two or three sites in addition to OH. The other 14% of patients had HH in four or more sites.

The sites of HH that were associated with axillary malodor are shown in Table 1. Palmar or plantar HH were present in almost half of the patients.

The effect of OH and HH on QoL before and after six weeks of treatment as well as the evolution of OH and HH (considering OH and the most disturbing site of HH in each patient) after 3 and 6 weeks according to the Sweating Evolution Scale are presented in Table 2.

Before treatment, almost all patients (98%) ranked their QoL as poor or very poor. After six weeks of treatment, the improvement in QoL was substantial and most patients (70%) considered their QoL as slightly or much better, with a statistically significant difference ($p<0.001$).

After three weeks of treatment, we observed an improvement of 31% in symptoms of OH and a 41% improvement in symptoms of HH, with no statistical difference. After six weeks of treatment, nearly 70% of the patients experienced moderate to great improvement in symptoms of both OH and HH.

Considering only OH, we observed that patients taking subdoses of oxybutynin (results of three weeks) showed less improvement. However, when the full dose of oxybutynin was taken (results of six weeks), patients experienced a significant improvement. The same occurred with HH symptoms, showing that clinical efficacy depends on the correct oxybutynin dose.

We also observed that the improvement in OH symptoms was significantly greater when the axillary region was the first most disturbing site of HH if compared to the results in patients with plantar and palmar areas as the first most disturbing sites of HH.

Discussion

OH is a disease that disrupts patients' social and professional lives. Its prevalence is about 4.5% in Han Chinese.[8] The exact etiology of OH has not been elucidated yet,[9] but it is known to be a familial hereditary disease, with the involvement of genetic mechanisms and the influence of androgens on the secretion of the apocrine glands.[8,10-12] The influence of sex hormones on the pathophysiology of OH justifies its larger frequency during puberty.[8]

Similar to other authors, we observed a higher frequency of OH among female patients, although the reason is unknown.[13,14] Nokita et al.[15] suggested that cultural, psychological, hormonal and physiologic factors may make women more sensitive to malodor.

Surgical excision of the subcutaneous tissue and/or the overlying skin, which entails a complete excision of the apocrine and eccrine glands,[16] can be performed to

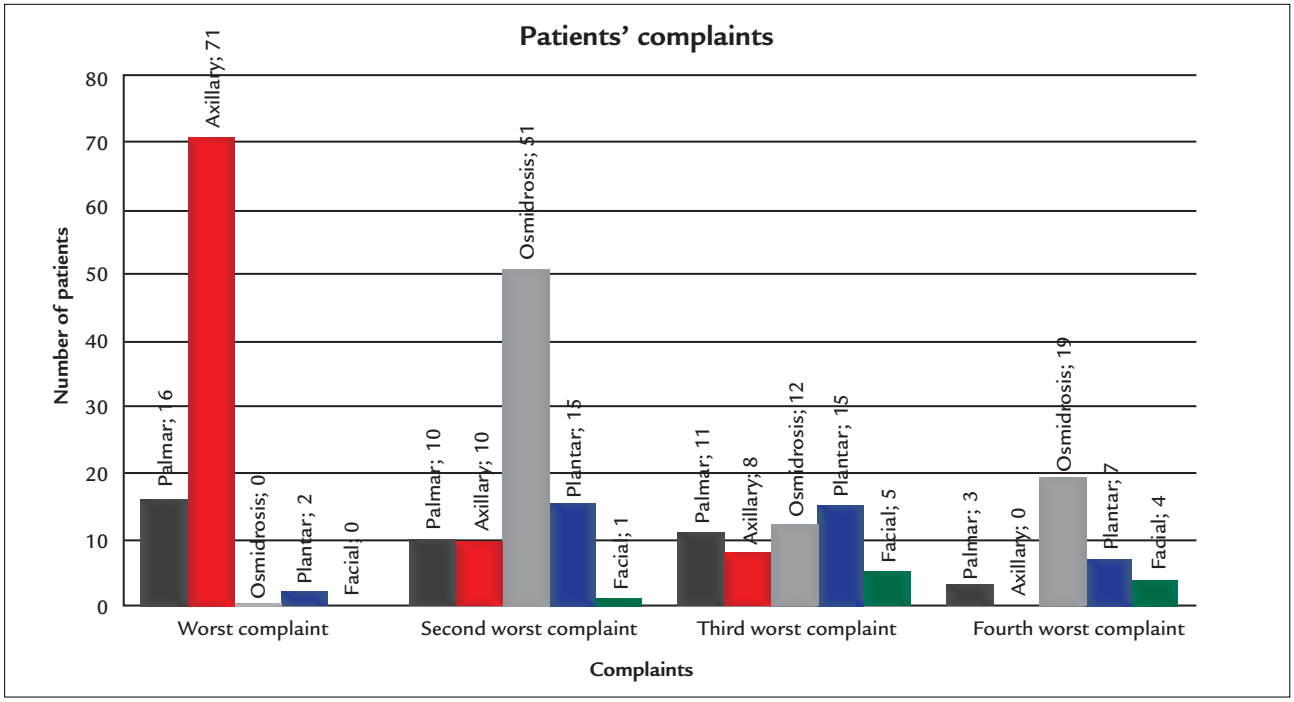

FIGURE 1 Distribution of patients according to sites of complaint.

TABLE 1 Number and locations of hyperhidrosis sites in addition to axillary osmidrosis. Hyperhidrosis sites associated with osmidrosis.

Number and locations of hyperhidrosis sites	n	%
1 site	**29**	**33**
Axillary	29	33
2 sites	**19**	**22**
Axillary and Palmar	8	9.5
Axillary and Plantar	8	9.5
Axillary and Legs	1	1
Axillary and Back	1	1
Axillary and Facial	1	1
3 sites	**28**	**31**
Axillary and Palmar and Plantar	19	22
Axillary and Palmar and Abdominal	2	2
Axillary and Palmar and Facial	1	1
Axillary and Palmar and Scalp	1	1
Axillary and Palmar and Legs	1	1
Axillary and Thorax and Legs	1	1
Axillary and Thorax and Back	1	1
Axillary and Facial and Back	1	1
Axillary and Plantar and Inguinal	1	1
4 sites	**9**	**10**
Axillary and Palmar and Plantar and Facial	5	6
Axillary and Palmar and Plantar and Back	1	1
Axillary and Palmar and Plantar and Legs	1	1
Axillary and Abdominal and Back and Breast	1	1
Axillary and Abdominal and Back and Thorax	1	1
5 sites	**2**	**2**
Axillary and Plantar and Abdominal and Legs and Inguinal	1	1
Axillary and Palmar and Plantar and Back and Backside	1	1
6 sites	**2**	**2**
Axillary and Back and Breast and Plantar and Facial and Backside	1	1
Axillary and Back and Breast and Plantar and Facial and Palmar	1	1
Total	**89**	**100**

	Axillary hyperhidrosis n=89 (100%)	Facial hyperhidrosis n=11 (12%)	Palmar hyperhidrosis n=40 (45%)	Plantar hyperhidrosis n=39 (44%)	Other sites of hyperhidrosis n=18 (20%)
Male	15 (17%)	6 (55%)	8 (20%)	7 (18%)	2 (11%)
Female	74 (83%)	5 (45%)	32 (80%)	32 (82%)	16 (89%)

TABLE 2 Quality of life before treatment and six weeks later. Evolution of osmidrosis and hyperhidrosis after 3 and 6 weeks of treatment.

QoL	Before treatment n (%)			QoL	6 weeks later n (%)		
Very poor	50 (56%)			Much worse	0		
Poor	37 (42%)			Slightly worse	0		
Good	2 (2%)			The same	27 (30%)		
Very good	0			Slightly better	59 (67%)		
Excellent	0			Much better	3 (3%)		
Improvement in OH	**3 weeks n (%)**	**6 weeks n (%)**	**p#**	**Improvement in HH**	**3 weeks n (%)**	**6 weeks n (%)**	**p#**
Slight	49 (69%)	31 (35%)	<0.001	Slight	36 (59%)	27 (30%)	0.004
Moderate	14 (20%)	27 (30%)	<0.001	Moderate	17 (28%)	39 (44%)	0.004
Great	8 (11%)	31 (35%)	<0.001	Great	8 (13%)	23 (26%)	0.004

QoL: quality of life; OH: osmidrosis; HH: hyperhidrosis.
#McNemar's test.

reduce malodor and sweating. Minimally invasive procedures[17-20] such as liposuction, laser therapy, subdermal shaving, microwave-based device and ultrasonic surgical aspiration are also used to reduce malodor and sweating caused by the excessive secretion of these glands.

However, recurrence of malodor is more frequent with minimally invasive procedures. Complete excision of the glands, although having a lower recurrence rate, leads to significant scarring, longer periods of bandaging and a higher risk of complications.[10,17]

Nonsurgical methods for the treatment of HH and OH include topical antiperspirants, iontophoresis, Botox injection and the use of anticholinergic drugs.[9,21,22] Unless there are formal contraindications such as closed-angle glaucoma, intestinal obstruction and severe dermatologic complaints, we empirically treat our patients with both HH and OH with a soap containing salicylic acid and sulfur (SASTID®) which has a fungicidal and keratolytic action, associated to a gel containing topical antibiotic (CLINAGEL®), combined with oxybutynin. The oxybutynin is an anticholinergic drug used for HH with a high efficacy rate and scientific evidence to support its use.[3,23]

All the patients with OH had an association with axillary HH. In Western countries, people tend to ask for treatment of HH rather than of OH. In Asian countries, patients are more concerned about controlling OH.[24] This is the reason why most of the studies on OH are from Asian countries.

In our study, all the patients sought medical care for HH rather than for OH. The fact that we are a referral center for patients with HH may also account for why all the patients in our study had HH.

The axillary region was the only HH site in patients presenting with malodor, while excessive sweat was present in different sites of the body. HH was more frequent in the axillary region, a fact noted by all the patients. The palmar region was the second most affected site of HH (45%) followed by the soles (44%); the other sites of HH were present in 20% of the patients. These rates are similar to those of the population affected by HH.[25] The face was affected by excessive sweat in 12% of the patients in our study, probably because our sample had a median age of 27 years; the symptoms of facial HH commonly start in adulthood and patients tend to seek treatment for this condition in their 40s.[26]

To the best of our knowledge, no previous study has evaluated QoL in patients with both HH and OH. Most studies analyze only the improvement in symptoms and the presence of complications related to the therapy. In our study, however, we evaluated patients' QoL before treatment and six weeks after treatment started. Seventy percent (70%) reported that their QoL had improved slightly or was much better after six weeks of treatment. Before treatment, none of the patients considered their QoL very good or excellent; only 2% reported it as good.

The treatment of both OH and HH with the combination of topical agents and subdoses of oxybutynin (clinically insufficient dose) led to a significantly lower improvement when compared to patients using topical agents and the full dose of oxybutynin (10 mg). The full dose of oxybutynin was effective (moderate or great improvement) in reducing malodor in 65% of the patients; 70% experienced a reduction in sweating and 70% reported that their QoL was slightly or much better than before treatment.

We have not found any study that evaluated the results in patients with both HH and OH who had been treated with noninvasive methods. Comparing our results with other publications, we achieved similar results to those of Seo et al.,[27] who showed 72.1% of good to excellent results in patients with axillary OH after liposuction with curettage. The same author reported that 8 out of 43 patients (19%) had complications such as ecchymosis, focal skin necrosis, induration, hematoma and seroma. Lee et al.[28] reported that excellent results were achieved in 76% of the patients and 22% experienced good results after tumescent liposuction with dermal curettage for treatment of axillary HH and OH. Other surgical treatments showed higher rates of satisfaction among patients (80.6% to 98.9%), but these patients experienced a higher number of complications (10.7% to 45.2%).[29-31]

A weakness of our study is the assessment of the relative influence of topical agents on the amelioration of OH. Would the results be different if patients had received only oxybutynin or just topical treatment? Only a prospective and randomized study (with a topical agent as placebo) could definitely provide an answer to this question; such a trial is under consideration in our centers. Nevertheless, because all of our patients presented with HH in at least one site in addition to OH, oral and topical treatment were beneficial to the majority of the patients.

Although the treatment of OH with topical agents and oxybutynin is not the solution for every patient, it is effective for most of them. Therefore, they should be used as the first alternative at the beginning of the treatment for patients with OH associated with HH before indicating other therapeutic modalities.

Conclusion

We observed a significant improvement in QoL and a reduction in sweating and malodor after six weeks of treatment with oxybutynin and topical agents in patients with both HH and OH. The combination of oxybutynin and topical agents is a good alternative for patients with both HH and OH.

Resumo

Uso combinado de agentes tópicos e oxibutinina para tratamento de pacientes com osmidrose e hiper-hidrose

Introdução: A associação entre osmidrose e hiper-hidrose com frequência causa problemas emocionais e sociais que podem deteriorar a qualidade de vida dos pacientes. O objetivo deste estudo foi analisar os resultados terapêuticos do uso de oxibutinina associada a agentes tópicos em 89 pacientes com osmidrose e hiper-hidrose.
Método: Nós conduzimos um estudo observacional em dois centros especializados em hiper-hidrose entre abril de 2007 e agosto de 2013. Oitenta e nove (89) pacientes com osmidrose associada a hiper-hidrose foram tratados com oxibutinina e agentes tópicos. Os pacientes foram avaliados antes do tratamento e após 3 e 6 semanas do início do tratamento, por meio do Questionário de Qualidade de Vida e da Escala de Evolução da Sudorese.
Resultados: Antes do tratamento, 98% dos pacientes apresentavam qualidade de vida ruim ou muito ruim. Após seis semanas de tratamento, 70% classificou sua qualidade de vida como sendo pouco ou muito melhor ($p<0.001$) e aproximadamente 70% dos pacientes relataram melhora moderada ou grande de sudorese e odor. Houve melhora significativamente maior da osmidrose quando a região axilar era o sítio em que a hiper-hidrose mais incomodava.
Conclusão: Houve melhora significativa da qualidade de vida e uma redução da sudorese e do odor após seis semanas de tratamento com agentes tópicos e oxibutinina em pacientes com hiper-hidrose associada a osmidrose. Dessa maneira, a terapia clínica deve ser considerada antes de técnicas invasivas.

Palavras-chave: Hiperidrose. Glândulas Apócrinas. Antagonistas Muscarínicos. Doenças das Glândulas Sudoríparas.

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Associations among body composition, inflammatory profile and disease extent in ulcerative colitis patients

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Summary

Objective: The aim of our study was to assess body composition status and its association with inflammatory profile and extent of intestinal damage in ulcerative colitis patients during clinical remission.
Method: This is a cross-sectional study in which body composition data (phase angle [PhA], fat mass [FM], triceps skin fold thickness [TSFt], mid-arm circumference [MAC], mid-arm muscle circumference [MAMC], adductor pollicis muscle thickness [APMt]), inflammatory profile (C-reactive protein [CRP], α1-acid glycoprotein, erythrocyte sedimentation rate [ESR]) and disease extent were recorded.
Results: The mean age of the 59 patients was 48.1 years; 53.3% were women. Most patients were in clinical remission (94.9%) and 3.4% was malnourished according to body mass index. PhA was inversely correlated with inflammatory markers such as CRP (R=-0.59; p<0.001) and ESR (R=-0.46; p<0.001) and directly correlated with lean mass: MAMC (R=0.31; p=0.01) and APMt (R=0.47; p<0.001). Lean mass was inversely correlated with non-specific inflammation marker (APMt vs. ESR) and directly correlated with hemoglobin values (MAMC vs. hemoglobin). Logistic regression analysis revealed that body cell mass was associated with disease extent (OR 0.92; 95CI 0.87-0.97; p<0.01).
Conclusion: PhA was inversely correlated with inflammatory markers and directly correlated with lean mass. Acute inflammatory markers were correlated with disease extent. Body cell mass was associated with disease extent.

Keywords: Body Composition. Ulcerative Colitis. C-Reactive Protein. Biomarkers. Severity of Illness Index.

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Introduction

Ulcerative colitis (UC) is one of the main forms of inflammatory bowel disease (IBD) characterized by chronic inflammation of the gastrointestinal tract. It represents an important public health problem, for it begins in young adulthood, lasts throughout life and may affect education, working ability, long-term productivity, social life and the quality of life of the patients.[1] Studies showed increased incidence of IBD in developing countries, including Brazil.[2-6] Although its pathogenesis remains unknown, genetic, immunological and environmental factors have been associated with UC.[7,8]

Follow-up of inflammatory biomarkers has been considered useful to measure disease activity and severity.[9,10] It is also known that nutritional status has strong correlation with disease severity.[11] On the other hand, the nutritional status of patients during clinical remission still remains to be clarified.[12] It is plausible that the body composition status, inflammatory profile and disease severity are associated with active disease. However, to the best of our knowledge, that association is unknown during disease remission. Therefore, the purpose of our study was to assess body composition status and its association with inflammatory profile and extent of intes-

tinal damage in UC patients during clinical remission or mild disease activity.

Method

Patients

A total of 61 UC patients treated at the IBD outpatient care of our hospital from March 2009 to March 2010 were prospectively evaluated. Inclusion criteria were patients of both genders in clinical remission or with mild disease activity according to clinical and laboratory findings. Exclusion criteria were individuals with moderate or severe disease, those who had partial or total resection of the colon and those with severe disease that led to decreased food intake compared with the usual food intake. Disease activity was assessed according to the Truelove and Witts criteria.[13] Patients were evaluated according to the clinical course of disease, body composition and inflammatory profile. To determine disease extent (distal colitis, left-sided colitis or pancolitis), data at diagnostic were used. Time of diagnosis, time of disease remission and drugs being used were also recorded. The study was approved by the Research Ethics Committee of the São Paulo State University (Unesp), Medical School, Botucatu (protocol #3190/2009). An informed consent form was signed by all participants.

Body composition assessment

Body composition was evaluated using anthropometry and bioelectrical impedance analysis (BIA).

Anthropometric measurements

Body height and weight were measured and used to calculate body mass index (BMI).[14] Mid-arm circumference (MAC) was measured using a measuring tape, as previously described.[15] Triceps skin fold thickness (TSFt) was measured according to previous standardization.[16] Mid-arm circumference (MAC) was measured at the midpoint between the acromioclavicular joint and olecranon process. Mid-arm muscle circumference (MAMC) was obtained from the following respective formulas: MAMC=MAC-(pxTSFt).[17] The adductor pollicis muscle thickness (APMt) was assessed as previous study.[18] Nutritional status was classified using BMI, MAC and TSFt variables. The stratification for BMI (kg/m^2) depended on the age. Subjects < 60 years: malnutrition (< 18.4), eutrophic (18.5-24.9), overweight (25.0-29.9), obese (> 30).[14] Subjects ≥ 60 years: low weight (≤ 22.0), eutrophic (22.1-26.9) and overweight (≥ 27.0).[19] The classification for MAC and TSFt occurred according to percentiles as follow: malnourished (< 10th), eutrophic (10th-90th), obese (> 90th).[20]

Bioelectrical impedance analysis (BIA)

BIA was performed using a tetrapolar single-frequency apparatus (50 kHz and 0.8 mA; Biodynamic-450, Biodynamics Corporation, USA) applied to the skin using adhesive electrodes. Phase angle (PhA) derived from the BIA was determined as previously described[21] and its values were calculated as follows: PhA=arc tangent reactance/resistance*(180°/π). Body cell mass (BCM) and fat mass (FM) were recorded according to the parameters given by the device. Measurements were taken in patients after 12-hour overnight fast, voiding the urine bladder and laying in the supine position for 15 minutes.[12]

Inflammatory profile

A venous blood sample (50 mL) was obtained from patients after overnight fasting and analyzed in the routine laboratory for hemoglobin, C-reactive protein (CRP), α1-acid glycoprotein and erythrocyte sedimentation rate (ESR). All determinations were made by means of standardized laboratory techniques.

Statistical analysis

Statistical analysis was performed using SAS, version 9.2.3 (SAS Institute Inc., Cary, NC, USA). $p<0.05$ was considered statistically significant. Results were expressed in medians (percentile range 25-75th). The significance of differences among groups was calculated by Kruskal-Wallis's test complemented by Tukey's test. For correlation analysis, Pearson correlations were computed in each case. In order to verify the possible association between disease extent and body composition variables, logistic regression was used for ordinal data with adjustment for proportional hazards model.

Results

Sixty-one (61) consecutive patients were evaluated and two patients were excluded (one pregnancy, one non-reliable data). A total of 59 patients (32 women and 27 men; 48.14±13.9 years) were studied. Twenty-six (26, 44.1%) patients had distal colitis, 11 (18.6%) had left-sided colitis and 22 (37.3%) had pancolitis. The time (median [percentile range 25th-75th] months) of diagnose among the three types of extent of intestinal injury was similar (p=0.13) (distal colitis: 114.0 [60.0-144.0] months, left-sided colitis: 120.0 [48.0-156.0] months and pancolitis: 96.0 [48.0-132.0] months). Most patients (94.9%; n=56) were in clinical remission (≥ 6 months: n=43; < 6 months: n=13) and only three (5.1%) displayed mild disease activity. The longest remission time (months) was found in patients with distal colitis (distal colitis: 24.0 [12.0-72.0] > pancolitis: 12.00

[4.0-24.0] > left-sided colitis: 3.00 [0.5-18.0]; p<0.001, by Kruskal-Wallis's test complemented by Tukey's test). Fifty-three (53, 89.8%) patients used daily medication, most commonly aminosalicylates (mesalamine and sulfasalazine), and five (8.5%) used low-dose corticosteroids. Most patients were classified as eutrophic according to MAC (84.70%) and TSFt (83%). Few (3.40%) patients were stratified as malnourished, 40.60% as eutrophic and 56% as overweigh/obese, according to BMI.

The values (median [percentile range 25th-75th]) of hemoglobin (13.85 [13.10-14.90] g/dL), albumin (4.40 [3.90-4.50] g/dL), CRP (5.00 [3.00-11.00] mg/L), α1-acid glycoprotein (103.00 [79.00-124.00] mg/dL) and ESR (21.00 [14.00-39.00] mm h^{-1}) were normal according to reference ranges.

Phase angle was directly correlated with hemoglobin values and inversely correlated with acute (CRP) and non-specific (ESR) inflammatory markers (Table 1). Phase angle also was positively correlated with lean mass indicators (MAMC and APMt) (Figures 1A and 1B). Fat mass (FM and TSFt) was directly correlated with acute-phase protein (α1-acid glycoprotein), while lean mass (APMt) was inversely correlated with non-specific inflammation marker (ESR). Additionally, lean mass (MAMC) also was directly correlated with hemoglobin values (Table 1).

Furthermore, acute inflammatory markers were associated with duration of clinical remission and extension of disease. Alfa-1-acid glycoprotein was inversely correlated with remission time (R=-0.23; p<0.05). Subjects with more extensive injury (pancolitis) displayed higher CRP levels (median [percentile range 25th-75th] mg/dL) than those with less extensive lesion (distal colitis) (0.8 [0.4-1.9] > 0.3 [0.2-0.6]; p=0.02, by Kruskal-Wallis's test complemented by Tukey's test).

Logistic regression was used to assess possible association between disease extent and body composition variables. After adjustment for energy, gender, age and CRP, logistic regression analysis showed that BCM was associated with disease extent. There was no association with other parameters (Table 2).

Discussion

The results revealed that body composition parameters, inflammatory markers and disease extent were associated in UC patients. Phase angle was inversely correlated with inflammatory markers such as CRP and ERS and directly correlated with hemoglobin values and lean mass indicators (MAMC and APMt). Logistic regression analysis revealed that body cell mass was associated with disease extent. This is the first time that association among body composition, inflammatory profile and disease extent was studied in UC patients in clinical remission.

Ulcerative colitis is frequently associated with changes in nutritional status. This may vary from only mild alterations in trace elements to severe malnutrition with great weight loss due to the involvement of the gastroin-

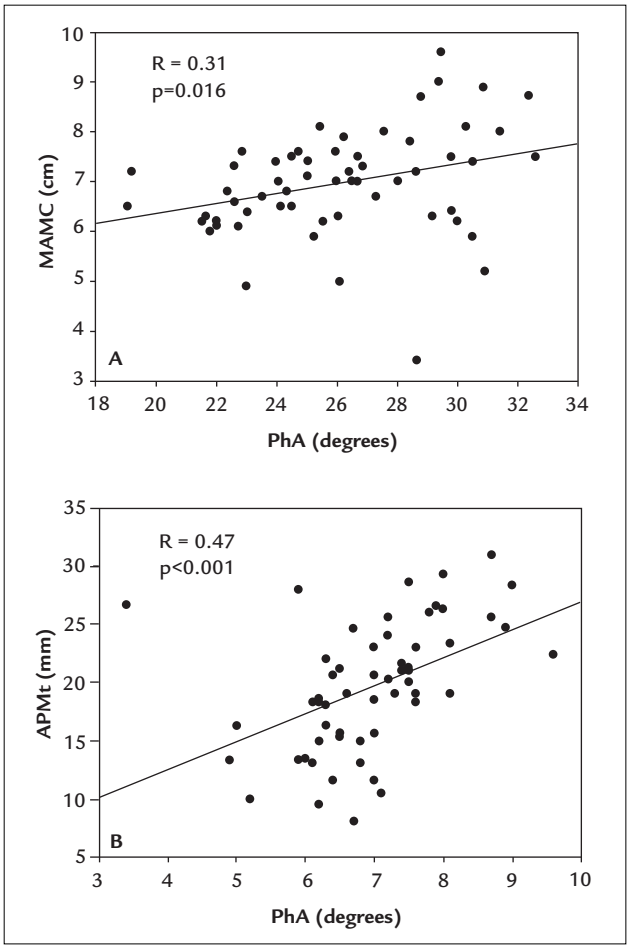

FIGURE 1 Pearson's correlation between phase angle and anthropometric variables. A. PhA versus MAMC. B. PhA versus APMt.
R: Pearson's correlation coefficient; MAMC: mid-arm muscle circumference; APMt: adductor pollicis muscle thickness; PhA: phase angle.

TABLE 1 Correlation between biochemical and body composition parameters in patients with ulcerative colitis.

	BMI	FM	TSFt	MAC	MAMC	APMt	PhA
Hb	0.44	0.01	-0.10	0.21	0.30[3]	0.23	0.49[1]
CRP	-0.008	0.01	0.08	0.90	-0.09	-0.16	-0.59[1]
ESR	0.02	0.12	0.07	0.49	-0.18	-0.40[2]	-0.46[1]
α1-AG	0.36[1]	0.26[2]	0.29[2]	0.25[3]	0.03	-0.02	-0.23[3]

Values represent Pearson's correlation coefficient (R); Hb: hemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; α1-AG: α1-acid glycoprotein; BMI: body mass index; FM: fat mass; TSFt: triceps skin fold thickness; MAC: mid-arm circumference; MAMC: mid-arm muscle circumference; APMt: adductor pollicis muscle thickness; PhA: phase angle; superscript numbers represent statistical significance: [1]p<0.001; [2]p<0.01; [3]p< 0.05.

TABLE 2 Association between body composition variables and disease extent in patients with ulcerative colitis.

Variables	OR	CI	p-value
BMI	0.94	0.84-1.04	0.24
MAC	0.95	0.83-1.08	0.42
TSFt	0.99	0.94-1.05	0.93
MAMC	0.94	0.81-1.09	0.43
APMt	1.01	0.92-1.10	0.74
PhA	1.02	0.65-1.62	0.90
BCM	0.92	0.87-0.97	<0.01

Logistic regression: Data adjusted by sex, age, ingested calories and CRP; OR: odds ratio; CI: 95% confidence interval; BMI: body mass index; MAC: mid-arm circumference; TSFt: triceps skin fold thickness; MAMC: mid-arm muscle circumference; APMt: adductor pollicis muscle thickness; BCM: body cell mass; PhA: phase angle.

testinal tract and its effects on food intake and absorption.[4,22-24] Malnutrition is especially common in active UC patients after long-term hospitalization;[11,25] however, few studies have evaluated the nutritional status in patients with UC during remission.[4,12,26,27] Only one trial found a more compromised nutritional status (body weight and BMI) in UC patients during remission than in a control group.[28] In our study, we identified a low incidence of calorie malnutrition. Most patients had normal levels of fat mass and muscle mass, according to the MAC and TSFt parameters, respectively. Besides, 56% were overweight/obese, according to BMI. The low rate of underweight identified (3.4%) can be partly explained by the remission status of patients, and confirms data shown by other authors.[11,12,28] Most of the patients presented distal colitis in our study; this is not reflective of the general UC population and can be explained by the exclusion of those with moderate-severe disease.

BIA is a method frequently used for body composition measurements and offers advantages such as simplicity, portability, cost and absence of radiation exposure.[29] It is known that PhA and body cell mass (BCM) are good prognosis indicators in several clinical situations.[12,21,30,31] Although the biological meaning is not completely understood, PhA is applied as a surrogate marker for quality of lean body mass[32] and is considered a marker of cell health since high PhA values reflect a strong cell function.[33] Previous studies have shown an association between low values of PhA and BCM with prognosis worsening in patients with hepatitis C and hemodialysis patients.[30,34] However, few studies have approached PhA and BCM in UC.[12,32] It is important to emphasize that the gold standard method for assessing body composition is dual-energy X-ray absorptiometry (DEXA), which allows direct and non-invasive measurement of bone mass, fat-free mass and fat mass. However, DEXA requires skilled personnel, has low affordability, high radiation exposure and is considered a costly examination.[35,36] In addition, studies show good correlation between the parameters of body composition assessed using either BIA or DEXA.[37]

Our study showed that anthropometric and biochemical parameters were correlated with PhA. The lean body mass anthropometric variable (MAMC) currently correlated with PhA has been reported in hemodialysis patients.[34] A direct association between PhA and lean body mass parameter has also been suggested by the positive correlation found between grip strength and PhA in IBD children with mild activity.[32] In addition to the anthropometric indicators, Pearson's correlation analysis revealed that PhA presented inverse correlation with inflammatory markers such as CRP and ESR and direct correlation with hemoglobin, although these markers were in the normal range. Modest CRP changes have been observed in the active UC[38] and the utility of α1-acid glycoprotein, ESR[39] and hemoglobin have been questioned in UC. The lack of studies analyzing the relation between PhA and those markers in UC patients prevents further comparisons.

In the present study, we found that lean mass was inversely correlated with the non-specific inflammation marker (APMt vs. ESR) and directly correlated with hemoglobin values (MAMC vs. hemoglobin). The results indicate a role of inflammatory reactants in the body composition of UC patients. There are few studies evaluating body composition in UC patients[12,28,39-41] and some of them[12,40] included inflammatory variables in the analysis. Examining inactive UC patients, absence of associations was found between inflammatory and body composition variables in two studies[40,42] and decreased BCM in subjects with supranormal CRP values (≥ 8 mg/dL) was identified in one.[12]

The inverse correlation found between α1-acid glycoprotein and remission time has not been reported in UC patients. High serum concentration of α1-acid glycoprotein was associated with high susceptibility to induce colitis in rodents[43] and positively correlated with the risk of relapse in UC patients.[44]

Although the acute phase protein, CRP, has been positively correlated with IBD activity,[10] its association with disease extent in UC patients in clinical remission was presently identified. Remission time was lower in patients with pancolitis (12 months) compared to those with distal colitis (24 months). Therefore higher CRP levels were found in this group. Even though CRP short half-life of 19 h could not support such explanation, a recent study showed that a mean CRP levels of 5.4 mg/L

(normal range) was associated with high histological inflammation scores in patients with ulcerative colitis during clinical remission.[45] Such results raise awareness to the fact that patients in clinical remission from UC still may have inflammation.

It is valid to evaluate the inflammatory profile of IBD patients, even in clinical remission. But it is important to bear in mind that the classification of the disease activity was based on clinical criteria (Truelove and Witts[13]). The best classification of clinical remission is based on a combination of clinical parameters (stool frequency ≤ 3/day with no bleeding) and absence of mucosal lesions at endoscopy.[46] This was not performed in our study, which is a limitation. Because of that, patients could be classified as clinical remission and still present active inflammatory process with changes in inflammatory markers and intestinal inflammation. Besides, inflammatory markers such as CRP and ESR are not specific[47] and may not reflect the intestinal inflammation accurately. On the other hand, fecal markers such as calprotectin and lactoferrin can be considered accurate markers of colonic inflammation.[47]

We also evaluated possible associations between disease extent and body composition variables. High BCM levels were associated with better prognosis and quality of life[12,31] and low BCM levels were associated with supranormal CRP values in UC patients,[12] but studies approaching BCM and disease extent are lacking. After adjustment for confounders (energy, gender, age and CRP), logistic regression analysis revealed that body cell mass was associated with extension of the disease. BCM is a marker for combined visceral and somatic protein deposits. It represents the most metabolically active compartment of the body and catabolic conditions may lead to its reduction.[17] It is plausible that more extensive UC is associated with less protein deposits, as seen in other diseases,[45] and/or related with high catabolic conditions.[17] Considering the results found in our population we might suggest that patients with better lean body mass had a lower susceptibility to the development of more extensive injury.

It is important to emphasize that these patients cannot be considered representative of the population of ulcerative colitis, since they derive from a hospital for individuals in the range of low income and low education. UC disease activity was assessed based on Truelove and Witts criteria, although the Mayo score is preferable. No endoscopic data were available at the time of the study to ascertain disease activity, and disease remission was based on clinical aspects. We do not have fecal calprotectin test available. Other limiting factors should also be mentioned, namely sample size and study design (cross-sectional), as well as the absence of a control group for comparison.

In spite of the limitations above, the outcomes of our study contribute for the expansion of knowledge about the associations of body composition, inflammatory status and disease extension in clinical remission or mild disease activity in patients with ulcerative colitis. These findings are of great importance for clinical practice, since bioelectrical impedance analysis can be considered a simple examination, noninvasive and rapidly implemented. Additionally, the results indicate that some factors could be modified to prevent inflammation and extension of ulcerative colitis. The factors deserving attention include free fat and body cell masses.

Conclusion

Patients with ulcerative colitis in clinical remission do not present impairment of nutritional status according to BMI and BIA parameters. There were associations between body composition, inflammatory profile and disease extent; acute inflammatory markers were inversely correlated with phase angle, duration of remission and directly correlated with fat mass anthropometric indicators and also disease extent. Furthermore, body cell mass was associated with disease extent.

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Associações entre composição corporal, perfil inflamatório e extensão da doença em pacientes com retocolite ulcerativa

Objetivo: Avaliar a composição corporal de pacientes portadores de retocolite ulcerativa em remissão clínica e sua associação com o perfil inflamatório e a extensão da lesão intestinal.

Método: Foi realizado um estudo transversal. Os dados relacionados à composição corporal foram ângulo de fase (AF), massa adiposa (MA), dobra cutânea triciptal (DCT), circunferência do braço (CB), circunferência muscular do

braço (CMB) e espessura do músculo adutor do polegar (EMAP). O perfil inflamatório foi avaliado através da dosagem da proteína-C reativa (PCR), α1-glicoproteína ácida e velocidade de hemossedimentação (VHS) e a extensão da doença foi avaliada de acordo com o exame endoscópico. **Resultados:** Foram avaliados 59 pacientes. A média de idade foi de 48,1 anos e 53,3% eram mulheres. A maioria dos pacientes (94,9%) estava em remissão clínica da doença e 3,4% foi classificada como desnutrida de acordo com o IMC. Observou-se uma correlação inversa entre AF e marcadores inflamatórios como a PCR (R=-0,59; p<0,001) e VHS (R=-0,46; p<0,001) e uma correlação direta entre AF e os indicadores de massa magra como CMB (R=0,31; p=0,01) e EMAP (R=0,47; p<0,001). A massa magra foi inversamente correlacionada com marcadores inflamatórios não específicos, como a VHS, e diretamente correlacionada com a hemoglobina. De acordo com a análise de regressão logística, a massa celular corporal foi associada com extensão da lesão intestinal (OR 0,92; IC95% 0,87-0,97; p<0,01). **Conclusão:** AF foi inversamente correlacionado com marcadores inflamatórios e diretamente correlacionado com a massa magra. Marcadores inflamatórios de fase aguda e massa celular corporal foram correlacionados com extensão da lesão intestinal.

Palavras-chave: Composição Corporal. Colite Ulcerativa. Proteína C-Reativa. Biomarcadores. Índice de Gravidade de Doença.

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Impact of written information on control and adherence in type 2 diabetes

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Summary

Introduction: Diabetes therapeutic education and information by leaflets is important. This study aimed to understand the effectiveness of written information to diabetic patients, after six months, in the control of diabetes and medication adherence.
Method: Non-pharmacological clinical trial. Randomized sample of diabetic patients of 65 volunteer doctors, distributed among the five health regions in Portugal. At the first appointment, patients were randomized in four groups (three intervention with validated leaflets and one control), leaflet reading being reinforced at the follow-up appointments in a 6-months period. Variables collected: HbA_{1c}, home blood glucose, weight, waist circumference, blood pressure, cigarettes smoked, physical activity level, adherence to medication, medication, height, diabetes progression, age, sex and educational background. Descriptive and inferential statistics.
Results: From the 709 patients recruited, 702 were studied in this 6-months period with no statistical differences in the baseline variables studied. After six months of intervention, the adherence to medication improved in the leaflet group (p=0.034). This was noticed in those under 65 years of age (p=0.027), with diabetes for ≤ 5 years (p=0.010), with educational background up to 4 years (p=0.030) and 9 years (p=0.006) and with $HbA_{1c} \geq 7\%$ at the beginning of the study.
Conclusion: Interventions with leaflets handed in primary healthcare to people with diabetes type 2 can bring benefits in what concerns adherence to therapeutics, namely in younger people with a less studies.

Keywords: Diabetes Mellitus. Medication Adherence. Patient Education as Topic.

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Introduction

Diabetes may become one of the leading causes of morbidity and total/partial disability in the 21st century, with an estimated 642 million diabetics by 2040.[1]

Good glycemic control in diabetes is essential for retarding microvascular and neuropathic complications and, if initiated in time, macrovascular complications as well.[2-9] In diabetes, decreasing blood pressure values decreases mortality, the risk of cardiovascular events, albuminuria and retinopathy.[5,10,11] Other cardiovascular risk factors with an impact on mortality include dyslipidemia[12] and smoking habits, with an NNT of 11 to 10 years in reducing mortality.[13]

It is known that many people with diabetes do not achieve the goals recommended for controlling their disease.[14-16] Following health professionals' recommendations[17,18] and patients' adherence to pharmacological measures,[19,20] as well as their lifestyles,[21-23] are far from desirable.

A structured educational intervention appears to be beneficial to people with diabetes in the short term in improving not only their knowledge, but also markers such as glycated hemoglobin (HbA_{1c}),[24,25] blood pressure, and blood lipids.[26,27] Interventions targeted at multiple behaviors and done in primary health care seem to be promising.[28] Leaflet intervention seems to have a positive effect on knowledge,[29-31] adherence to treatment in short-term treatments[32] and physician-person communication, leading to greater shared discussion.[33]

There are few published studies on written information given to people with diabetes, particularly in primary care. Those that do exist refer to improvement in HbA_{1c} levels,[34-37] postprandial glycemia[38] and adherence to treatment.[39]

We thus carried out this study to evaluate the effectiveness of the information given to the person with diabetes by means of leaflets and compare the results with those of a control group that only received the usual advice given during medical visits. Our objective was also to check whether there are differences among leaflets about diabetes, its treatment and the importance of physical activity in controlling the disease. We also sought to determine if the impact of the intervention was anyhow influenced by gender, age, academic background, diabetes progression time and initial control of HbA_{1c}.

Method

Non-pharmacological clinical trial conducted as a prospective, randomized, controlled, non-blind and multicenter study with type 2 diabetes patients receiving primary care. Those who agreed to participate were included if they could read or had someone in the household who could read the leaflet to them. Persons who already had a relative or coinhabitant participating in the study, those under 18, pregnant, bedridden or wheelchair-bound, and all those with a diagnosis of depression were excluded.

The sample size calculation (n=1,170) was based on a previous study done in the central region of Portugal,[40] with significance level [α] = 0.05, [β] = 0.20, study power 1 - [β] = 0.80 (n = 175 for each group), including a 10% margin for dropouts. The sample consisted of the first 18 people with type 2 diabetes who had a consultation with their general practitioner (family physician), as from October 15, 2014. The individuals were randomized according to their order of arrival by using random numbers generated by computer software in four groups: 585 sample units were given a validated leaflet (195 on diabetes, 195 on diabetes treatment, 195 on the importance of physical activity in diabetes management), and the other 585 were not given any of the leaflets and received the usual care.

General practitioners were invited over social media. Voluntaries were accepted until they reached 65 doctors from continental Portugal, distributed across the five areas (25 in the North, 11 in the Center, 23 in Lisbon and Vale do Tejo, three in Alentejo, and three others in Algarve).

The intervention was done at the first visit: the leaflet was delivered and the person receiving it was asked to read it or to have someone else read it to them at home. They were asked to try and understand the information contained therein. At each subsequent visit, the request for reading the brochure was reinforced and any queries were answered.

The variables collected throughout the visits were: HbA_{1c} (%), capillary glycemia was recorded in the outpatient clinic over the past four months both while fasting and in the postprandial period – the readings were then classified as controlled (all those within the 70-130 mg/dL were classified as fasting and all others < 180mg /dL as postprandial) or uncontrolled; weight (kg); abdominal perimeter along the iliac crests in the horizontal position (AP, cm); blood pressure (BP, mmHg); smoking habits (number of cigarettes/day); physical activity (PACE instrument scale, validated in Portuguese);[41] adherence to the pharmacological treatment of diabetes (MAT scale, validated in Portuguese,[42] consisting of seven questions 1-6, with the total score of 42 corresponding to maximum adherence); medications for diabetes and high blood pressure; insulin medication; reading of the leaflet. The variables collected at the beginning and end were: height (meters), diabetes progression time (years), age (years), sex, education (number of school years).

The leaflets were previously validated following content development according to the existing recommendations,[43,44] reviewed by 14 scientific experts and one Portuguese-language expert. Subsequently, they were qualitatively evaluated by ten people with type 2 diabetes having different levels of education.

Statistical analysis was performed with the purpose of analyzing the impact of six months following the intervention: we compared the beginning-end differences between the intervention and control groups, by using the Mann-Whitney U test, and among the various groups of leaflets, by using the Kruskal-Wallis test. We performed the same analysis of the intervention's impact at the six months across subgroups by sex, age, level of schooling, diabetes duration, and initial HbA_{1c} levels. The significance level we adopted in all tests was 0.05.

A text about the study was previously made available to each participant user, whose informed consent was requested in writing. We then gave them two copies of the form, one of which we requested in return once the participants had signed it. Our study received a positive opinion from the ethics committees of Faculdade de Medicina at Universidade de Coimbra, from continental Portugal's Regional Health Administrations (Administrações Regionais de Saúde, ARS) and from the National Commission on Data Protection (Comissão Nacional de Proteção de Dados).

Results

Initial sample

The initial sample consisted of 709 people with diabetes recruited by 41 general practitioners throughout Portugal. In it, 60.2% of the people were males, the average age was

66.12 ± 10.47 years, and the mean number of school years was 6.26 ± 3.90, whereas 1.7% were illiterate. They had had diabetes for 9.25 ± 7.83 years on average, 13.0% were insulin-treated, the mean HbA_{1c} was 6.79% ± 1.04%, and 65.7% had a controlled disease (HbA_{1c} < 7%). There were no outpatient records for glycemia in 41.6% of participants while fasting versus 52% of them postprandially. Total adherence to treatment was found in 34.4% of them (42 points on the MAT scale),[42] with 90% adhering to medication (value ≥ 5).[45-47] Blood pressure was controlled (BP < 140/90) in 54.6% of participants, the mean BMI was 29.39 ± 4.87 kg/m², BP was high in 88.3% of females and 72.1% of males. Relative to their lifestyle, 71.1% reported practicing physical activity, 26.2% of them five or more times per week, 10.6% were smokers with an average of 16.39 ± 10.11 cigarettes/day.

Intervention

Of the 709 people recruited, follow-up of 702 continued up to six months (Figure 1). There were no significant differences between the initial and final samples, as well as no differences between the intervention and control groups, across groups according to the type of leaflet distributed (p=0.991) or among those who reported either having read the leaflet at home or not (p=0.691).

Comparing the intervention group with the control group, after six months, we found a significant improvement in adherence to treatment (p=0.034), as shown in Table 1. There were no significant differences between the variables at the beginning and end across the various groups of leaflets.

Complementary analysis

We repeated the analysis including only those who reported having read the leaflets and the results were similar across groups for changes in antidiabetic and antihypertensive medication.

In the subgroup analysis, we found improvement in adherence to treatment in the intervention group: in the

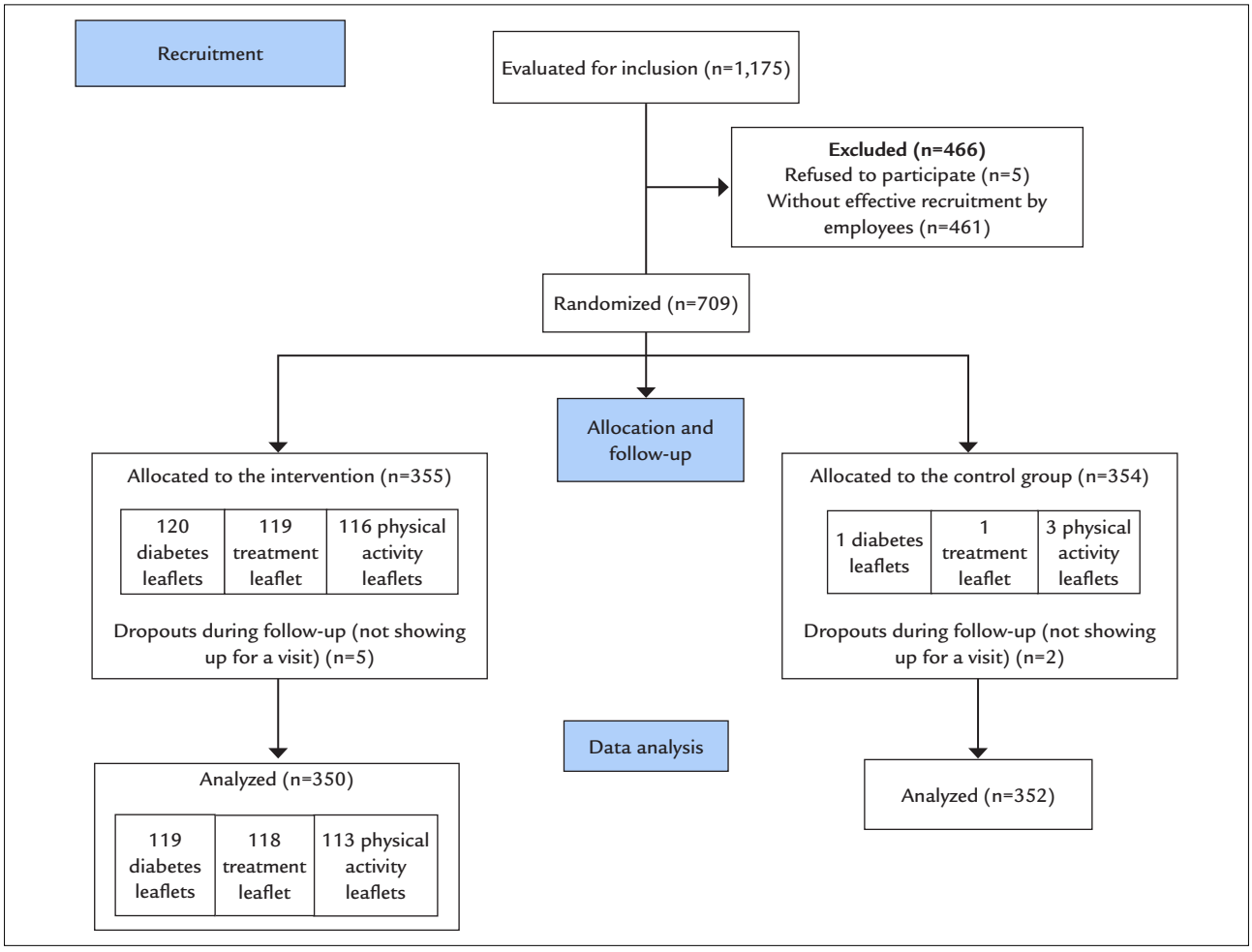

FIGURE 1 CONSORT diagram used to the study.

TABLE 1 Mean±SD and percentage of variables in the control and intervention groups at the beginning of the study and six months later, and results from the comparison of the beginning-end differences between the two groups.

Variable	Time	Control group	Intervention group	Total	n	p*
HbA_{1c} (%)	Baseline	6.74±0.97	6.85±1.10	6.79±1.04	633	0.898
	Final	6.84±1.04	6.85±0.99	6.85±1.02		
Systolic BP (mmHg)	Baseline	137.41±17.09	136.77±15.83	137.09±16.47	693	0.078
	Final	134.75±16.02	136.29±17.16	135.51±16.60		
Diastolic BP (mmHg)	Baseline	76.50±10.90	76.60±10.31	76.55±10.61	689	0.522
	Final	75.43±10.81	76.22±10.42	75.83±10.61		
BMI (kg/m^2)	Baseline	29.50±4.75	29.25±5.00	29.37±4.88	686	0.627
	Final	29.31±4.79	29.14±4.94	29.23±4.86		
Abdominal perimeter (cm)	Baseline	102.89±11.29	102.30±11.67	102.60±11.47	563	0.783
	Final	102.48±11.97	101.84±11.75	102.16±11.85		
Treatment adherence	Baseline	39.80±2.76	39.63±2.92	39.72±2.84	608	0.034
	Final	40.22±2.63	40.22±2.47	40.22±2.56		
Physical activity	Baseline	3.43±1.67	3.59±1.69	3.51±1.68	654	0.943
	Final	3.31±1.55	3.57±1.71	3.44±1.63		
Controlled outpatient fasting blood glucose	Baseline	45.5%	41.8%	43.8%	409	0.482
	Final	46.9%	45.1%	46%	389	
Controlled outpatient post-prandial blood glucose	Baseline	40.3%	34%	37.3%	335	0.270
	Final	40.8%	42.3%	41.5%	337	
Number of cigarettes/day (smokers only)	Baseline	15.92±9.47	16.64±10.83	16.33±10.183	54	0.739
	Final	14.09±11.07	13.74±12.15	13.89±11.60		

*Mann-Whitney U test (for non-normal distribution).
HbA_{1c}: glycated hemoglobin (HbA_{1c}); BMI: body mass index; BP: blood pressure.

population under 65 years of age (p=0.027), in the population having up to four school years and also in those with up to nine years of formal education (p=0.030 and p=0.006, respectively). We also observed this improvement in participants who had had diabetes for ≤ 5 years (p=0.010), but not in the other diabetes duration subgroups nor in those with uncontrolled HbA_{1c} at the beginning of the study (HbA_{1c} ≥ 7%) (p=0.008).

Systolic blood pressure decreased more notably in the control group (p=0.046). The same observation applies to the individuals who had had DM2 for ≤ 5 years and ≤ 7 years (p=0.025 and p=0.018, respectively) and also in those with controlled HbA_{1c} (< 7%) at the beginning of the study (p=0.046).

Among leaflets, as shown in Table 2, we found differences among participants with up to nine years of formal education, whose adherence to treatment improved upon receiving the leaflets about the disease compared to others (p=0.023). In people with more than nine years of formal education, postprandial capillary glycemia results progressed more positively among outpatient participants than it did among those who received the leaflet about physical activity leaflet (p=0.023).

Discussion

One of our study's limitations is interobserver bias, as there were 41 investigators involved in taking measurements, using scales and administering the intervention. An attempt to minimize this was made by means of on-site face-to-face meetings and detailed written instructions. The choice of variables was limited, and no other sociodemographic or risk factors were included. Neither were factors that could characterize the participants' dietary and nutritional habits, diabetes complications, polypharmacy or multimorbidity that could influence adherence to treatment and control of the disease so as to avoid work overload among investigators, who contributed to our study as volunteers. Still, there were many who did not report recruitment data, as there were also participants with diabetes who did not show up for a visit. All things being considered, at the end of six months, we obtained only 60% of the initially calculated sample.

The study is performance-biased due to its non-blinded method, which is inherent in a non-pharmacological clinical trial with educational intervention in the real world. The control group itself always receives some sort of educational intervention (it would be unethical if it

TABLE 2 Differences across the various groups of leaflets under analysis of subgroups of people having more than or fewer than nine years of formal education at the beginning of the study and at six months.

Variable	Time	Control group	Diabetes leaflet group	Treatment leaflet group	Physical activity leaflet group	Total	n	p* (among groups)
Treatment adherence	Baseline	39.84±2.60	39.72±2.77	39.53±2.76	39.86±2.60	39.78±2.65	497	0.023
(≤ 9 years of formal education)	Final	40.18±2.49	40.23±2.47	40.29±2.29	40.28±2.22	40.22±2.41		
Controlled outpatient	Baseline	26.7%	33.3%	66.7%	14.3%	34.5%	53	0.023
post-prandial blood glucose	Final	35.7%	33.3%	45.5%	57.1%	40%		
(> 9 years of formal education)								

*Kruskal-Wallis test (for non-normal distribution).

did not), even if such intervention is not structured exactly the same way. This consequently limits the magnitude of the results and the drawing of conclusions.[48,49] In addition, the study was carried out during a period of six months of observation only, which therefore prevents any assessments of the consequences diabetes has on health.

This methodology led to losses as far as control of variables was concerned, but allowed for gains in perceiving the applicability of the intervention. It was a simple and replicable intervention, as recommended elsewhere in the literature,[26,28,50] of low intensity and medium duration, and is more likely to have an impact on the health of populations.[51] On the other hand, more complex or group interventions, in turn, imply more motivated people failing to reach the general population.[52,53]

This was the first national clinical trial in primary health care to be conducted in Portugal and, although the sample did not have the desired size at six months, the groups did have a distribution with no significant differences, which increases the power of the conclusions we can draw.

Intervention results

Six months after intervention, adherence to pharmacological therapy improved significantly in the leaflet group (p=0.034). Other studies, analyzing the impact of written information given out to people with diabetes on adherence pharmacological treatment at three months, also showed improvements.[37,39,54] A review by Cochrane[32] also states that written information is useful in short-term treatments. It would be presumably logical that these results implied improvement in glycemic control.[15,55-60] In our study, glycemic control worsened in the control group (from 6.74% to 6.84% HbA_{1c}), whereas it remained unchanged in the intervention group (mean 6.85%), but without any difference (p=0.888). This was also observed in other studies.[61] We are left to wonder what the level of adherence to be achieved will be in order to improve metabolic control and to what extent other factors may have influenced this control, such as adherence to physical activity (which worsened over six months) or to diet (which has not been studied). These are some of the questions that should still be resolved. It is known that, regardless of metabolic control, nonadherence to medication seems to have more micro- and macrovascular complications,[62] as well as increased risk of hospitalization and death.[52,62-65] Thus, it is important to consider interventions such as this one in populations like younger people, with diabetes for a shorter period of time, with less formal education, and with uncontrolled HbA_{1c}.

The fact that older people did not experience an improvement can be explained by multimorbidity and chronic polypharmacy and less literacy. The leaflet on treatment appeared to be specifically more beneficial for people with less schooling. Among people with more schooling, in turn, the leaflet on physical activity was the one with the greatest impact on postprandial glycemias, which were shown to be more related to the complications from diabetes and cardiovascular mortality than were HbA_{1c} and fasting glycemia.[66] In addition, physical exercise proved to specifically and effectively decrease postprandial glycemias.[67] This difference in impact on people with more schooling may be due to a greater ease in perceiving the relation between exercise and postprandial glycemia.

As limiting factors of more robust results, we can mention the low level of literacy,[68,69] even though we do not yet know which type of intervention would be the most beneficial to the Portuguese population.[70,71] The use of written materials seems to improve literacy and health behaviors.[72] In order to analyze the results, it is not necessary to neglect the fact that the intervention was done by the general practitioner who is already familiar to the person with diabetes and with whom he or she has an established relationship. It is known that educational interventions, when made by a single person, seem to yield better results. There are studies showing that there is no relation between knowledge and better metabolic

control[73-75] in diabetes. Nevertheless, educational interventions are related to this control,[52] which suggests that there is more to influencing this variable than solely transmitted knowledge.[24,25]

The leaflets' lack of customization to the needs of each person[76,77] and the short contact time between educator and the person with diabetes (because the leaflet was read at home) may have led to lesser efficacy of the intervention.[24] There also appears to be greater effectiveness of educational interventions when these are more often repeated over time, at short intervals.[49,78] Accordingly, the fact that the leaflets were delivered only at the beginning of our study may have triggered a poorer effect on its potential benefit.

It will be important to conduct longer follow-up studies to perceive the impact of educational interventions on morbidity and mortality and also studies with more frequent and ongoing interventions that can help identify the most effective type of intervention in populations with low health literacy.

Conclusion

Written information given to people with diabetes by their general practitioner did not have a statistically significant impact on metabolic control. However, it did increase adherence to pharmacological treatment six months later compared to usual counseling given at the visits (p=0.034).

We found differences among people with diabetes who received the various leaflets and also in those individuals with up to nine years of formal education. Improvement in adherence to treatment was significantly greater in those who received the leaflet (p=0.023).

In those with more than nine years of formal education, the outpatient postprandial glycemias were better than in those who received leaflets on physical activity (p=0.023). Leaflet impact was influenced by age, academic background, duration of diabetes, and glycemic control at the beginning of the study. It improved adherence to treatment in people younger than 65 years (p=0.027), who had had diabetes for five years or less (p=0.010), with up to four (p=0.030) and up to nine years of formal education (p=0.006), and with $HbA_{1c} \geq 7\%$ at the beginning of the study (p=0.008).

In Portugal, it will be interesting to have validated leaflets to be distributed by health professionals during the follow-up visits to this population.

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Resumo

Impacto da informação escrita no controle e adesão na diabetes tipo 2

Introdução: A educação terapêutica e a informação dada à pessoa com diabetes parece ser importante nesta doença de prevalência crescente. Estudar a efetividade da informação escrita dada ao utente diabético, após 6 meses, no controle e na adesão terapêutica.

Método: Ensaio clínico não farmacológico. Amostra aleatorizada de diabéticos de 65 médicos de família voluntários, distribuídos pelas cinco regiões de Portugal continental. Na primeira consulta, as pessoas foram aleatorizadas (em grupos de intervenção com folhetos validados e grupo controle) e foi reforçada a leitura do folheto nas consultas de seguimento até 6 meses. Foram recolhidas as seguintes informações: HbA_{1c}, glicemias em domicílio, peso, altura, perímetro abdominal, pressão arterial, cigarros fumados, atividade física praticada, adesão terapêutica, medicamentos tomados, tempo de evolução da diabetes, idade, sexo e educação. Estatística descritiva e inferencial.

Resultados: Das 709 pessoas recrutadas, foram estudadas 702, sem diferenças significativas para as variáveis epidemiológicas medidas. Aos seis meses da intervenção, a adesão à terapêutica farmacológica melhorou mais no grupo que recebeu folheto (p=0,034), nas pessoas com menos de 65 anos (p=0,027), com diabetes há cinco anos ou menos (p=0,010), com formação de até quatro anos (p=0,030) e até nove anos (p=0,006) e com a $HbA_{1c} \geq 7\%$ no início do estudo (p=0,008).

Conclusão: Folhetos dados nos cuidados de saúde primários a pessoas com diabetes tipo 2 podem beneficiar a

adesão terapêutica a curto prazo, nomeadamente em pessoas mais novas e com menor formação.

Palavras-chave: Diabetes Mellitus. Adesão à Medicação. Educação de Pacientes como Assunto.

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Assessing cardiovascular risk in ATM heterozygotes

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Summary

Objective: To evaluate the carotid intima-media complex (CIMC) thickness and lipid metabolism biomarkers associated with cardiovascular risk (CR) in parents of patients with ataxia-telangiectasia and verify an association with gender.
Method: A cross-sectional and controlled study with 29 ATM heterozygotes and 14 healthy controls. Biochemical tests and CIMC thickness measurement were performed.
Results: The mean CIMC measurement in heterozygous ATM was 0.72 ± 0.1 mm (minimum: 0.5 mm and maximum: 1.0 mm). Noticed high percentage of amounts above 75 percentile compared to the population referential (16 [76.2%]), without any significant statistical differences between the female and the male gender (11/15 [73.3%] vs. 5/6 [83.3%]; p=0.550). The comparison between heterozygous and controls, stratified by gender, showed that in heterozygous ATMs, women had higher concentrations of HDL-c compared to men, as well as higher values of hs-CRP in relation to the control women. In heterozygous ATMs, stratified by gender, the correlation between HDL-c and hs-CRP was inversely proportional and stronger among women, with a tendency to statistical significance.
Conclusion: Heterozygous ATMs did not differ from controls in relation to the biomarkers studied related to CR. However, most of them presented increased CIMC, independent predictor of death, risk for myocardial infarction and stroke, compared to the referential for the same age group. This finding suggests CR in the heterozygous ATM and shows to the need to monitor CIMC thickness and nutritional orientations.

Keywords: Ataxia Telangiectasia. Atherosclerosis. Carotid Intima-Media Thickness. Insulin Resistance. Heterozygote.

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Introduction

Ataxia-telangiectasia (A-T) is a rare autosomal recessive syndrome that affects 1:40,000 live births in the United States.[1] The classic symptoms, which gave rise to the name for the disorder, are ataxia (loss of motor coordination – onset in early childhood) and telangiectasias (venous capillaries dilated in the corners of the eyes and skin, occurring around 4-6 years of age).[2]

Caused by mutations of the *ATM* gene (ataxia telangiectasia mutated),[3,4] which is encoded on chromosome 11q22-23, the protein associated with this gene is composed of 3,056 amino acids, belongs to the PIKK (phosphatidylinositol 3-kinase-related kinases) superfamily,[4] and is involved in DNA damage-response regulation.[2,5]

The ATM protein follows several molecular events. Its absence or failure induces the collapse of several mechanisms related to the development of disorders, including cardiovascular (CV) diseases. These mechanisms are described in the literature by means of experimental studies[6-14] and, more recently, by virtue of increased patient survival in studies with humans.[15] The mechanisms involved in CV risk associated with ATM failure entail increased c-jun

N-terminal kinase (JNK, related to metabolic syndrome), insulin resistance, dyslipidemia, angiogenesis, myocyte apoptosis and oxidative stress.[6,8-13,16]

ATM heterozygotes, who carry a mutant allele to the A-T locus, account for from 1.4 to 2% of the population.[1,17] A systematic review and a recent meta-analysis showed that first-degree relatives, parents and grandparents of A-T patients have an increased risk of ischemic heart disease.[18]

A retrospective controlled cohort study was conducted over 28 years with grandparents of A-T patients, i.e. individuals having the mutation, with the purpose of describing mortality rates. A total of 405 grandparents (204 ATM heterozygotes, as assessed by genotyping, and 201 controls) were included. Compared to controls, ATM heterozygotes had a significantly higher risk of death (between 20 and 79 years RR 1.9, 95CI 1.3-2.8, p<0.001). On average, death occurred 7 to 8 years earlier among ATM heterozygotes. The relative risk of death from cancer and ischemic heart disease before age 80 was 2.6 (95CI 1.4-4.7, p=0.002) and 2.0 (95CI 1-4, p=0.062), respectively. With respect to ischemic heart disease, death among ATM heterozygotes occurred 11 years earlier than in the control group (p=0.006), which was not observed for cancer.[19]

Studies describing CV risk mechanisms in A-T carriers[20] and ATM heterozygotes,[8,12,13,15] conducted either in humans or involving animal experimentation — as well as the scarcity of studies identifying such risk by biochemical and imaging techniques — highlight the need to expand research in this field. The aim of our study was to describe the carotid intima-media complex (CIMC) thickness and lipid metabolism biomarkers associated with CV risk and then to check whether there is an association with gender.

Method

A prospective, controlled cross-sectional study evaluated 29 fathers and mothers of patients clinically diagnosed with A-T (herein referred to as ATM heterozygotes). The control group consisted of 14 age/sex-matched healthy volunteers.

The inclusion criteria for the parents were: having offspring diagnosed with A-T in accordance with the PAGID-ESID criteria[21,22] and consenting to participate in the study. The inclusion criteria for the control group were: consenting to participate in the study, being eutrophic and a non-smoker. The exclusion criterion for both groups was not meeting the abovementioned inclusion criteria.

The study was approved by the Research Ethics Committee of UNIFESP-EPM (No. 921407/2014), and all participants signed a free informed consent form.

Demographic and clinical data were collected by means of a standardized questionnaire. The level of physical activity was assessed by a short version of the International Physical Activity Questionnarie (IPAQ). The individual CV risk was assessed based on the Framingham score.[23]

The anthropometric evaluation was based on weight, height, skin folds (tricipital, subscapular, bicipital, and supra-iliac skin folds), and circumferences (neck, abdominal, and brachial). Neck circumference (NC) measurements were taken and classified according to Ben-Noun et al.[24,25] The waist-to-height ratio (WhR) was used as a marker of risk for coronary disease.[26] Food consumption was obtained with the aid of a 24-hour food recall (R24hs).[27]

The following biochemical markers were used: total cholesterol and fractions, triglycerides, fasting glycemia, AST, ALT, GGT, us-CRP, IL-6, PON1, Apo A-I and Apo B. The TC/HDL-c, LDL-c/HDL-c, and Apo B/Apo A-I ratios were calculated.[28,29]

A single examiner took all CIMC thickness measurements, and only from ATM heterozygotes. We used a Medison Accuvix V10 unit with a high-frequency linear transducer (6-12 MHz) and adjusted its focal area to the area of interest (posterior wall of the common carotid artery) and its gain so as to avoid artifacts inside the vessel and yield a 4x magnification. The cutoff point we adopted for percentile classification was an adapted table from the CAPS Study, by age group and gender.[30]

We then entered and consolidated the data in Excel® Office spreadsheets. For the analysis, we used the SPSS 24.0 (IBM®) statistical package. Categorical variables were presented as total numbers (%) and compared using the Chi-squared test or Fisher's exact test. Continuous variables were tested for their normality. Parameters were presented as mean±standard deviation and non-parametric as median (interquartile range). Because they are not parametric, triglycerides, interleukin-6 and Apo-B values were submitted to the logarithmic transformation for analysis. For bivariate comparison, we used Student's t-test and ANOVA for two or more stations, respectively. In order to evaluate the association between us-CRP and HDL-c, we used Pearson's correlation. For multivariate analysis involving BMI, us-CRP and gender, in turn, we used logistic binary regression, enter method. We adopted a significance level of 5%.

Results

The general traits found in the ATM heterozygote and control groups can be seen in Table 1. We can observe that there was no difference between the groups in terms of age (41.0±9.3 years versus 43.3±8.9 years, p=0.420), gender and years of formal education (Table 1).

No serious CV events, such as acute myocardial infarction or stroke in the family, were reported in either group. Other previous conditions preceding CVDs (dyslipidemia, obesity, HBP and diabetes) were cited by 16 (55%) and eight (57.1%) participants in the ATM heterozygote and control groups (p=0.583), respectively (Table 1). The smoking frequency and level of physical activity were similar between both groups (Table 1). Only two women in each group reported having reached menopause.

Dietary intake did not differ between groups for any of the items evaluated: total energy (2,031.0±718.6 kcal versus 2,210.5±627.2 kcal, p=0.449), protein % (15.9±3.9 versus 17.3±3.4, p=0.180), carbohydrate % (45.9±11.0 versus 44.9±8.4, p=0.787), fiber (20.5±10.5 g versus 24.1±17.2 g, p=0.680), cholesterol (296.8±55.8 versus 316.3±40.1 mg, p=0.320), total fat % (31.8±9.0 versus 37.7±7.8, p=0.245), saturated fat % (4.5±0.7 versus 4.7±0.9, p=0.418), monounsaturated fat % (2.3±0.4 versus 2.1±0.5, p=0.796) or polyunsaturated fat % (2.0±0.3 versus 2.8±0.9, p=0.329).

Mean CIMC measure in the ATM heterozygote group was 0.72±0.1 mm (minimum: 0.5 mm and maximum: 1.0 mm). We found a high percentage of values above the 75th percentile in comparison to the population reference (16 [76.2%]), with no statistically significant difference between females and males (11/15 [73.3%] versus 5/6 [83.3%]; p=0.550).

We found no difference between the ATM heterozygote and the controls while comparing the variables in a categorized manner with respect to nutritional status and body composition (Table 1). With regard to CVD risk factors, only HBP showed a trend to be more frequent in the ATM heterozygote group (62.0% versus 28.6%, p=0.055). We observed no differences regarding changes in lipid profile, fasting glycemia and MetS (Table 1).

TABLE 1 General characteristics of ATM heterozygotes and controls.

Variable		ATM H group (n=29)	Control group (n=14)	p-value
Sex	Female	21 (72.4%)	9 (64.3%)	0.726
Education	> 4 years	22 (24.1%)	12 (14.3%)	0.693
Family history	CVD	16 (55.2%)	8 (57.1%)	0.583
Use of oral contraceptives		4 (19.9%)	4 (44.4%)	0.195
Use of alcohol	Social	17 (70.8%)	7 (29.2%)	0.745
Smoking habit	Yes	3 (10.3%)	0 (0.0%)	0.539
Physical activity	Very active	8 (27.6%)	4 (28.6%)	0.615
	Active	15 (51.7%)	7 (50.0%)	
	Irregularly active A	3 (10.3%)	1 (7.1%)	
	Irregularly active B	1 (3.4%)	2 (15.3%)	
	Sedentary	2 (6.9%)	0 (0.0%)	
BMI	> 30 kg/m²	5 (17.2%)	0 (0.0%)	0.156
Abdominal circumference	> 0.5 cm/cm	19 (65.6%)	5 (35.7%)	0.102
Fat percentage	High	23 (79.3%)	10 (71.4%)	0.704
Neck circumference	High	10 (34.5%)	1 (7.1%)	0.071
Blood pressure	High	18 (62.1%)	4 (28.6%)	0.055
Total cholesterol	Inadequate	15 (51.7%)	6 (42.9%)	0.747
LDL-c	Inadequate	13 (44.8%)	5 (35.7%)	0.744
HDL-c	Low	4 (13.8%)	2 (14.3%)	0.649
Triglycerides	Inadequate	1 (3.6%)	2 (14.3%)	0.254
Non HDL-c	Inadequate	11 (37.9%)	3 (21.4%)	0.324
Apolipoprotein B	Inadequate	17 (60.7%)	12 (85.7%)	0.159
Fasting blood glucose	> 100 mg/dL	3 (10.7%)	1 (7.1%)	0.593
us-CRP	Increased	9 (32.1%)	1 (7.1%)	0.125
Metabolic syndrome	Yes	3 (10.7%)	1 (7.1%)	0.607

Level of significance of the Chi-square test or Fisher's exact test (p<0.05).
CVD: cardiovascular disease; BMI: body mass index; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; us-CRP: ultra-sensitive C-reactive protein.

Laboratory test results and anthropometric variables referring to bodily condition were also compared in a continuous fashion between groups. In the bivariate analysis, we found us-CRP to be higher in the ATM heterozygote group (2.24±2.30 versus 1.11±0.97 mg/dL, p=0.015). However, this difference did not hold in the multivariate analysis when we adjusted us-CRP values for BMI and gender (OR = 1.646, 95CI 0.75-3.62, p=0.214) (Table 2).

A comparison between both groups, stratified by gender, showed that females in the ATM heterozygote group had higher concentrations of HDL-c compared to men in the same group and higher values of us-CRP in women in the control group. The other laboratory variables and BMI did not show a statistically significant difference relative to gender.

In the ATM heterozygote group, stratified by gender, the correlation between HDL-c and us-CRP was inversely proportional and stronger among women, with a tendency to statistical significance (r = -0.318; p=0.083) (Chart 1).

TABLE 2 Odds ratio of ultra-sensitive C-reactive protein in the ATM heterozygote group adjusted for body mass index and gender.

Variable	B	β	95CI	p-value
us-CRP (mg/dL)	0.499	1.646	0.75-3.62	0.214
BMI (kg/m²)	0.459	1.583	1.11-2.25	0.011
Gender (female)	1.048	2.851	0.44-17.45	0.285
Age (years)	0.004	1.004	0.91-1.10	0.934

Variables in the model: BMI (kg/m²), age (years) and gender (p<0.05).
us-CRP: ultra-sensitive C-reactive protein.

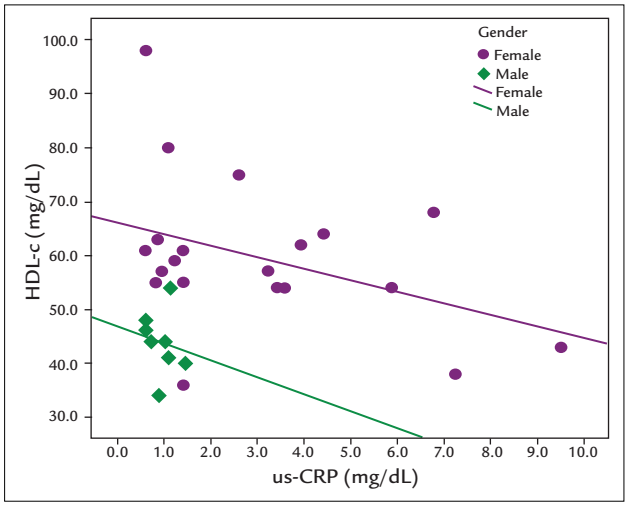

CHART 1 Correlation of HDL-c and us-CRP in the heterozygous ATM group by gender.

*Pearson's correlation (HDL-c and us-CRP)
Females (r = -0.397; p=0.083)
Males (r = -0.160; p=0.704)

Discussion

Our study was pioneer in analyzing CV risk based on the increase in CIMC thickness in heterozygous carriers of the ATM mutation. Specifically in females, there was also an increase in us-CRP compared to females in the control group. HDL-c concentrations were higher in females as compared to males.

A greater CIMC thickening was observed for both genders and was mostly classified as equal to or above the 75th percentile according to the reference value proposed by Lorenz et al. This indicates the existence of subclinical carotid atherosclerosis in this population.[30] A meta-analysis encompassing 15 studies showed that a 0.1-mm increase in CIMC was predictive of myocardial infarction (RR 1.15, 95CI 1.12-1.17) and stroke (RR 1.17, 95CI 1.16-1.21). A cohort of eight population-based studies (n = 37,197) with a follow-up of approximately five years demonstrated that a difference of only 0.1 mm in CIMC could increase the risk of myocardial infarction by 10% to 15% and stroke by 13% to 18%.[31] A study involving 3,067 participants from six cohorts showed that the increase in CIMC was positively associated with the risk of first infarction or stroke in individuals younger than 45 years, thus validating the use of this measurement in identifying risk, even in individuals whose age was similar to that which we studied.[32] A recent review article emphasizes the importance of the CIMC ultrasound evaluation procedure in identifying risk and as a means for predicting CV events.[33]

Some authors suggest that patients with the ATM mutation are at a high risk of diseases such as neoplasms and acute myocardial infarction.[19,34-37] A systematic review and recent meta-analysis concluded that there is no need to screen heterozygous carriers of the ATM mutation any differently than the general population for assessing CV risk. Still, it proposes that counseling towards healthy eating habits and lifestyle should be reinforced in that group.[18] The first publication addressing mortality from ischemic heart diseases in ATM heterozygotes dates from 1983.[38] Subsequently, other studies suggested a higher susceptibility to coronary atherosclerosis, MS and hypercholesterolemia.[8,12] Reduced MIRNI25B concentrations found in ATM heterozygotes resulting in overexpression of the CV susceptibility TNFS4 gene might be a possible causal explanation for this association.[15] In addition, studies with experimental animals have shown that ATM deficiency induces structural and functional changes following myocardial infarction, suggesting problems in remodeling, inflammation and apoptosis following ischemic events.[13]

A study conducted with grandparents of A-T patients undergoing genotyping in order to investigate the mutation showed an increase in the risk of death compared to

individuals from the same family not carrying the mutation. Compared to non-carriers, death from ischemic heart disease occurred 11 years earlier in carriers.[19]

The heterozygous ATM females in our study had higher us-CRP concentrations compared to the controls. Neutrophils isolated from A-T patients produce a greater amount of proinflammatory cytokines, which is an effect that can be partially explained by the increase in activation in p38MAP kinase.[39]

The association between increased CIMC and lower HDL-c concentrations suggests an even higher CV risk in male ATM heterozygotes. An observational cohort study (CANHEART – Cardiovascular Health in Ambulatory Care Research Team) of 631,762 Canadian individuals, mean age 57.2 years, reported that low HDL-c concentrations were associated with the risk of death from CVD in an independent fashion when compared to individuals with adequate HDL-c levels.[40] HDL-c can be converted from an anti-inflammatory particle to a pro-inflammatory particle in acute-phase situations of the inflammatory response. In this situation, HDL-c loses its antiatherogenic properties, becoming dysfunctional. Proinflammatory HDL particles are characterized by altered protein composition, namely increased levels of ceruloplasmin and serum amyloid A and reduced levels of Apo AI, paraoxonase and acetyl hydrolase PAF-AH (plasma platelet activating factor-acetylhydrolase).[41] Oxidative stress and inflammation (mechanisms accompanying ATM failure or absence) may contribute to the presence of dysfunctional HDL in ATM heterozygotes.

A study conducted with 13 A-T patients, offspring of the ATM heterozygotes assessed in our study, showed that triglycerides, total cholesterol and LDL-c and HDL-c concentrations were significantly higher in patients — and HDL-c concentrations were lower – when compared to healthy controls. The ratios associated with atherosclerosis (TC/HDL-c, LDL-c/HDL-c and Log TG/HDL-c) and non-HDL cholesterol (N-HDL-c) levels were also significantly higher in the group of patients.[42] There are no studies assessing the concordance between the changes in the lipid profile of patients and their parents, heterozygous carriers of the ATM mutation.

Studies in the literature suggest that healthy eating habits and an appropriate lifestyle should be reinforced among ATM heterozygotes.[18] In practice, this does not appear to be the case with these individuals, considering that we observed that their food consumption was similar to those in the control group. We found obesity in 17% of participants, increased abdominal circumference in 65.6%, metabolic syndrome in 11% and increased CIMC thickness, which is an early marker of atherosclerosis, in 76% of them. These findings indicate the need to effectively implement such counseling in the routine care given to those families.

Our study had some shortcomings: lack of genotyping for the ATM mutation, a transversal design, and lack of investigation of other biomarkers related to CV risk, such as lipoprotein a (Lpa), LCAT (lecithin cholesterol acetyltransferase) and adhesion molecules, i.e. ICAMs (intercellular adhesion molecules) and VCAM-1 (vascular cell adhesion molecule-1).

Conclusion

ATM heterozygotes did not differ from control individuals relative to the CV risk-related biomarkers that we studied. However, most of them had increased CIMC thickness, which is an independent predictor of death, risk of myocardial infarction and stroke, in comparison to reference values for the same age group. This finding suggests a CV risk in ATM heterozygotes and indicates the need for monitoring CIMC thickness, reinforcing nutritional counseling, and stimulating the practice of physical activity.

Resumo

Avaliação do risco cardiovascular de ATM heterozigotos

Objetivo: Avaliar a espessura do complexo médio-intimal da carótida (CMIC) e os biomarcadores do metabolismo lipídico associados ao risco cardiovascular (RC) em pais de pacientes com ataxia-telangiectasia (AT) e verificar associação com gênero.
Método: Estudo transversal prospectivo e controlado com 29 ATM heterozigotos e 14 controles saudáveis. Foram realizados exames bioquímicos e a espessura do CMIC por ultrassonografia.
Resultados: A média da medida do CMIC nos ATM heterozigotos foi de 0,72± 0,1 mm (mínimo: 0,5 mm e máximo: 1,0 mm). Observou-se elevado percentual de valores acima do percentil 75 em relação ao referencial populacional (16 [76,2%]), sem diferença estatisticamente significante entre o gênero feminino e o masculino (11/15 [73,3%] vs. 5/6 [83,3%]; p=0.550). A comparação entre os ATM heterozigotos e os controles, estratificados por gênero, mostrou que, nos ATM heterozigotos, as mulheres tinham maiores concentrações de HDL-c em comparação aos homens, e valores mais elevados de PCR-us em relação às mulheres controle. Nos ATM heterozigotos, estratificando segundo gênero, a correlação entre HDL-c e PCR-us foi inversamente proporcional e mais forte entre as mulheres, com tendência à significância estatística.

Conclusão: Os ATM heterozigotos não diferiram dos controles em relação aos biomarcadores estudados relacionados ao RC. Entretanto, a maioria deles apresentou aumento na espessura do CMIC, preditor independente de morte, risco para infarto do miocárdio e AVC, quando comparado ao referencial para a mesma faixa etária. Esse achado sugere RC nos ATM heterozigotos e aponta para a necessidade de monitoramento da espessura do CMIC e de orientações nutricionais.

Palavras-chave: Ataxia Telangiectasia. Aterosclerose. Espessura Íntima-Média Carotídea. Resistência à Insulina. Heterozigoto.

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Assessment of the prevalence of vertical hepatitis B transmission in two consecutive generations

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Summary

Introduction: Hepatitis B is an important public health problem in the world and one of the forms of contagion would be through vertical transmission. Precose diagnosis allows the adoption of prophylaxis measures, which results in prevention in more than 90% of cases.
Objective: To describe the prevalences of vertical transmission and compare two generations (mother/patient and patient/child).
Method: This was a cross-sectional study, which included 101 patients. The interviews were performed through the application of the instrument of data collection and information of the physical file before the medical consultation.
Results: The mean ± SD of age was 50.9 ± 13.1 years, the male gender predominated, with 56.4% of the patients, and the predominance was white, with 43.6%. Vertical transmission between mother and patient occurred in 17.8% and between patient and child, in 7.9%. In all of the eight cases of vertical transmission, the diagnosis was after the birth of children infected with HBV, and in 3/8 (37.5%), there was more than one case of infection by this mechanism per patient, totaling 13 children with the disease.
Conclusion: There was a reduction in vertical transmission, showing that preventive measures were effective.

Keywords: Hepatitis B. Infectious Disease Transmission, Vertical. Antiviral Agents.

Introduction

Chronic infection caused by hepatitis B virus (HBV) is a major public health problem.[1-3] According to the World Health Organization (WHO), approximately 2 billion people have been exposed to the virus. Of these, 240 million are estimated to have the chronic form of the disease. Hepatitis B accounts for about 786,000 deaths per year worldwide.[2,4,5]

Hepatitis B is the most common form of chronic hepatitis and is caused by a DNA virus that belongs to the *Hepadnaviridae* family. There exist ten genotypes of HBV, which are named from A to J. They differ from one another in their nucleotide sequence in the genome, varying as to geographic distribution. The infection can cause acute or chronic hepatitis, both forms being usually oligosymptomatic.[5]

Chronic hepatitis B can be divided into four phases. First phase: immune tolerance; second phase: immune clearance; third phase: inactive carrier; and fourth phase: reactivation. The main goal of treatment is to reduce the risk of progression of liver disease and its primary outcomes, specifically cirrhosis, hepatocellular carcinoma (HCC) and, consequently, death. Pharmacological options for the treatment of hepatitis B are: interferon-alpha, lamivudine, peg-interferon-alpha 2a and 2b, adefovir, entecavir, telbivudine, and tenofovir.[1,5,6]

Vertical hepatitis B transmission may occur during acute or chronic maternal infection through exposure of fetal mucous membranes to HBV-infected blood or maternal bodily fluids, which may occur before birth, transplacentally (intrauterinely) or at the time of childbirth (perinatally). Occasionally, the child's infection occurs in the

postnatal period through contact with infected adults. When acute HBV infection occurs during the first trimester of pregnancy, the risk of transmission to the newborn (NB) is less than 10%. However, when the infection occurs in the second or third trimesters, transmission may occur in more than 60% of cases. Therefore, it is recommended that all pregnant women perform a rapid test for HBV at their first visit, in the first trimester, or when they begin prenatal care. The diagnosis makes it possible to adopt prophylaxis measures, therefore ensuring that the vaccine and human anti-hepatitis B immunoglobulin will be administered during the first 12 hours of life of the newborn. This prevents perinatal transmission in more than 90% of cases.[3,5-7]

Care to pregnant women with hepatitis B should be given so as to prevent the vertical transmission of infection to newborns and treat the disease in mothers. Family planning should always be discussed with women of childbearing potential before starting any therapeutic procedure, especially antiviral therapy for hepatitis B.[3,4,7,8]

Method

Study design

This is a cross-sectional study conducted from June 2016 to December 2016 with patients having chronic hepatitis B infection and who were being followed up at the Clinical Hepatology Outpatient Clinic of Instituto Central, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (ICHC-FMUSP), a tertiary-level university hospital that operates seamlessly with Brazil's Unified Health System (Sistema Único de Saúde, SUS, in the portuguese acronym). It is internationally well-known for providing medical care and treatment for high-complexity patients.

By using the Hospital Information and Management System (Sistema de Informação e Gestão Hospitalar, SIGH, in the Portuguese acronym), it was possible to generate a Report of Scheduled Visits (Relatório de Consultas Agendadas) and thus obtain patient listings. The interviews were conducted by administering a data collection instrument and supplemented with the medical record information prior to the visit with a medical consultation with the purpose of assessing the prevalence of vertical hepatitis B transmission in two generations (mother/patient and patient/offspring).

Inclusion and exclusion criteria

Inclusion criteria: patients from the clinical hepatology outpatient clinic at HC-FMUSP, of both genders, aged ≥ 18 years, diagnosed with chronic hepatitis B infection (tested positive for HBsAg for more than six months), with children and who agreed to sign a free informed consent form. Exclusion criteria: co-infection with the hepatitis C virus and HIV.

Ethical aspects

Our project was submitted for evaluation by the Research Ethics Committee of HC-FMUSP (Cappesq) and over Plataforma Brasil (a national and unified database of research records involving human subjects) alongside with its CAEE (a submission protocol number): 56746916.4.0000.0068, opinion No. 1.592.921 on June 16, 2016. All patients meeting the inclusion criteria and none of the exclusion criteria were asked to read, discuss and sign a free informed consent form prior to the interviews.

Statistical analysis

The data collected were stored in an Excel® database. The results from the descriptive analysis were expressed as mean, median, standard deviation, maximum and minimum values, and frequency distribution. They were then depicted in graphs and tables.

Results

We selected 193 patients, of whom 92 were excluded: 39 who did not show up in the outpatient clinic, nine because they did not accept to participate in the study, six who tested negative for HBsAg, 36 for not having had children, and two because they met the exclusion criteria. Once the selection criteria were applied, a total of 101 patients comprised the study sample.

With respect to the distribution by gender, age, ethnicity and number of school years completed, the data obtained are shown in Table 1. The mean ± SD age was 50.9 ± 13.1 years, with a larger number of male participants, i.e. 57/101 (56.4%) of all selected patients, and also a larger number of caucasians, i.e. 44/101 (43.6%). The distribution according to number of school years completed showed similar values of patients who completed primary education 37/101 (36.6%) and high school 40/101 (39.6%).

Regarding the pharmacological regimen currently used, the use of tenofovir 300 mg as monotherapy was predominant, with 20/101 (19.8%) patients. Still, the non-use of antivirals was found in 46/101 (45.5%) patients, a larger number when compared to monotherapy, 40/101 (39.6%) or combination therapy, 15/101 (14.9%).

With regard to the likely form of transmission, vertical transmission was found in 18/101 (17.8%) patients. Most patients, 50/101 (49.5%), do not know how they got infected. Yet, 4/101 (3.9%) patients reported causes that are known not to be forms of infection, such as "lack of hygiene when living in the countryside," "working with charcoal," subway/train, or "bathing in the river."

TABLE 1 Distribution of traits according to gender, age, ethnicity and number of school years completed. June/2016 to December/2016 (n=101).

Variable	N (%)	Mean (minimum and maximum)	Standard deviation	Median
Gender				
Female	44/101 (43.6)			
Male	57/101 (56.4)			
Age		50.9 (25-82)	13.1	52
20-30 years	5/101 (4.9)			
31-40 years	13/101 (12.9)			
41-50 years	24/101 (23.8)			
51-60 years	30/101 (29.7)			
61-70 years	23/101 (22.8)			
71-80 years	5/101 (4.9)			
> 81 years	1/101 (1.0)			
Race				
White	44/101 (43.6)			
Black	12/101 (11.9)			
Yellow	14/101 (13.8)			
Brown/Mixed	30/101 (29.7)			
Indigenous	1/101 (1.0)			
Education				
Illiterate	1/101 (1.0)			
Primary and Middle school	37/101 (36.6)			
High school	40/101 (39.6)			
Higher studies	23/101 (22.8)			

Vertical transmission can occur at two moments: mother/patient and patient/offspring. The vertical transmission rates we found in our study were 18/101 (17.8%) and 8/101 (7.9%), respectively (Figure 1).

Regarding the use of prophylaxis tools in the offspring, we found that immunoprophylaxis after childbirth represented 10/101 (9.9%); of these, there was no transmission of hepatitis B, and 68/101 (67.3%) were vaccinated, with only 3/68 (4.4%) patients having hepatitis B. With regard to the unvaccinated offspring, 33/101 (32.7%), 6/33 (18.2%) had hepatitis B.

When analyzing the vertical transmission rate among the patients interviewed, 8/101 (7.9%), we found that 7/8 (87.5%) are females and the only male has a wife with HBV. Offspring with HBV were 34 ± 6.2 (mean ± SD) years old. None of them received immunoprophylaxis, whereas 4/13 (30.8%) were vaccinated.

We found that all eight cases of vertical transmission were diagnosed after the birth of the HBV-infected offspring. In 3/8 (37.5%), there was more than one case of infection by this mechanism per patient, therefore totaling 13 children with the disease, as shown in Table 2.

Discussion

In the period from 1999 to 2015, 196,701 cases of hepatitis B in Brazil, a notifiable disease, were notified through the Notification Information System (Sistema de Informação de Agravos de Notificação, SINAN). Of these, 106,371 (54.1%) correspond to affected males, which is in agreement with the findings of our study, i.e. 56.4%. However, that difference in the number of cases according to gender has been decreasing over the years. The 2015 distribution of cases according to ethnicity/skin color shows that most cases are of Caucasians/white people (50.2%), which is similar to the value we found, 43.6%.[9]

One way to promote health is by investing in health education actions so that the population has access to information on the disease. This also contributes to the debunking of myths and prejudices. Of the patients interviewed, 4/101 (3.9%) reported "causes" that are known not to be mechanisms of infection. This is indicative that there are still patients who do not know about their disease, since hepatitis B is known to be a parenterally transmitted; or through the sharing of needles, syringes, manicure and pedicure gear, razor and shave blades; tattooing;

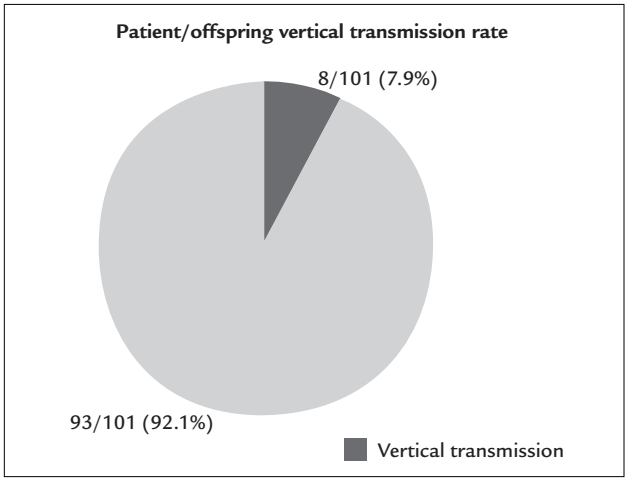

FIGURE 1 Distribution of patients according to patient/offspring vertical transmission. June/2016 to December/2016 (n=101).

TABLE 2 Description of cases of vertical transmission cases — patient/offspring. June/2016 to December/2016 (n=101).

Patient	Gender	Patient diagnosis	Number of offspring	Offspring with HBV	Year of birth of the offspring
1	Female	2006	5	1	1981
2	Female	2002	1	1	1981
3	Female	1993	3	3	1982, 1987, 1989
4	Female	1997	3	1	1974
5	Male	1999	2	1	1988
6	Female	2008	4	3	1980, 1982, 1992
7	Female	2005	2	2	1977, 1981
8	Female	1996	1	1	1995

piercing; dental or surgical procedures not meeting biosafety standards; unprotected sex (this being the predominant route); blood transfusion; and vertical transmission (mother/child) — with this being an important route and associated with unfavorable disease progression, with a higher risk of chronification.[2,5,10]

In the transmission between patient/offspring, only 8/101 (7.9%) were infected through this route, a lower number when compared to mother/patient transmission, 18/101 (17.8%). Studies show that the infection rate from HBV-carrying mothers to their children amounts to about 90% of cases when the mother tested positive for HBsAg and antigen "e" (HBeAg-positive) and to 10% of cases when positive only for HBsAg.[8]

Of the 8/101 (7.9%) patients presenting vertical transmission to their children, the last infected child was born in 1995. This shows that, as from that date, the installed measures were effective in preventing this type of transmission, as well as in reducing the vertical transmission rate.

In Brazil, since 1998, the Ministry of Health's National Immunization Program (Programa Nacional de Imunizações, PNI, in the Portuguese acronym) recommends that all children from birth be universally vaccinated against hepatitis B.[11] The first dose, allied to immunoglobulin within the first 12 hours of birth, results in 95% efficacy in preventing vertical infection. As from 2001, the age range was extended to 19 years of age. Several studies show that hepatitis B vaccines have good immunogenicity and are effective, providing protection in more than 90% of healthy young adults and in more than 95% of infants, children and adolescents. Efficacy decreases gradually after 40 years of age, and other factors such as obesity, stress, smoking habits and alcohol consumption are also associated with lower vaccine efficacy.[11-14]

Despite the introduction of vaccination and progressive efforts in campaigns, it was found that 9/13 (69.2%) cases involving vertical transmission had not been vaccinated or did not know whether they had been vaccinated. Among patients who had children, this occurred in 33/101 (32.7%) cases – and of these, 6/33 (18.2%) have HBV. The low vaccine adherence can be explained by the long period necessary for completing the vaccination schedule (three doses: in months 0, 1, and 6). This highlights the need for health education programs geared to raise the population awareness and reinforce the importance of immunization strategies for compliance with the complete HBV vaccination scheme.[3,11]

With increased access to information and a larger number of campaigns on the disease, the number of new infections is expected to decline. Health promotion begins with prevention measures and educating the population, who need to be informed about everything involving their disease.

Conclusion

There was a reduction in vertical transmission when comparing the two generations. This shows that even with low immunoprophylaxis rates, the installed measures have been effective in preventing this type of transmission. The importance of health education, raising awareness about vaccination and disseminating information on hepatitis B contributes to the debunking of myths and prejudices.

Resumo

Avaliação da prevalência de transmissão vertical de hepatite B em duas gerações consecutivas

Introdução: A hepatite B é um importante problema de saúde pública no mundo e uma das formas de contágio seria através da transmissão vertical. O diagnóstico precoce possibilita a adoção de medidas de profilaxia, o que resulta na prevenção em mais de 90% dos casos.
Objetivo: Descrever as prevalências de transmissão vertical e comparar duas gerações (mãe/paciente e paciente/filho).
Método: Trata-se de um estudo transversal, que incluiu 101 pacientes. As entrevistas foram realizadas por meio da aplicação do instrumento de coleta de dados e informações do prontuário físico antes da consulta médica.
Resultados: A média ± DP de idade foi de 50,9 ± 13,1 anos, houve predomínio do gênero masculino, com 56,4% dos pacientes, e predominou a cor branca, com 43,6%. A transmissão vertical entre mãe do paciente/paciente ocorreu em 17,8% e entre paciente/filho, em 7,9%. Em todos os oito casos de transmissão vertical, o diagnóstico foi posterior ao nascimento dos filhos infectados por HBV; em 3/8 (37,5%), houve mais de um caso de infecção por esse mecanismo por paciente, totalizando 13 filhos com a doença.
Conclusão: Houve uma redução na transmissão vertical, mostrando que as medidas preventivas foram efetivas.

Palavras-chave: Hepatite B. Transmissão Vertical de Doença Infecciosa. Antivirais.

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Subcutaneous emphysema, a different way to diagnose

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Summary

Introduction: Subcutaneous emphysema (SE) is a clinical condition that occurs when air gets into soft tissues under the skin. This can occur in any part of the body depending on the type of pathology. The most common site is under the skin that covers the chest wall or neck. It is characterized by painless swelling of tissues. The classic clinical sign is a crackling sensation upon touch, resembling that of touching a sponge beneath your fingers.
Objective: To describe a new way to diagnose subcutaneous emphysema.
Method: Our finding was a matter of serendipity while inspecting a patient with subcutaneous emphysema using a stethoscope. Instead only hearing the patient's chest, the stethoscope was gently pressed against the skin with SE and so we were able to detect a different sound.
Results: This new way to diagnose subcutaneous emphysema consists in pressing the diaphragm part of stethoscope against the patient's skin where SE is supposed to be. Thus, we are able to hear a sound of small bubbles bursting. Crackle noise has an acoustic emission energy that varies between 750-1,200 Hz, considered high frequency.
Conclusion: Although currently the use of imaging methods is widespread worldwide, we would like to strengthen the value of clinical examination. Auscultation is an essential diagnostic method that has become underestimated with the advances of healthcare and medicine as a whole. We therefore propose a different approach to diagnose SE.

Keywords: Subcutaneous Emphysema. Pneumothorax. Thorax.

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Introduction

In 1834, René Laennec said: "I recalled a well-known acoustic phenomenon: if you place your ear against one end of a wood beam, the scratch of a pin at the other end is distinctly audible".[1]

Subcutaneous emphysema (SE) is a clinical condition that occurs when air gets into soft tissues under the skin. This can occur in any part of the body depending on the type of pathology. The most common site is in the skin that covers the chest wall or neck.

It has a particular characteristic because air travels from its initial location to other sites along the fascia. One of the most common is the travelling of air from the mediastinum to the neck and face along the fascia planes, but it can also travel from the retro peritoneum to the neck or retro peritoneum to scrotum.

The first description was by Laennec in 1819, who described pneumomediastinum.[1]

The gas entrapped under the skin can result from a lesion on the respiratory or gastrointestinal systems. It often does not need treatment itself, but its presence indicates other possible serious injuries that do require urgent management.

This article discusses the chest and neck presentation only.

Pathophysiology

The pathophysiology of subcutaneous emphysema originated from the lung involves air leak that may reach subcutaneous plane by means of two different routes:

1. In 1939, in Ontario, Canada, Macklin demonstrated, in a series of experiments on cats and other animals,

that air leaked from pulmonic alveoli enter pulmonary interstitial space and can travel along the sheaths of pulmonary blood vessels through artificial channels from the lungs to the mediastinum and later to the neck through the fascia planes;[2]

2. The simplest mechanism occurs when the parietal pleura is torn, so that air which has entered the pleural space may pass directly into the chest wall and subcutaneous tissues.[3]

Signs and symptoms

It is characterized by painless swelling of tissues commonly seen over the chest wall, neck and head, around drain sites (Figure 1) and around wound sites, but it can be seen in any place of the body.

The classic clinical sign is a crackling sensation to the touch, resembling the feeling of touching Rice Krispies or the sensation of having a sponge under the fingers.

Chest pain, sore throat, trouble in swallowing, aching neck, breathlessness and wheezing can be found.

In severe cases, there can be swelling of the entire face and neck sometimes associated with cardiopulmonary symptoms.

Causes

- Pneumothorax (blunt trauma occurring with a rib fracture or open due to stabbing or gunshot wound and barotrauma).
- Bronchial rupture.
- Esophageal rupture.
- Facial bone fracture.
- Posterior duodenal perforation; in this case, the crackling sensation is identifiable by digital rectal examination.
- Infection in any part of the body, such as gangrene.
- Posterior colon perforation.
- Spontaneous occurrence (while shouting, singing, child birth, violent coughing, straining defecation).[4]
- Following chest tube insertion, tracheal intubation and surgical procedures in upper gastrointestinal tract.
- Complication of asthma from nebulization of bronchodilators.

Diagnosis

The diagnosis of subcutaneous emphysema is simple due to its characteristic signs and symptoms, but elucidating the primary cause is sometimes difficult and requires an imaging method.

Chest radiograph

Subcutaneous emphysema may be seen as radiolucent area on soft tissue (Figure 2), which is the most common way of finding it. Sometimes, striations are noticed in the pattern expected from the pectoralis major muscle group (Figure 3), which is called ginkgo leaf sign of the chest. The air that outlines the fibers of the pectoralis major muscle creates a pattern that resembles the veins of a ginkgo leaf (Figure 4).

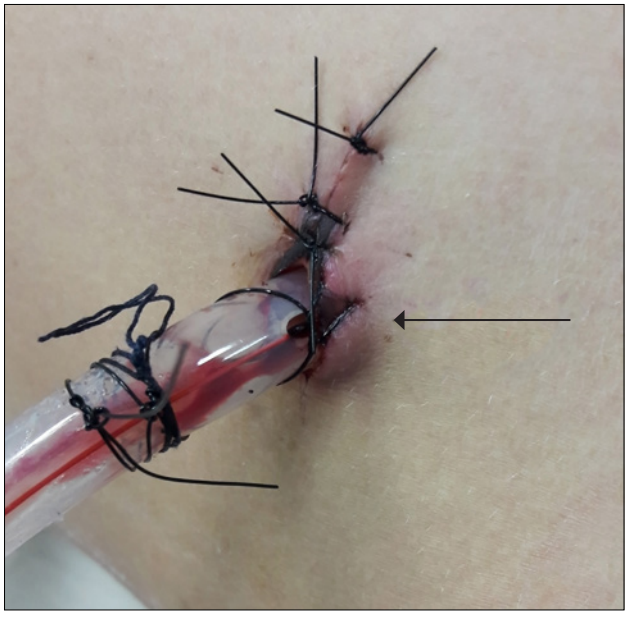

FIGURE 1 The last hole of thoracic drain at the level of the skin predisposing to the appearance of SE.

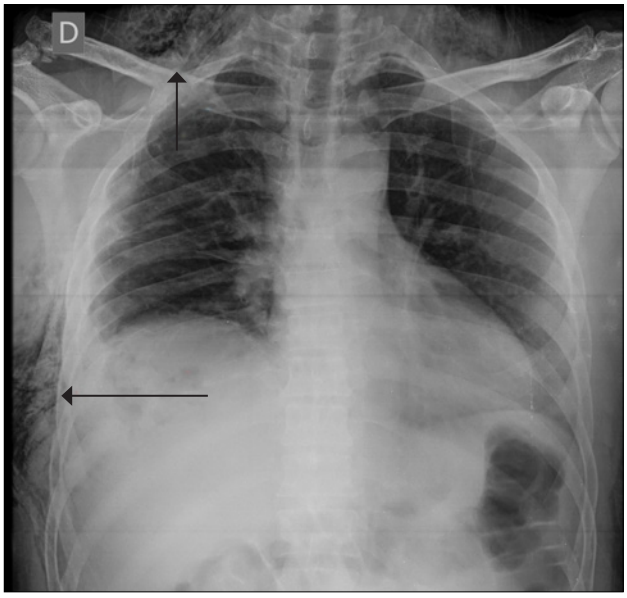

FIGURE 2 Subcutaneous emphysema on X-ray: arrows show SE at right side of chest and at supraclavicular site.

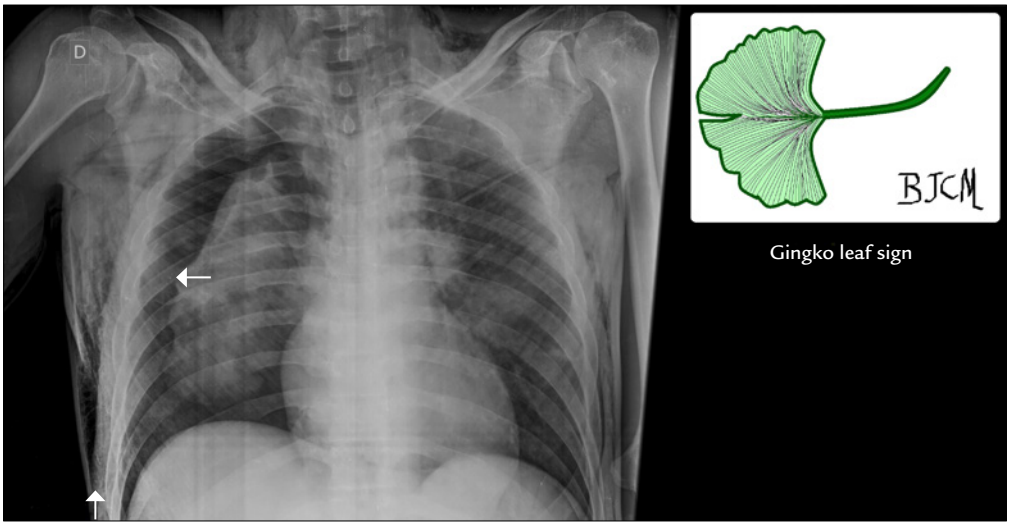

FIGURE 3 Gingko Leaf Sign: observe the air that outlines the fibers of the pectoralis major muscle. The upper arrow indicates a pneumothorax. Bottom arrow indicates SE on right chest.

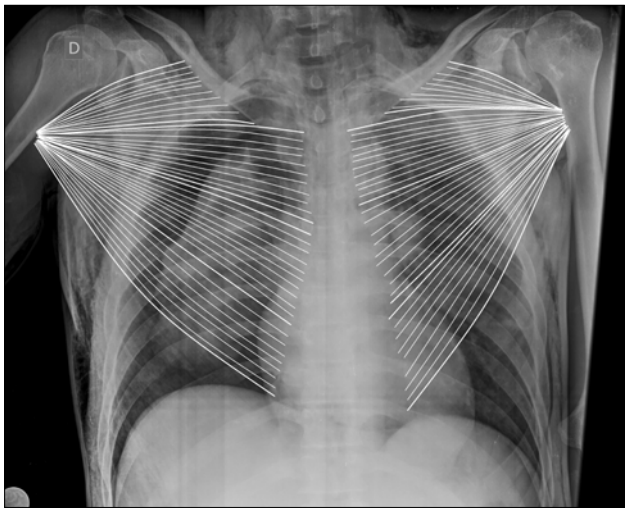

FIGURE 4 The pattern of pectoralis major muscle outlined by the air.

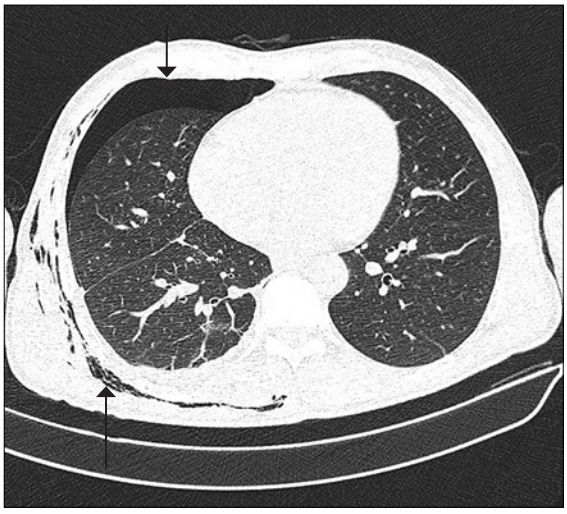

FIGURE 5 Bottom arrow indicates the SE at computed tomography. Upper arrow indicates a pneumothorax.

Computed tomography (CT scan)

Air trapped in subcutaneous tissue appears as dark spots on CT scan. It is easier to see than in the X-ray (Figure 5).

Classification for severity

In 2013, Aghajanzadeh et al.[5] classified subcutaneous emphysema into five grades according to severity: grade 1, base of the neck; grade 2, all of neck area; grade 3, sub pectoralis major area; grade 4, chest wall and all of the neck area; and grade 5, chest wall, neck, orbit, scalp, abdominal wall, upper limbs and scrotum.[5]

Treatment

The treatment of subcutaneous emphysema itself is expectant: controlling the main cause solves this situation, for example: properly inserting a chest tube to treat pneumothorax and making sure that the last hole of the tube is inside the pleural space; closing bronco pleural fistulas; surgically treating and removing skin infections that can cause gangrene; properly draining and correcting ruptured esophagus.

Three types of treatment have been proposed for subcutaneous emphysema with cardiac and respiratory involvement:

1. The drain is positioned in subcutaneous space through blunt dissection in the compromised chest (midclavicular line, midway between the clavicle and nipple) and later connected to a vacuum device at low pressure (5 cmH_2O). This was suggested in case of extensive disease with airway and cardiovascular compromise by compression of structures in the neck.[6]
2. Use of subcutaneous incisions to decompress massive spontaneous subcutaneous emphysema to neck and head with no obviously remediable intrathoracic process. Bilateral 3-cm infraclavicular incisions made down to the pectoralis fascia in these patients with acute decompression and alleviation of the case.[7]
3. Use of needles has been described in the past.[8]

Method

Search for the articles included in this review was done on the Medline, Lilacs and Cochrane library databases using the Medical Subject Headings (MeSH): subcutaneous emphysema.

The new way to diagnose subcutaneous emphysema was discovered as serendipity during the normal clinical inspection of patients with suspected subcutaneous emphysema. The patients underwent usual clinical inspection: auscultation, inspection, palpation and percussion of chest and neck.

During the clinical exams, instead of only hearing the patient's chest, the stethoscope was gently pressed against the swollen skin with SE, with the purpose of performing a classic clinical examination.

While pressing the stethoscope's diaphragm onto the swollen skin with SE, an incidental finding was noted: a new noise could be detected coming from the skin and not from the lungs or pleural space.

Results

The result of this incidental finding was a new way to diagnose SE. It consists in pressing the diaphragm part of the stethoscope against the patient's chest, neck or belly, where SE is present.

This way, it is possible to hear the noise of lots of small bubbles bursting. Very audible crepitation comes from the stethoscope. It has an acoustic emission energy that varies between 750-1.200 Hz, which is considered high frequency.[9]

This treble (acute) sound produced can be heard using the diaphragm part of a stethoscope, which was designed to hear acute sounds.

Discussion

Currently, the use of imaging methods is widespread but we would like to highlight the value of clinical examination. Although auscultation is an essential diagnostic method, it has become underestimated in many cases as healthcare and medicine have advanced. However, it is a simple, noninvasive, quick diagnostic technique and is appropriate to rapidly investigating the pathological condition, and is still very useful for medical care in emergencies and disasters. Making a diagnosis based on auscultation requires sufficient experience.[10]

In this context, we would like to propose a different way to diagnose subcutaneous emphysema. A new diagnostic and qualitative sign.

When a patient has SE, we can feel a crackling sensation in the patient's skin to the touch. This different way to diagnose consists in pressing the diaphragm part of a stethoscope against the patient's chest, neck or belly, and hear small bubbles bursting. Hearing the emphysema is even more sensitive than touching it (Figure 6).

We therefore propose this different and simple manner to diagnose this particular clinical condition.

Conflict of interest

The author declares no conflict of interest.

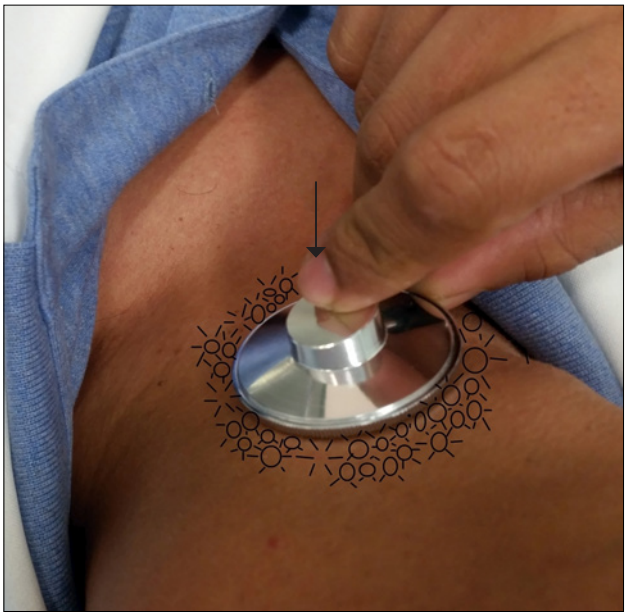

FIGURE 6 When the diaphragm part of the stethoscope is pressed against the skin with SE, is possible to hear the noise of small bubbles bursting.

Resumo

Enfisema subcutâneo: uma forma diferente de diagnosticar

Introdução: O enfisema subcutâneo é uma condição clínica que ocorre quando o ar entra nos tecidos sob a pele. Isso pode ocorrer em qualquer parte do corpo, dependendo do tipo de patologia. O local mais comum é sob a pele que cobre a parede torácica ou o pescoço. É caracterizado por inchaço indolor de tecidos. O sinal clínico clássico é a sensação de crepitação quando se toca a região afetada, assemelhando-se à sensação de se tocar uma esponja.
Objetivo: Descrever uma nova maneira de diagnosticar enfisema subcutâneo.
Método: Este achado foi uma serendipidade, caracterizada por inspeção clínica de pacientes com enfisema subcutâneo com uso de estetoscópio. Além da auscultação do tórax do paciente, o estetoscópio foi suavemente pressionado contra a pele com enfisema subcutâneo, sendo possível detectar um ruído diferente.
Resultados: Essa nova maneira de diagnosticar enfisema subcutâneo consiste em pressionar o diafragma do estetoscópio contra a pele do paciente supostamente afetada por enfisema subcutâneo, sendo possível ouvir o ruído de pequenas bolhas estourando. O ruído de crepitações tem uma energia de emissão acústica que varia de 750-1.200 Hz, considerada alta frequência.
Conclusão: Atualmente, o uso de métodos de imagem é generalizado em todo o mundo, mas gostaríamos de fortalecer o valor do exame clínico. Embora a ausculta seja um método de diagnóstico essencial, foi subestimado à medida que os cuidados de saúde e os medicamentos avançaram. Propomos uma maneira diferente de diagnosticar enfisema subcutâneo.

Palavras-chave: Enfisema Subcutâneo. Pneumotórax. Tórax.

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Maternal attachment and breastfeeding behaviors according to type of delivery in the immediate postpartum period

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Summary

Introduction: Breastfeeding is nutritious and has physiological benefits regarding the immunological aspect; also, it has an important role on maternal attachment and on raising a healthy baby.
Objective: Our study was conducted to analyze maternal attachment and breastfeeding behaviors in the immediate postpartum period of mothers who had vaginal and cesarean birth.
Method: This descriptive and comparative study was conducted with women who sought the childbirth clinic of a university hospital in Izmir, Turkey. In the study, 175 mothers were attended; 83 of them had vaginal birth and 92 had cesarean birth. Data were collected by using Demographic Identification Form, Maternal Attachment Inventory and LATCH Breastfeeding Assessment Score Tool. Descriptive and correlational statistics were used for data analysis.
Results: We found that Maternal Attachment Inventory and the LATCH breastfeeding charting system of mothers that had vaginal birth was higher than that of mothers who had cesarean delivery. There was a positive correlation between Maternal Attachment Inventory and LATCH total score average for both cesarean and vaginal birth.
Conclusion: Mothers who delivered their babies by cesarean section had problems related to maternal attachment and breastfeeding more often than those who delivered vaginally.

Keywords: Breastfeeding. Cesarean Section. Natural Childbirth. Delivery, Obstetric. Parturition. Mother-Child Relations.

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Introduction

Early infancy is a special period that shapes the development of human beings. There are four factors related to each other for parents to provide a positive environment for the development of a baby after birth; (1) protection from danger/injury, (2) responsive care, (3) breastfeeding, (4) healthy attachment.[1] Attachment was first defined in 1950 as "strong connection between two people" by Ainsworth and Bowlby,[2] who developed the attachment hypothesis. Bowlby defined maternal attachment as "warm, continuous and intimate relation between the mother and the baby. Both sides are delighted and take pleasure in the relationship". Maternal attachment starts with breastfeeding after birth, as the baby turns its attention to the mother, looking for the breast, turning the head, catching, sucking and swallowing. Breastfeeding is one of the most important encouraging factors in maternal attachment. Maternity feeling might develop in a stronger fashion as if the interaction between a mother and her baby is close and healthy.[3-5]

Maternal attachment, meaning a loving connection between the mother and her baby, is one of the most important encouraging factors in healthy infant development. The first attachment experience of the baby is the basis for her/his future attachment experiences. In summary, attachment feelings experienced as dependable or undependable in the newborn period will continue for the whole life.[6-10] If dependable attachment necessities between the baby and mother could not be satisfied in the first year, the baby might have emotional, social, physical, men-

tal and speaking developmental problems. In insufficient maternal attachment conditions, the baby runs the risk of negligence and exploitation. Alhusen et al.[11] declared in their study that mothers who have higher maternal attachment levels were more sensitive, tender and participating parents, affecting the development of the baby positively in their early infancy period. Schwarze et al.[12] stated in their study that breastfeeding is important in maternal attachment and less breastfeeding is a risk factor for borderline personality disorder.

The first 60-90 minutes after birth and the mother-baby connection in the first three days of the neonatal period are very important for maternal attachment. In the literature, it was declared that mothers who received their baby just after their vaginal birth exhibit compassionate behavior and hug much more often compared to the ones that had cesarean birth.[13-16] In the literature, there are reports that the risk of problems and difficulties that might seen in the postpartum period was higher using cesarean section compared with vaginal birth.[4-6,10-13] However, the rate of cesarean births continues to increase. According to the literature, mothers who were not able to stand up for 6-12 hours after the cesarean birth, who could not have oral feeding after intestine activity starts, who had severe pain or who needed to use a bladder catheter might have difficulties in the first days after the birth. There are reports in the literature that mothers who had cesarean birth showed difficulties in their own self-care, in carrying on their daily life activities, in assuring the aftercare needs of the newborn, as well as presented breastfeeding problems.[3,5,10] Delay in maternal attachment is obvious in cesarean birth because of common problems regarding surgery and because of common problems observed in postpartum period.[13]

This study was conducted in the first three days of the newborns' life, which is the most important and the earliest period for maternal attachment. It was conducted to evaluate the maternal attachment and feeding behavior of mothers who delivered their babies vaginally or by cesarean section. Another aim of the study was to analyze the relation between maternal attachment and breastfeeding, which is thought to be effective to trigger maternal attachment in early postpartum period.

Method

This descriptive and comparative study was conducted with women who attended the childbirth clinic of a university hospital in Izmir, Turkey from July 15, 2014 to May 30, 2015. In the study, 175 mothers were attended, 83 of them had vaginal birth and 92 delivered their babies via cesarean section. Mothers who (1) were primipara, (2) had been born mature (≥ 38th week), (3) did not have risky pregnancy and had not had risky birth, (4) were literate and (5) were willing to participate in the study.

Data were collected using the Demographic Identification Form, the Maternal Attachment Inventory (MAI) developed by Muller (1994) and validated by Kavlak and Sirin,[15] and the LATCH Breastfeeding Assessment Score Tool validated by Yenal and Okumus[16] in Turkish.

Demographic Identification Form

This form was developed by a review of the literature.[4,5,10,11,13] It consisted of 12 questions adapted to determine the mother's sociodemographic characteristics (age, education, income, and employment status) as well as information on breastfeeding behavior.

Maternal Attachment Inventory (MAI)

This measurement tool was developed by Mary E. Muller in 1994. The validation of it was done by Kavlak and Sirin in 2009 and the Cronbach alpha value found was 0.77. Because it was applied by the participant herself to measure maternal feelings and behaviors representing love, this scale is applicable only for literate women. The scale consists of 26 items with four Likert type answers ranging from "always" to "never." Each item involved direct statements with the following scores for the answers: always, 4 points; frequently, 3 points; sometimes, 2 points; and never, 1 point. A general score is calculated by summing up the scores of each item. A high total score shows that maternal attachment is high. The lowest score is 26 and the highest score is 104.[15] The Cronbach alpha value for this study was 0.94.

LATCH Breastfeeding Assessment Score Tool

LATCH is one of the measuring tools to evaluate breastfeeding and is represented as a visual scale similar to that of the Apgar system. This measurement tool has five evaluation criteria as follows:

- L: Latch on breast.
- A: Audible swallowing.
- T: Type of nipple.
- C: Comfort breast/nipple.
- H: Hold.

The validation study of the LATCH Breastfeeding Assessment Score Tool was performed in 1997 by Adams and Hewell in the USA. In Turkey, the validation study was performed by Yenal and Okumus in 2003 and the Cronbach's alpha value was determined as 0.95. Each statement evaluated scored between 0-2 points, so that

the total score obtained with the scale is 10. Higher scores show that the breastfeeding assessment is better.[16] In our study the Cronbach's alpha value was 0.89.

Official permission was given by the clinical research ethics committee of the hospital where the study was conducted (Date: 03.07.2014, Number: 2014-131). Participants were informed about the purpose of the research and gave their written permission before data were collected.

In our study, a face-to-face structured interview with each mother was conducted by the researchers 48-72 hours after the birth. The time allocated for a woman to complete the questionnaires was approximately 15-20 minutes. All the data were analyzed using SPSS version 21.0 for Windows. The sociodemographic characteristics of women participating in the study were reported as number and percentage distribution. To analyze the average score of the Maternal Attachment Inventory and the average score of LATCH Breastfeeding Assessment Score Tool, confirmation of normal distribution was obtained, and parametric (variance analyze, independent sample t-test) and non-parametric tests (Mann-Whitney U and Kruskal-Wallis) were performed. Correlation analysis was used to determine the relationship between the Maternal Attachment Inventory and LATCH Breastfeeding Assessment Score Tool. p-values <.05 were accepted as statistically significant.

Results

Sociodemographic characteristics of participants are displayed in Table 1. In this study, 175 mothers were included; 83 had vaginal birth and 92 had cesarean birth. The average age of mothers who had vaginal birth was 23.59 years, 67.5% of them had completed primary school, 90.4% were unemployed, 60.2% had middle-class income, 48.2% had knowledge about the postpartum period and 55.4% had a female baby. On the other hand, the average age of mothers who had cesarean birth was 24.92 years, 59.8% of them had completed primary school, 89.1% were unemployed, 58.7% had middle-class income, 60.2% had knowledge about the postpartum period, and 51.1% of them had a female baby. There were no significant differences between the mothers that had vaginal and cesarean birth in terms of age (F=3.608, p=0.059), education (x^2=1.190, p=0.551), employment status (x^2=0.072, p=0.789), income level (x^2=0.043, p=0.835), gender of baby (x^2=0.741, p=0.389) and having knowledge about postpartum period (x^2=3.346, p=0.067) (Table 1).

In our study, MAI score average of mothers who had vaginal birth was 97.07±7.01 points, while the score of the mothers who had cesarean birth was 91.86±14.11 points. The difference was statistically significant (F=9.193, p=0.003). As for LATCH score average, mothers who had vaginal birth scored 7.83±1.88, while those who underwent cesarean section scored 7.04±2.31 points. Again, the difference between them was statistically significant (F=6.027, p=0.015). There is a positive significant relation between the MAI score average and LATCH total score average for both vaginal birth (r=0.675, p=0.000) and cesarean birth (r=0.376, p=0.000) (Table 2) (Figure 1) (Figure 2).

Discussion

Attachment is a behavioral pattern showing the emotional relationship between the mother and her baby. There are different results in the literature regarding the studies conducted to analyze the effect of birth type on the mother-baby interaction. Contrary to our findings, some studies reported that there is no relation between maternal attachment and the birth type.[17-19] Hergüner et al.[4] conducted a study (n=80, vaginal birth=40, cesarean birth=40) to analyze the effect of birth type on depression in the postpartum period, perceived social support and maternal attachment. They used MAI and, similarly to our results, found that MAI score average of mothers who had vaginal birth was higher compared to the ones who had cesarean birth. In vaginal birth, oxytocin released from the posterior pituitary together with spasms of uterus and vaginocervical irritability occur. Oxytocin is a hormone related with maternal behavior.[9,20-23] Swain et al. found in their study that cerebral activity increased more in vaginal birth compared to cesarean birth.[20]

Alus Tokat et al.[6] found in their study, which was conduct to analyze self-sufficiency on breastfeeding and breastfeeding situation in the first 24 hours regarding to the birth type, mothers that had cesarean birth had more breastfeeding problems. Similar to our study, other studies declared also that mothers who had cesarean birth experienced more breastfeeding problems compared to those that had vaginal birth.[17,21-24] In the study by Zanardo et al.,[25] in which the ratio of breastfeeding was compared in cesarean and normal birth, the authors declared that breastfeeding ratio was lower in cesarean birth. Additionally to common problems seen after the cesarean surgery, inability to have an appropriate position for breastfeeding is another preventive factor to start breastfeeding in the early period. It was thought in this study that the difference on breastfeeding regarding to birth type was resulted because of all these factors. Also differences related to birth type were thought to be the factors affecting nutrition in postpartum early period. In the study by Heidarzadeh et al.,[26] which was conducted to compare breast crawl times regarding birth type, found that babies born via cesarean section crawled

TABLE 1 Demographic characteristics.

	Vaginal birth (n=83)	Cesarean birth (n=92)	Significance
Age[a] (years)	23.59±4.53	24.92±4.72	F=3.608
(Min-max)	(18-41)	(19-42)	p=0.059
Education[b]			
Primary school	56 (67.5)	55 (59.8)	x^2 =1.190
High school	17 (20.5)	22 (23.9)	p=0.551
University	10 (12.0)	15 (16.3)	
Employment[b]			
Employed	8 (9.6)	10 (10.9)	x^2 =0.072
Unemployed	75 (90.4)	82 (89.1)	p=0.789
Income[b]			
Low	33 (39.8)	38 (41.3)	x^2 =0.043
Moderate	50 (60.2)	54 (58.7)	p=0.835
Infant sex[b]			
Female	46 (55.4)	45 (48.9)	x^2 =0.741
Male	37 (44.6)	47 (51.1)	p=0.389
Had they received on postpartum period?[b]			
Yes	40 (48.2)	57 (62.0)	x^2 =3.346
No	43 (51.8)	35 (38.0)	p=0.067

Values in parentheses are percentages.
[a]Mean±SD is supplied.
[b]Frequencies.

TABLE 2 Maternal Attachment Inventory and LATCH score averages regarding the birth type.

	Vaginal birth (n=83)	Cesarean birth (n=92)	Significance
Maternal Attachment Inventory	97.07±7.06	91.86±14.11	F=9.193
Score Average			p=0.003
LATCH total score average	7.83±1.88	7.04±2.31	F=6.027
			p=0.015
Significance	r=0.675	r=0.376	
	p=0.000	p=0.000	

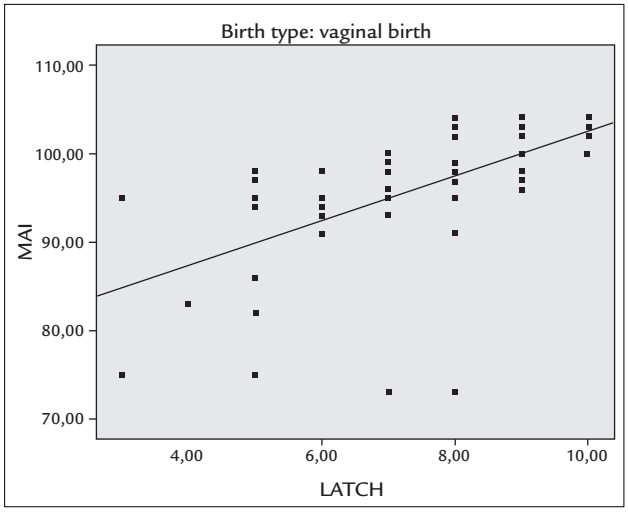

FIGURE 1 The relationship between Maternal Attachment Inventory and LATCH in vaginal birth.

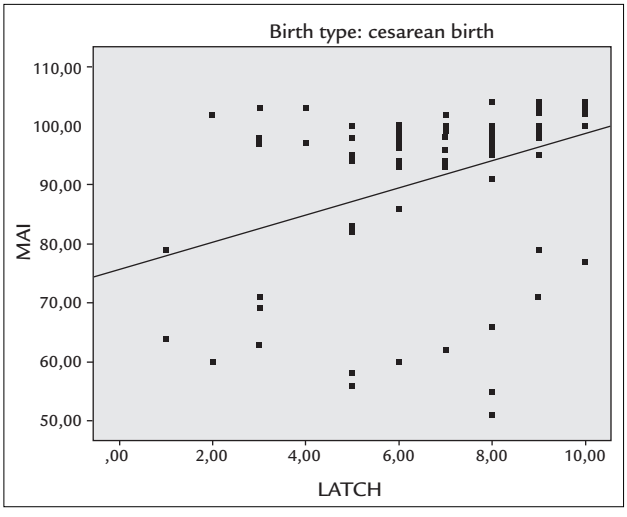

FIGURE 2 The relationship between Maternal Attachment Inventory and LATCH in cesarean birth.

to the breast in a shorter time compared to babies born vaginally. Nurses who work closely with mother and baby in the early postpartum period should know that differences might be seen during breastfeeding regarding the birth type and they should determine possible problems and plan the care.

In this study, a relation was determined between maternal attachment and breastfeeding behaviors in both vaginal and cesarean birth. Similarly to our findings, a positive relation was found between maternal attachment and breastfeeding and the importance of breastfeeding in the immediate postpartum period is emphasized in the literature.[12,27-30] In the systematic review by Moore et al., it was determined that newborns that had early skin-to-skin contact cried less and made more physical contact with their mothers.[31] Also, they stated that maternal attachment was better and the newborns had a tendency to breastfeed more and for longer. Breastfeeding plays an important role on maternal attachment and healthy development of a child in addition to its nutritive and physiological benefits in terms of immunology. In the study by Liu et al.,[32] the authors stated that breastfeeding was an important factor affecting mother-baby attachment, while the internalization of behavior disorders by the child would be related to weak mother-baby attachment. Similarly, in the studies by Alhusen et al.[11] and Schwarze et al.,[12] the authors stated that psychological problems related to lack of attachment in childhood were observed in babies that were not breastfed at all or were seldom breastfed. Breastfeeding increases maternal attachment and develops a deep and indelible connection with the baby. Nurses play a key role in starting and continuing of breastfeeding in early postpartum period. It has an important effect on maternal attachment. In postpartum services, nurses should plan the care of the mothers based on birth type, implementing it attentively.

Conclusion

Women develop maternal-infant attachment through feeding and baby-care activities during the postpartum period. Any forces detrimental to mother-infant interaction may delay the development of maternal-infant attachment. More problems and difficulties are experienced in the postpartum period of cesarean birth compared to vaginal birth. As declared in the results section of our study, cesarean birth leads to more frequent problems in maternal attachment and breastfeeding. Thus, healthcare professionals should encourage mothers to deliver their babies vaginally, eventually increasing the current rates of breastfeeding and to start the maternal attachment in the immediate postpartum period. Also, if healthcare professionals support the mother in the postnatal period to prepare them for the act of breastfeeding in a short time, potential problems related to breastfeeding can be recognized earlier.

Conflict of interest

The authors declare no conflict of interest.

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Comparative study of computed tomography (CT) and pathological diagnosis toward mediastinal lymph node metastasis in esophageal carcinoma

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Summary

Objective: To investigate the diagnostic criteria of mediastinal lymph node metastasis (MLNM) in esophageal carcinoma (EC) by comparing the lymph node sizes measured by computed tomography (CT) and obtained by postoperative pathological examination.
Method: A total of 305 EC patients were selected. MLNM location, shortest diameter and number were investigated one week before surgery, and then compared with their pathological findings.
Results: The receiver operating characteristic (ROC) curve analysis revealed that the minimum diameters of MLNM in the thoracic cavity was 8 mm (area under curve [AUC] = 0.766, Youden index = 0.424), 5 mm in supraclavicular fossa (AUC = 0.785, Youden index = 0.494), 6 mm in tracheoesophageal groove (AUC = 0.755, Youden index = 0.405); the sensitivity was increased significantly, and the Youden index was increased significantly when compared with 10 mm.
Conclusion: The shortest diameter of diagnostic criteria of lymph nodes in EC could be less than 10 mm on CT.

Keywords: Esophageal Neoplasms. Lymph Nodes. Tomography, X-ray Computed.

Introduction

Esophageal carcinoma (EC) is a common gastrointestinal cancer, with about 481,000 new cases worldwide in 2008, and accounts for 3.8% of the total number of cancers. Its incidence has a clear regional distribution, and the morbidity and mortality of EC in developing countries account for more than 80%.[1] The morbidity and mortality of EC in China ranks the first in the world.[2] EC still has high incidence in China, and in 2012 it ranked the fifth of malignant tumors with its mortality raking the fourth.[3] Lymph node metastasis and the number of metastases are important factors that will impact the prognosis of EC.[4-6] Compared with the sixth edition, the seventh edition of tumor-node-metastasis (TNM) staging standards[7] emphasizes more the impact of the number of lymph node metastasis on the staging. Presently, most Chinese and foreign scholars[8-10] believe that the seventh edition of staging criteria is better than the sixth edition in evaluating the treatment options and prognosis, so, it is very important to accurately diagnose lymph node metastasis. The current standard of positive lymph node set the shortest diameter as 10 mm,[11] but this standard is one clinical estimated value while without any pathological evidence; so, there are some controversies, because clinical metastatic lymph nodes in some parts are often smaller. This study compared the features of lymph nodes measured by CT and obtained by postoperative pathology, aiming to investigate the diagnostic criteria of the shortest diameter of EC-MLNM, thus providing guidance for accurate preoperative staging and outlining radiotherapeutic target areas.

Method

Clinical data

A total of 305 patients with thoracic esophageal carcinoma admitted into the Fujian Cancer Hospital from January 2012 to December 2014 were collected, including 236 males and 69 females; aging 34-82 years, with the

mean as 58.3±8.2 years. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Fujian Medical University. Written informed consent was obtained from all participants.

Inclusion criteria: newly diagnosed, without distant metastasis or other malignant tumor, without any anticancer treatments before surgery and performed surgery within one week of CT scanning. The basic pathological situations of the patients are shown in Table 1.

Methods and parameters of CT scanning

PHILIPS Brilliance 256-slice spiral CT scanner (Eindhoven, Holland) was used for the scanning with the parameters as: tube voltage 120 kV, tube current 300-350 mA, scanning collimator 1 mm, pitch 0.9, scanning layer thickness 5 mm, layer spacing 5 mm, reconstruction layer thickness 2.5 mm, and layer spacing 2 mm. The enhanced scanning used one high-pressure syringe to rapidly inject 100 mL of non-ionic contrast agent (iodohydrin) from the elbow vein (injection rate 3 mL/s). Each patient was placed in the supine position when scanning, and the scanning area started from the supraclavicular fossa to the superior mesenteric artery level, the data of which was then transmitted into the Vitrea 2 workstation for multi-window and multi-planar reconstruction.

The classification criteria of intrathoracic lymph nodes referred to the standards revised by the American Joint Committee on Cancer-Union for International Cancer Control (AJCC-UICC) in 2009. Because partial surgical lymph node distribution methods are inconsistent with imaging methods, this study was based on the CT findings and compared with the pathological findings. In order to produce a better comparison, we requested that the surgeons divided the patients into different groups according to the locations of their individual lymph nodes resected surgically, namely the supraclavicular fossa group (SCF), the tracheoesophageal groove group (TEG), the paratrachea group (pT), the paraesophagus group (pE), the subcarina group (sC) and the lung hilum group (LH). Patients who could not be confirmed were excluded, and the biggest lymph node was calculated if more were in the same CT region. Other cases that cannot be concluded into corresponding areas were excluded.

TABLE 1 General pathological information of the patients.

Pathological information	n
Site	
Upper thoracic segment	15
Middle thoracic segment	206
Lower thoracic segment	84
T staging	
T0-1	57
T2	59
T3	142
T4	47
Pathological type	
Poorly differentiated SqCa	25
Moderately differentiated SqCa	254
Highly differentiated SqCa	15
Other	11

Imaging data acquisition

The best window width and position were adjusted and enlarged appropriately, targeting the grouping positions of the lymph nodes. Position, shortest diameter and number of the lymph nodes in the visual field were recorded and determined jointly by two physicians to obtain a consensus as the final result; at the same, one senior physician was arranged to be in charge of the quality control.

Pathological examination

The lymph nodes were dissected by EC radical correction as well as intraoperative thoracic + abdominal or cervical + thoracic + abdominal lymph node dissection, followed by pathological examination according to the grouping.

Statistical analysis

SPSS for windows 19.0 software package was used for the data entry and analysis; the diagnostic tests used the receiver operating characteristic (ROC) curve for the analysis, and the area under the curve, corresponding sensitivity, specificity, accuracy and the Youden index were also calculated.

Results

General information

Among the 305 patients with thoracic esophageal cancer enrolled into our study, the total number of the lymph nodes found by CT and confirmed pathologically was 1,043, including 203 with positive pathological confirmation and 840 with negative pathological confirmation. The lymph nodes of different zones are shown in Table 2.

Minimum diameter for diagnosing intrathoracic MLNM in esophageal carcinoma-mediastinal lymph node metastasis (EC-MLNM)

ROC curve analysis revealed that the shortest diameter of lymph node ≥ 8 mm can be set as the best standard for

TABLE 2 Lymph nodes found by CT in different zones (mm).

Distribution	SCF	TEG	pT	pE	sC	LH
Number of pathological positive	13	47	30	50	45	18
Min short diameter of pathological positive	3.5	3.0	4.4	4.2	4.2	5.2
Max short diameter of pathological positive	8.0	14.1	14.1	16.5	17.2	15.1
Number of pathological negative	40	132	191	146	245	86
Min short diameter of pathological negative	3.0	3.0	3.0	3.3	3.5	3.5
Max short diameter of pathological negative	9.3	12.8	17.7	10.1	22.8	12.4

SCF: supraclavicular fossa; TEG: tracheoesophageal groove; pT: paratrachea; pE: paraesophagus; sC: subcarina; LH: lung hilum.

diagnosing intrathoracic EC-MLNM, with area under curve (AUC) as 0.766 (Figure 1A), sensitivity as 54.5%, specificity as 87.9%, accuracy as 82.0% and the Youden index as 0.424. When the shortest diameter was set ≥ 10 mm, the sensitivity, specificity, accuracy and Youden index were 19.6%, 95.8%, 82.4% and 0.154, respectively; when the shortest diameter was set ≥ 5 mm, the sensitivity, specificity, accuracy, and Youden index were 93.7%, 21.4%, 34.2% and 0.151, respectively.

Minimum diameter for diagnosing EC-MLNM at supraclavicular fossa

The ROC curve analysis revealed that the shortest diameter of lymph node ≥ 5 mm can be set as the best standard for diagnosing EC-MLNM at supraclavicular fossa, with AUC as 0.785 (Figure 1B), sensitivity as 76.9%, specificity as 72.5%, accuracy as 73.6%, and the Youden index as 0.494. When the shortest diameter was set ≥ 10 mm, the sensitivity, specificity, accuracy, and Youden index were 0, 1, 75.4% and 0.000, respectively.

Minimum diameter for diagnosing EC-MLNM at tracheoesophageal groove

The ROC curve analysis revealed that the shortest diameter of lymph node ≥ 6 mm can be set as the best standard for diagnosing intrathoracic EC-MLNM at tracheoesophageal groove, with AUC as 0.755 (Figure 1C), sensitivity as 61.7%, specificity as 78.8%, accuracy as 74.3% and the Youden index as 0.405. When the shortest diameter was set ≥ 10 mm, sensitivity, specificity, accuracy and the Youden index were 8.5%, 97.7%, 74.3% and 0.062, respectively; when the shortest diameter was set ≥ 5 mm, sensitivity, specificity, accuracy, and the Youden index were 72.3%, 65.2%, 67.0%, and 0.375, respectively.

Discussion

The main clinical diagnostic methods against EC currently include:[12] esophageal barium contrast, chest CT scan, ultrasound or endoscopy; however, all these methods, except for CT, have obvious limitations in diagnosing esophageal carcinoma-lymph node metastasis (EC-LNM). Studies have shown that[13,14] CT can clearly show the existence of lymph node metastasis with high sensitivity, specificity and accuracy, so it can be used effectively to diagnose EC-LNM. Glazer et al.[15] proposed for the first time in 1984 that the shortest diameter of lymph nodes on CT is much more sensitive than the long and short diameters, which can avoid spatial errors. A shortest diameter of lymph node ≥ 10 mm is often used as the standard of CT to diagnose LNM; however, normal and metastatic lymph nodes overlap in size, so the accuracy of this diagnostic criterion is still controversial. Clinically, CT can reveal metastatic lymph nodes with shortest diameter of less than 10 mm. Takemura et al.[16] measured the shortest diameter of metastatic lymph nodes surgically dissected from patients with esophageal squamous cell carcinoma (ESCC) and found 65% of the samples had the shortest diameter less than 1 cm and 27% was less than 5 mm. A certain study has shown that[17] 63% of EC patients have the shortest diameter of metastatic lymph nodes measuring less than 10 mm. The results of our study showed that, compared with 10 mm, the shortest diameter set as 8 mm can effectively diagnose intrathoracic lymph node metastasis, and the sensitivity was increased from 19.6% to 54.5%, while the specificity and accuracy did not change much. So, 8 mm as the standard can exhibit more diagnostic value, and appropriately reducing the shortest diameter standard on CT toward EC-LNM is more rational.

Studies about the diagnostic criteria of CT in EC-LNM are many, while fewer studies are accompanied by pathological evidence, and recent studies just included mediastinal lymph nodes as part of their results for the sake of statistics.[18,19] Our study took into account the unique features of the lymph nodes at the supraclavicular fossa and tracheoesophageal groove, and performed statistical analysis toward them, respectively. Compared with simple intrathoracic lymph node metastasis, the prognosis of the patients with thoracic esophageal carcinoma, which metastasized toward the supraclavicular fossa, was signifi-

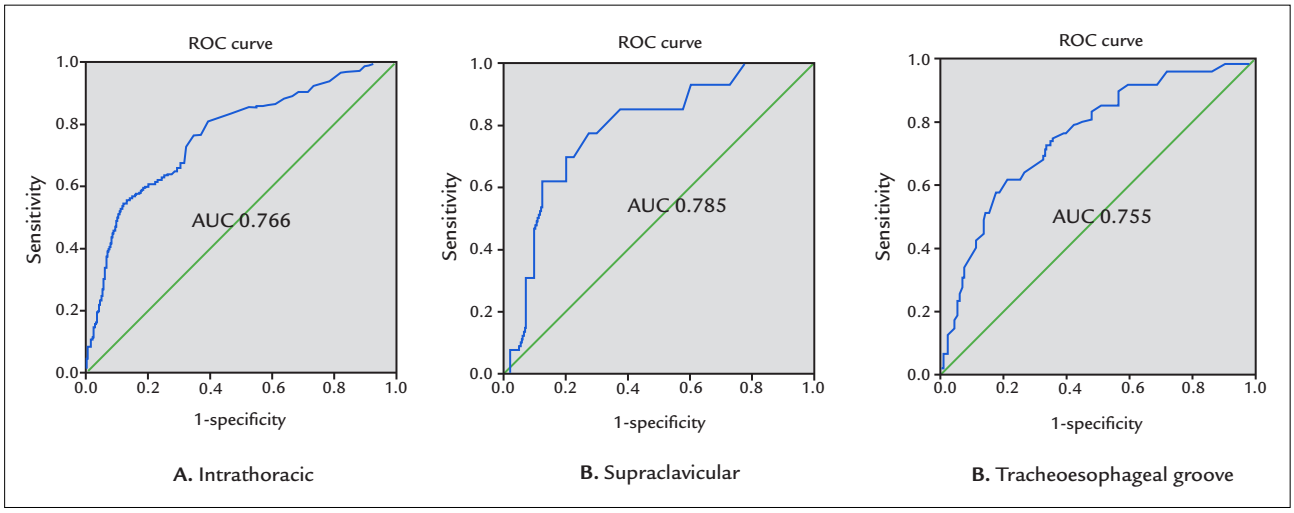

FIGURE 1 ROC curve of shortest diameter of lymph nodes in different areas.

cantly worse. At present, there is no related report about the CT diagnostic criteria targeting supraclavicular lymph nodes in EC. In our study, we considered that shortest diameter of EC-supraclavicular fossa LNM which can be diagnosed by CT is 5 mm. Patients with tracheoesophageal groove lymph node metastasis can present hoarseness, drinking cough, difficulty to breath or even death by asphyxia in severe cases, so it has become an independent risk factor of death. Kato et al.[20] considered that EC-tracheoesophageal groove lymph node metastasis can occur in any locations, lesions and tumor cell invasion ranges of primary tumor. Li et al.[21] believed that the rate of lymph node metastasis to cervical tracheoesophageal groove and medial supraclavicular zone from middle thoracic section of esophageal cancer was increased with later T stages. Schmidt et al.[22] considered that general people have lymph nodes in their tracheoesophageal groove, with an average of 3.24 and 5.52 lymph nodes in the left and right tracheoesophageal grooves, respectively. Clinically, lymph nodes at the tracheoesophageal grooves are often found with a shortest diameter significantly less than 10 mm on CT also confirmed on pathological examination. In our study, the shortest diameter for diagnosing EC-tracheoesophageal groove lymph node metastasis was 6 mm.

Lymphadenectasis may be caused by tumor metastasis as well as inflammatory enlargement, proliferative enlargement, or histiocytic hyperplasia-induced enlargement; some tumor cells may enter lymph nodes causing pathological features to take place despite any perceptible changes in nodal size. So, it will easily result in false-positive and false-negative conclusions if determining LNM only based on the lymph node size.[23,24] In addition to the sizes on CT, metastatic lymph nodes may also reveal changes in density, edge or shape to prompt the metastasis, so how to diagnose EC-LNM with both size standards and other diagnostic methods remains a unsolved problem that needs further studies. However, clinically, the shortest diameter is more practical and intuitive to be used as the standard.

Conclusion

The shortest diameters for diagnosing MLNM in the thoracic cavity, supraclavicular fossa and tracheoesophageal groove were 8 mm, 5 mm and 6 mm, respectively, and it is reasonable to reduce the CT diagnostic criteria of the shortest diameter of positive lymph nodes in EC.

Conflict of interest

The authors declare no conflict of interest.

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Postoperative local incision analgesia for acute pain treatment in patients with hepatocellular carcinoma

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Summary

Objective: The present study aimed to investigate the analgesic effect and safety of using local incision analgesia to treat acute postoperative pain in patients with hepatocellular carcinoma (HCC).

Method: A cohort of 60 patients undergoing liver cancer resection was randomly divided into three groups (n=20 per group): local incision analgesia (LIA) group, which received local infiltration with ropivacaine combined with a postoperative analgesia pump; intravenous patient-controlled analgesia (PCA) group, which received fentanyl intravenous analgesia postoperatively; and the control group, which received tramadol hydrochloride injection postoperatively according to the NRS scoring system. The postoperative analgesic effect in each group was compared and tumor recurrence (survival) was analyzed using the Kaplan-Meier method.

Results: NRS scores, rate of analgesic usage, ambulation time (h) and intestinal function recovery time (h) were significantly reduced in LIA group compared with the control group at each postoperative time point (6, 12, 24 and 48 hours; $p<0.05$). Additionally, the NRS scores of LIA patients at 12 hours post-surgery was significantly reduced compared with PCA group ($p<0.05$), and the occurrence of postoperative adverse events in LIA group was significantly lower than that in PCA group ($p<0.05$). Survival analysis demonstrated that the mean survival time (tumor recurrence) was significantly increased in LIA group compared with the control group ($\chi^2=4.749$; $p=0.029$).

Conclusion: Local incision analgesia improves the analgesic effect, causes fewer adverse reactions and increases postoperative survival time. Our study demonstrated that local incision analgesia is a safe and effective method of postoperative pain management following hepatectomy.

Keywords: Analgesia. Carcinoma, Hepatocellular. Pain, Postoperative. Survival Analysis.

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Introduction

Hepatocellular carcinoma (HCC) is an extremely malignant tumor that exhibits poor prognosis worldwide. Surgical intervention remains the most effective treatment for HCC;[1] however, open surgery to remove HCC tumors yields large surgical wounds, long incisions and excessive tissue damage, which can lead to severe acute postoperative pain. The pathophysiological changes induced by acute postoperative pain can cause systemic stress responses and immune function disorders; impact the circulatory, respiratory, digestive and endocrine systems; and increase postoperative complications. All of these are unfavorable events with poor prognosis.[2,3] Therefore, improving the management of postoperative acute pain in patients with liver cancer is important for postoperative rehabilitation. Previous studies suggest that[4-6] acute postoperative pain is predominantly caused by the surgical incision and that incision pain control is important for postoperative analgesia. The present study investigated the analgesic effect and safety of local incision analgesia in the treatment of acute postoperative pain in patients with HCC, providing clinical insight into the application of local incision analgesia.

Method

Setting

We conducted a blinded, parallel-group randomized controlled trial comparing the analgesic effect and safety of the three different methods of postoperative analgesia in patients undergoing hepatectomy in the Yinzhou Hospital Affiliated to the Medical School of Ningbo University. This work was approved by the ethics committee of the hospital and all patients signed an informed consent form.

Patients

Patients (n=60) who underwent scheduled hepatectomy between January 2014 and January 2016 were selected as subjects for the current study. All subjects were recruited through mass media advertisements, contact with professional groups, presentations at public events and a practice-based database, undergoing laparotomy with incision below the right costal margin. Exclusion criteria were: tumor status III or higher according to the American Society of Anesthesiologists; < 18 years of age; contraindication for ropivacaine or any other local anesthetics; presence of chronic pain; regular consumption of nonsteroidal anti-inflammatory drugs or opioids; psychiatric history; and cardiopulmonary dysfunction.

Randomization and blinding

The patients were randomized and divided into three groups according to the methods of postoperative analgesia: local incision analgesia group (LIA group; n=20), intravenous patient-controlled analgesia group (PCA group; n=20) and the control group (control group; n=20). For randomization, opaque and sealed envelopes were numbered consecutively, and a physician who was not involved in the trial kept the randomization list in a locked drawer until the trial was over and all follow-ups had been conducted. All patients were masked to the treatment groups assigned for the study.

Intervention

A total of 60 patients underwent tumor resection of the right liver. Of these, 20 patients had liver tumor located in the V and VI hepatic segments, 20 patients had their liver tumor located in the VI and VII hepatic segments, and 20 patients had their liver tumor located on the V and VII hepatic segments. In all of the patients, the incision was made below the right costal margin, with a wound measuring approximately 25 cm.

For treatment of the LIA group, 50 mL 0.25% ropivacaine was applied to the surrounding area and skin, the muscular layer and musculoaponeurotic layer of the incision using abdominal wall infiltration blocks. Simultaneously, a porous catheter was inserted through the skin at the incision site and connected to an external elastic transfusion pump (model TJPS120-1-100-2) filled with 250 mL 0.25% ropivacaine. The solution was released continuously at a 5 mL/h flow rate through the porous catheter. In the intravenous PCA group, patients were administered fentanyl solution (1.2-1.5 mg fentanyl and 10 mg tropisetron, diluted to 100 mL using 0.9% sodium chloride) using an intravenous pump device set with a 2 mL/h flow rate and 15 min locking time with 0.5 mL self-controlled solution. PCA patients received analgesia for two days. The control group (control group) received tramadol hydrochloride injections as postoperative analgesia following the numerical rating scale (NRS) scoring system.

The occurrence of other adverse reactions, including skin pruritus, respiratory depression, sleepiness and hepatic dysfunction were also observed and recorded. Patients themselves determined the pruritus of skin by their feelings, while doctors surveyed the incision exudation and sleepiness. ALT, a glutamic-pyruvic transaminase, is cited as the most sensitive monitoring indicator of liver function damage by the World Health Organization (WHO). Thus, ALT value was used to determine hepatic dysfunction.

All operations were performed using the same technique by the same surgeon with the patient under general anesthesia. Patient follow-up was conducted from the first day of surgical treatment until January 2016 in order to record time of survival (recurrence).

Outcomes

The primary outcome was rate of analgesia of all the patients at 6, 12, 24 and 48 hours postoperatively, which was recorded according to NRS scoring system[7] (0-10 points). The scoring system used was as follows: 0, painless; 1-3, mild pain, does not affect sleep; 4-6, moderate pain, affects sleep but is tolerable; 7-10, severe pain, intolerable and with lack of sleep.

Secondary outcomes included the adverse effects of analgesia and indicators of rehabilitation. Postoperative nausea and vomiting were recorded using the following scale: 1, no nausea or vomiting; 2, nausea, no vomiting; 3, nausea and vomiting. Adverse reactions, such as pruritus, respiratory depression, sleepiness or hepatic dysfunction were also observed. Indicators of rehabilitation, including the start time of off-bed activity, recovery time of bowel function and status of incision healing were recorded.

Statistical analysis

Statistical analysis of the data was performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Data are

presented as the mean ± standard deviation or a percentage. Comparisons between two groups were performed using an independent sample t-test. Enumeration data are described as rate and were analyzed using Pearson's Chi-square test. $p<0.05$ was considered to indicate a statistically significant difference. The Kaplan-Meier method was used to conduct survival analysis.

Results

Sixty (60) patients were recruited in the current study, and there was no patient lost at follow-up until hospital discharge (Figure 1). Among the three patient groups, no significant differences were found with respect to the gender, age, average height, average weight, average length of incision or average operating time ($p>0.05$; Table 1). Postoperative NRS scores at 6, 12, 24 and 48 hours in both LIA group and PCA group were significantly lower than those in the control group ($p<0.05$). Within 12 hours of the postoperative period, the NRS score in LIA group was significantly lower than that in PCA group ($p<0.05$); however, there were no significant differences between the NRS scores of LIA group and PCA group ($p>0.05$; Table 2) at the later time points (24 and 48 hours), which indicates that the effect of local incision analgesia was better than intravenous patient-controlled analgesia within 12 hours postoperatively. The nausea and vomiting scores of LIA group and the control group were 1.40±0.59 and 1.50±0.68, respectively, which were significantly lower than PCA group (2.20±0.77) ($p<0.05$); however, there was no significant difference between the scores of LIA group and the control group ($p>0.05$; Table 2).

The use of additional intramuscular injections of pain relievers, the start time of off-bed activity and the recovery

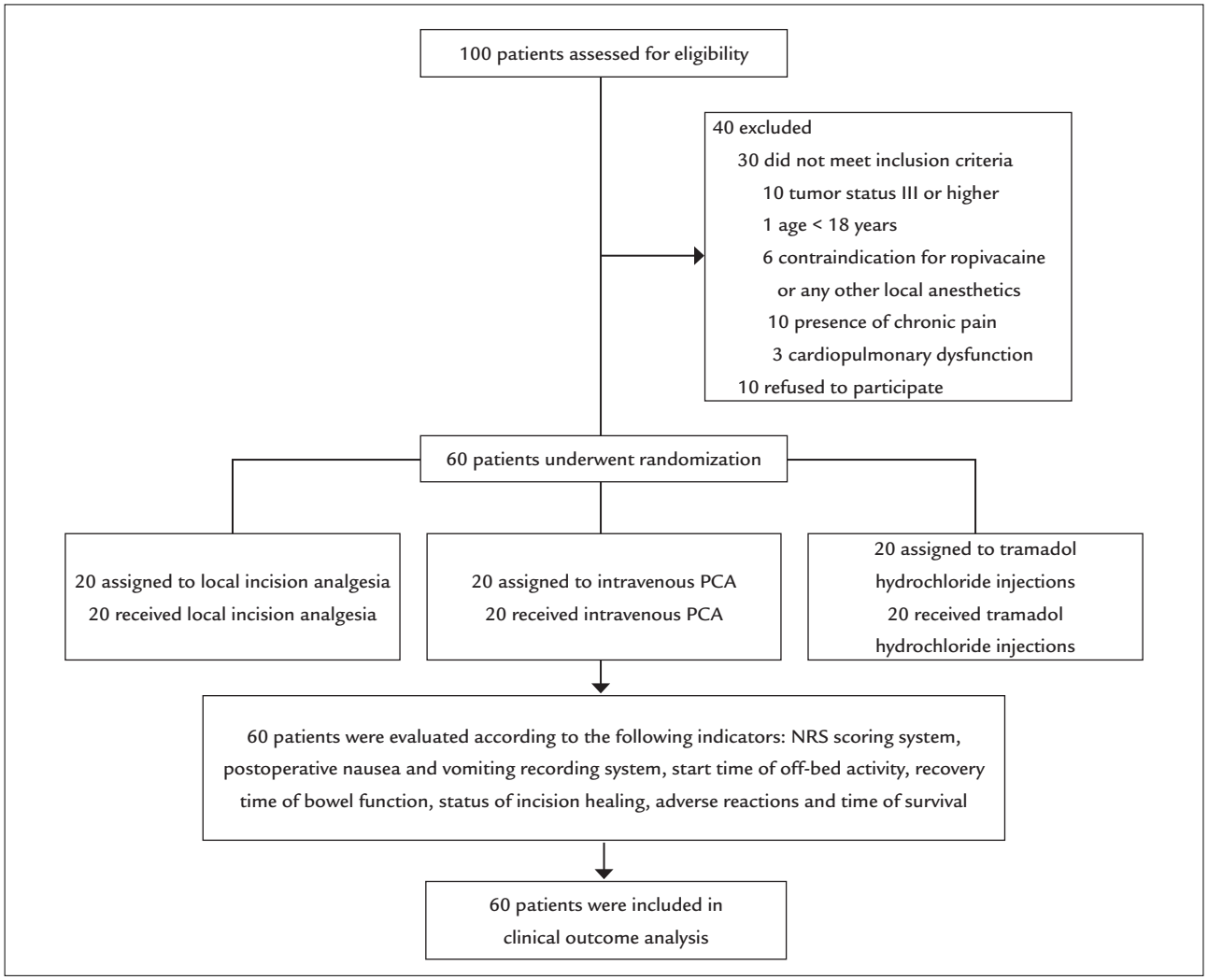

FIGURE 1 Flowchart of patient enrollment, allocation, follow-up and analysis.
PCA: patient-controlled analgesia.

TABLE 1 General characteristics of patients*.

Group	Male/female (n)	Age (year)	Height (cm)	Weight (kg)	Length of incision (cm)	Operative time (min)
LIA	15/5	47.61±10.26	165.89±6.53	63.58±9.71	20.35±1.31	150.10±24.31
PCA	14/6	46.92±10.60	163.72±6.82	65.21±8.71	20.01±1.52	152.21±25.11
Control	16/4	47.14±10.38	164.27±5.97	64.38±9.23	20.24±1.20	149.19±26.51

*Data are presented as mean ± SD (X ± SD).
LIA: local incision analgesia; PCA: patient-controlled analgesia.

TABLE 2 Scores of pain (NRS system) and nausea and vomit of the three groups (X ±S).

Group	n	Postoperative 6 h	Postoperative 12 h	Postoperative 24 h	Postoperative 48 h	Nausea and vomit score
A	20	1.95±0.99[a,b]	1.70±0.66[a,b]	1.55±0.51[a]	1.25±0.44[a]	1.40±0.59[b]
B	20	3.15±10.9[a]	2.90±0.97[a]	1.75±0.55[a]	1.45±0.51[a]	2.20±0.77
C	20	6.35±0.99	6.20±0.95	5.35±0.88	3.95±0.69	1.50±0.68[b]

Compared with group C, [a]p<0.05; compared with group B, [b]p<0.05.

time of bowel function in LIA group and PCA group were significantly different from that of the control group (p<0.05), while there was no significant difference between the two treatment groups (p>0.05). In LIA patients, four cases of incision exudation were observed, which was a significant increase compared with PCA group and the control group (p<0.05). However, timely detection of incision exudation ensured that no wound infection occurred and all wounds healed to grade A. The occurrence of other adverse reactions, including skin pruritus, respiratory depression, sleepiness and hepatic dysfunction (ALT values) were significantly higher in PCA patients compared with LIA and control groups (p<0.05), whereas no significant differences were detected between LIA group and the control group (p>0.05; Table 3).

Long-term follow-up was conducted for all 60 patients with HCC after surgery. Survival analysis demonstrated that the mean survival time (tumor recurrence) was 20.50±2.62 months for LIA and 20.40±3.64 months for PCA, with no statistically significant difference between the two groups (χ^2=0.012; p=.911). However, the mean survival time of patients in the control group was 11.22±0.86 months, which was significantly reduced compared with LIA (χ^2=4.749; p=0.029) and PCA (χ^2=3.904; p=0.048 (Figure 2).

Discussion

In addition to temperature, pulse, respiration and blood pressure, the control of postoperative acute pain has attracted increasing attention. In fact, control of postoperative pain remains a challenging problem. Postoperative acute pain is an acute noxious stimulation, predominantly resulting from direct damage of the nerve endings at surgical incision sites and inflammation caused by tissue damage. Acute pain can cause complications including physical trauma and psychological stress, induce coronary heart disease, lung infections, digestive dysfunction and deep vein thrombosis. Postoperative pain can also cause negative emotions, such as anxiety, fear, and depression, leading to disorders of the nervous, circulatory and immune systems, thereby delaying recovery and increasing medical costs.[8] Appropriate postoperative analgesia may prevent or reduce the occurrence of acute pain and associated conditions, improving postoperative recovery and quality of life. Therefore, the selection of analgesic methods is drawing increasing attention from surgeons. Currently, the most commonly used method of analgesia is an intravenous PCA pump, which is usually infused with opioid narcotic drugs, such as fentanyl. PCA pumps provide good analgesic effects that alleviate postoperative acute pain; however, they may cause adverse reactions, including respiratory depression, nausea and vomiting, sleepiness, cutaneous pruritus and hepatic dysfunction.[9,10] The results of the present study demonstrated that, compared with a control group, NRS scores in PCA patients gradually decreased over time, confirming the evident analgesic effects of PCA pumps. However, the incidence of postoperative adverse reactions, including nausea and vomiting, cutaneous pruritus, respiratory depression, sleepiness and hepatic dysfunction were significantly higher in PCA patients compared with the control group, indicating the potential risks of using a PCA pump as postoperative analgesic. These findings corroborate the results of studies previously reported by other authors.[10,11]

In our investigation, the efficacy and safety of incision local ropivacaine analgesia for patients undergoing hepa-

TABLE 3 Postoperative clinical indicators.

Group	n	Incision exudation (n, %)	Respiratory depression (n, %)	Sleepiness (n, %)	Skin pruritus (n, %)	Intramuscular injection tramadol (n, %)	Off-bed activity time (h)	Bowel function recovery time (h)	ALT value (U/L)
LIA	20	4 (20)[a,b]	0 (0)[b]	2 (10)[b]	1 (5)[b]	3(15)[a]	40.24±3.23[a]	70.54±7.72[a]	393.45±128.99[b]
PCA	20	0 (0)	7 (35)	8 (40)	6 (30)	4 (20)[a]	41.88±3.04[a]	71.71±5.97[a]	490.00±143.99
Control	20	0 (0)	1 (5)[b]	1 (5)[b]	0 (0)[b]	19 (95)	63.91±7.49	100.64±10.07	396.90±126.47[b]

Compared with control group, [a]p<0.05; compared with PCA group, [b]p<0.05.
LIA: local incision analgesia; PCA: patient-controlled analgesia; ALT: alanine aminotransferase.

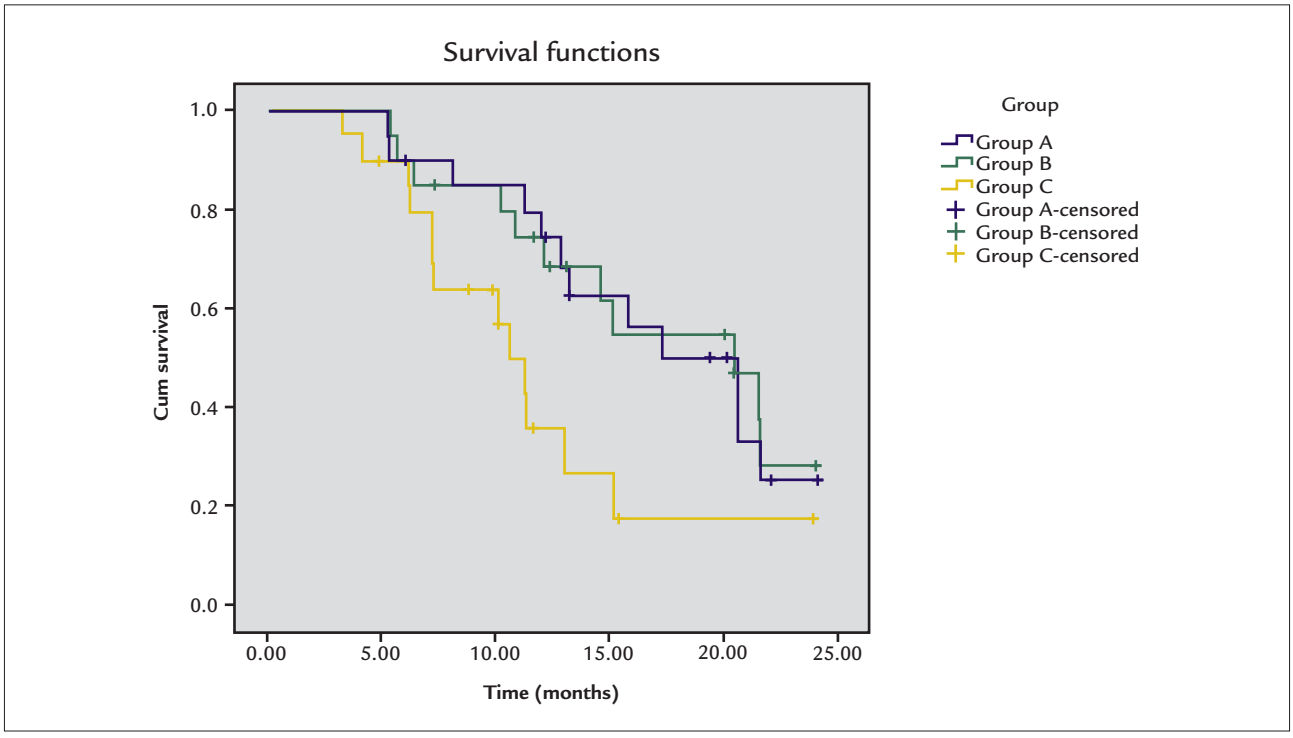

FIGURE 2 Postoperative survival curves (tumor recurrence time) of various treatment groups.

tectomy was evaluated by comparing the postoperative analgesic effect and adverse reactions following open hepatectomy. Ropivacaine is a long-acting local amide anesthetic with low neurotoxicity and cardiotoxicity. Ropivacaine is effective in alleviating postoperative incision pain, improving patient satisfaction with pain management and reducing the incidence of postoperative nausea and vomiting.[12-14] The present study using local infiltration with ropivacaine combined with a postoperative analgesia pump demonstrated a significantly increased analgesic effect in LIA patients compared with the control group. Compared with PCA group, the analgesic effect in LIA group was significantly higher at 12 hours after surgery. However, by 24 and 48 hours the analgesic effects in LIA group and B were not significantly different. Postoperative adverse reactions, including nausea and vomiting, cutaneous pruritus, respiratory depression, sleepiness and hepatic dysfunction were significantly reduced in LIA patients compared with the PCA group, suggesting that analgesia using ropivacaine may block the outer peripheral pain receptors and directly act on the peritoneum, muscle and fascia. Furthermore, this method may reach the areas with increased innervation, such as the subcutaneous tissues, and thus exert a more direct, rapid and efficient analgesic effect on postoperative acute pain. Additionally, ropivacaine reduced the side effects and overall impact on the patients. By reducing the impact of pain on breathing and circulation, this method enables the effective control of the incision pain during the early recovery of the patients, contributing to timely ambulation and early recovery of gastrointestinal function.

By promoting the timely rehabilitation of patients, it is also in line with the concept of fast-track surgery.[15]

Hepatic dysfunction is one of the most common postoperative complications following hepatectomy. The present study demonstrated that ALT levels of patients in PCA group were significantly higher than the scores in LIA group and control group at 24 hours ($p<0.05$). There was also a significant difference between the ALT levels of LIA group and the control group. This suggests that the systemic administration of opioids may interfere with the antioxidant defense system of the liver, triggering apoptosis in hepatocytes and elevation of liver enzymes.[16] As such, patients with liver cancer are at increased risk of hepatic dysfunction. Since intravenous PCA using opioids such as fentanyl increases the risk of hepatic damage leading to hepatic dysfunction or even liver failure, surgery should simultaneously remove HCC and the normal liver segment. Therefore, the local analgesic method using local incision infiltration combined with an incision analgesia pump may reduce the postoperative hepatic dysfunction and the incidence of complications. It should be noted, however, that postoperative hepatic dysfunction in patients with liver cancer is caused by the combined effect of various factors, including size of liver tumor that is removed, size of the remaining healthy liver tissue, duration of intraoperative hepatic portal occlusion, extent of invasion of the tumor and other perioperative indicators. Thus, to fully realize the benefits of incision local ropivacaine analgesia, the interactions and mechanisms of the various factors that causing postoperative hepatic dysfunction should be further explored.

Our study also demonstrated that the incidence of incision exudation in LIA group was significantly higher than the incidence in groups B and C. However, no incision infections were observed, as the incisions of patients in all LIA group achieved grade A healing. This indicates that the incision local analgesic method provides a safe and effective postoperative analgesic effect without affecting the healing of the surgical incision. The increase in the incidence of incision exudation in LIA group may be due to inadequate drainage, as postoperative incision infections are largely caused by local accumulation of inflammatory substances and tissue debris. The exudates were diverted out of the incision site via the porous penetration catheter of the analgesia pump, and wound dressings were frequently replaced to keep the incision clean and reduce the risk of infections. Kaplan-Meier analysis demonstrated that the use of local incision analgesia prolonged the postoperative survival time until tumor recurrence compared with the control group. This effect may be due to reduced immune dysfunction caused by improved control of the postoperative acute pain. Further research is, however, required to understand the mechanisms of such effects.

Conclusion

Incision local analgesia using ropivacaine provides an improved analgesic effect and increases the postoperative survival time of patients with HCC. Furthermore, the use of incision local analgesia results in fewer adverse reactions and complications, and increases patient satisfaction. Thus, incision local analgesia is a safe and effective analgesic method for managing postoperative acute pain in patients with HCC.

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Assessment of the prescription of red blood cell concentrates in the pediatric age group

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Summary

Objective: To verify the adequacy of red blood cell (RBC) prescription to pediatric patients in different sectors of a pediatric hospital.
Method: A retrospective study was conducted including 837/990 RBC transfusion requisition forms for children and adolescents (0 to 13 years old) filed in between January 2007 and April 2015 by the pediatricians of the emergency room (ER), infirmary ward and intensive care unit (pICU). Transfusion requisition forms belonging to patients with chronic anemia or acute hemorrhage, as well as incompletes requisition forms, were excluded.
Results: Trigger, prescribed volume and subtype of RBC concentrates were adequate in 532 (65.3%), 460 (58.8%) and 805 (96.2%) of the transfusions, respectively. When the clinical picture was considered, prescription adequacy was higher compared to the use of the hemoglobin level alone (70.9% vs. 41%). The pICU had the highest correct trigger percentage (343 [71.6%]; p<0.001) while the ER showed more often adequate prescribed volumes (119 [66.1%]; p=0.020). The most common inadequacy regarding volume was that of prescriptions above the recommendation > 15 mL/kg found in 309 cases (36.9%). Thirty-two (32) RBC subtypes were requested and none were consistent with current recommendations.
Conclusion: The results obtained in our study showed that RBC transfusion occurred more appropriately when the clinical picture was taken into account at request. There was a tendency to prescribe higher volumes and RBC subtypes without the justification of current protocols. Hemotherapic teachings at undergraduate level and medical residency must be improved.

Keywords: Transfusion Medicine. Erythrocyte Transfusion. Child. Prescriptions.

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Introduction

Performed since the 17th century, blood transfusion entered its scientific era in 1901 with the discovery of the ABO blood system by Karl Landsteiner.[1] Initially, the goal of transfusions was to maintain a hemoglobin (Hb) level greater than or equal to 10 g/dL.[2] Later, especially in the last two decades, publications have shown safety and superior results with lower triggers. Normovolemic patients were shown to tolerate Hb concentrations between 5 and 6 g/dL.[3] Regardless of the cause of anemia (decreased production of red blood cells, hemolysis or bleeding),[4] the goal of transfusion is to normalize the transport of oxygen[2] and, therefore, the transfusion trigger has different values in different situations, ranging from Hb 7 g/dL in clinically stable children,[5-8] with acute bleeding[9] and sepsis but no shock;[10] to 7-8 g/dL in the post-surgical period,[11-14] and 10 g/dL in case of severe sepsis or septic shock.[15,16]

Despite this knowledge, several services still adopt different transfusion protocols even for patients in similar clinical contexts, so that higher triggers relate to a greater frequency of transfusion reactions.[3,7,8,17,18]

Transfusion is a mortality risk factor in critically ill children[19] and may cause immune and non immune-mediated reactions including, more frequently: febrile non-hemolytic transfusion reaction, hemolytic reaction, alergies,

volume overload and infections.[1,2,5,20] Microcirculatory changes can also occur,[5,21] as well as increased incidence of cancers.[22] Reactions may occur in 0.95%[23] to 3.8% of cases.[24]

Calculation of the correct volume is also important, since low volume results in less than ideal yield and high volume is associated with risk of circulatory overload. This is one of the most common transfusion reactions, with a mortality rate of 12%.[20] In children with acute anemia and normovolemia, a volume of transfused red blood cells (RBC) concentrates between 10[25-27] and 15[25] mL/kg is indicated.

An appropriate choice of RBC subtype (filtered, irradiated, washed and phenotyped) influences the transfusion yield and causes fewer transfusion reactions in specific contexts.[2,25] Filtered RBC has 99% of its neutrophils removed and is indicated mainly to avoid febrile nonhemolytic reaction in polytransfusion and the transmission of cytomegalovirus in immunosuppressed patients.[25] RBC concentrates irradiated at 25 gray prevents clonal proliferation of donor lymphocytes in the immunodepressed recipient, thereby avoiding transfusional graft versus host disease.[25] Washed RBCs have the highest possible amount of their plasma replaced with 0.9% saline solution in order to remove plasma proteins that may cause anaphylactic reaction in individuals with congenital deficiency of some serum protein (immunoglobulin A, haptoglobin and ferritin) or who already presented a severe allergic reaction to the previous transfusion.[25] Phenotyped RBC is transfused to patients that required extended compatibility research between donor and recipient, in addition to ABO and Rh blood groups (kell, Duffy, Kidd and MNS). In pediatrics, this phenotyping procedure is carried out mainly in the poly-transfused to avoid erythrocyte alloimmunization.[25]

There are few studies evaluating the adequacy of RBC prescription in pediatrics[7,9,14], and those available in the literature evaluated the trigger, but not the volume and subtype indicated.

The objective of our study was to evaluate the transfusional trigger, the prescribed volume and the choice of red blood cell subtypes in children admitted into a public hospital and compare with current recommendations in the literature.

Method

A retrospective study carried out at Hospital e Pronto-Socorro Central de São Bernardo do Campo, in the Greater São Paulo area, Brazil. We reviewed the transfusion requisition forms for children and adolescents from 0 to 13 years of age, filled out by pediatricians from three sectors: Emergency room (ER), the infirmary ward and the pediatric intensive care unit (pICU) from January 2007 to April 2015.

During the study period, the pediatrics consisted of four beds in the emergency room, five in the observation room, 40 in the infirmary ward, and five pICU beds. The hospital did not include an obstetrical center, a nursery, a surgical center or oncology/hematology service. It did have a transfusion agency that stored some blood components and performed simple tests such as ABO and Rh blood typing, and direct and reverse cross-tests. Whenever a subtype of blood component was requested and the transfusion agency did not have it, the request was sent to the head office in the city of São Paulo. The supplied RBC preservative solution was CPDA-1 (citrate, phosphate, dextrose and adenine).

Of the 990 RBC transfusions performed during the study period, 837 were included in the series. In all, 94 and 59 transfusion requests were excluded because they were made for patients with chronic anemia (81-sickle cell disease, 11-bone marrow aplasia, 1-hemoglobinopathy C and 1-spherocytosis) and acute hemorrhage, respectively, on account of trigger variability in these two conditions and the absence of information in the form, which are essential for assessing adequacy. Later, we excluded 23 other requests from the transfusion trigger analysis and 55 from the prescribed volume analysis, as Hb value and the patient's weight, respectively, were not recorded.

In order to assess the adequacy of the transfusional trigger, prescribed volume and choice of RBC subtypes, we used the 2015 recommendations of the Brazilian Ministry of Health.[25] However, these guidelines do not discuss some of the situations found in our study. Therefore, to analyze the transfusion trigger in children older than 4 months, with acute normovolemic anemia but otherwise stable, we used the 2012 recommendations of the American Association of Blood Banks (7 g/dL).[6] To analyze the trigger in cases of septic shock, we used the recommendations of the American Heart Association – Pediatric Advanced Life Support (10 g/dL).[27]

Data collected from the transfusion requisition forms:

- General: age (months), gender, presence of underlying conditions and origin of the transfusion request form (ER, infirmary ward or pICU).
- Transfusion characteristics:
  - Trigger (reason and justification for transfusion): evaluated whether it was based solely on Hb value or clinical-laboratory correlation. All transfusions performed in patients with Hb levels below 7 g/dL were considered adequate. Requests for patients with Hb greater than or equal

to 7 g/dL were evaluated individually, taking into account the clinical reason, the presence of underlying disease and if there was hemodynamic decompensation.
- Volume prescribed: Volumes between 10 and 15 mL/kg were considered adequate.
- RBC subtype: the request for filtered, irradiated, washed or phenotyped components was evaluated, considering the presence of underlying disease and the patient's history.

The study was approved by the Research Ethics Committee of Faculdade de Medicina do ABC (Opinion no. 1.402.884).

The data were typed and consolidated into an Excel (Microsoft) worksheet and analyzed using SPSS 24.0 statistical program. Qualitative variables were described in the form of absolute numbers and percentages. Continuous variables were analyzed for their distribution and presented as mean ± standard deviation. To compare the qualitative data we used the Chi-square test. The confidence level was 5%.

Results

In our sample, the male gender predominated (471 [56.3%]), the mean age was 23.3 ± 8 months and the median was 8 months; 504 (60.2%) of the transfusions were performed in children less than 12 months old and the most common clinical contexts were hemodynamic and respiratory changes (Table 1). Regarding the origin of the transfusion request, 201 (24%) were made in the ER, 148 (17.7%) in the infirmary ward and 488 (58.3%) in the pICU (Table 1). A greater percentage of transfusions in patients older than 12 months were performed in the pICU compared to the ER and the infirmary ward (329 [65.2%] vs. 75 [14.9%] vs. 100 [19.8%], p<0.001). There was no difference between the places of origin of the transfusion request in relation to gender (p=0.441) and presence of underlying diseases (p=0.061).

The most common inadequacy, in relation to volume, was prescription above the recommendation (> 15 mL/kg; 309 [36.9%]) (Table 1). Mean Hb and mean prescribed volume were 8.3 ± 1.5 g/dL (range: 2.6 to 16.1 g/dL) and 15.2 ± 4.3 mL/kg (range: 4.9 to 57.1 mL/kg), respectively.

The clinical status was considered in 682 (81.5%) of transfusions (Table 1). There were 663 transfusions with a description of the clinical context that caused it (Table 1).

Trigger, prescribed volume and subtype of red cell concentrate were adequate in 532 (65.3%); 460 (58.8%) and 805 (96.2%) of transfusions, respectively (Table 2).

TABLE 1 General characteristics for the transfusions performed.

Variable		N	%
Gender	Male	471	56.3
	Female	366	43.7
Age	< 1 year	504	60.2
	1 to 2 years	123	14.7
	2 to 5 years	108	12.9
	5 to 10 years	74	8.8
	> 10 years	28	3.3
Clinical status	Septic shock	287	34.3
	Acute respiratory failure	124	14.8
	Pneumonia	117	14
	Hemodynamic decompensation	55	6.6
	Mechanical ventilation	32	3.8
	Other	48	5.7
	Not described	174	20.8
Underlying disease	Congenital heart disease	38	4.5
	NPCE	18	2.2
	Nephrotic syndrome	10	1.2
	Other	29	3.5
	No underlying disease	742	88.6
Origin	ER	201	24.0
	Infirmary	148	17.7
	pICU	488	58.3
Reason	Clinical	14	1.7
	Laboratorial	155	18.5
	Both	668	79.8
Pre-transfusion Hb	< 7 g/dL	125	14.9
	7 to 10 g/dL	582	69.5
	> 10 g/dL	107	12.8
	Lack of Hb record	23	2.7
Volume	< 10 mL/kg/day	13	1.5
	10 to 15 mL/kg/day	460	55
	> 15 mL/kg/day	309	36.9
	Lack of weight record	55	6.6
Subtype	Plain RBC	805	96.2
	RBC with subtype(s)*	32	3.8
	Filtered	24	2.9
	Irradiated	17	2.0
	Washed	10	1.2
	Phenotyped	0	0

*In some RBC concentrates there was a request for more than one subtype, so the sum of filtered, irradiated and washed is greater than the number of RBC packs with subtypes. ER: emergency room; NPCE: non-progressive chronic encephalopathy; Hb: hemoglobin; pICU: pediatric intensive care unit; RBC: red blood cells.

Among the clinical contexts that led to the indication of transfusion, there was a high adequacy in critically-ill children (94.5%, hemodynamic decompensation; 92.7%, acute respiratory failure; 87.5%, mechanical ventilation;

83.6%, septic shock). However, the adequacy was lower in children with non-severe conditions at the time of transfusion, such as pneumonia without respiratory failure or mechanical ventilation, with only 12% (Table 2).

pICU had the highest correct trigger percentage (343 [71.6%]; p<0.001), whereas ER had the prescribed volume right more often (119 [66.1%]; p=0.020) (Table 3) compared to the other groups.

There were 32 RBCs with subtype (3.8% of the total), 15 RBCs with only one subtype of red cells and 17 combining 2 or 3 subtypes. There was no difference between the sites of origin in relation to the subtype of red blood cells requested (Table 3).

Discussion

Our study identified that, among red blood cell transfusions performed, 1 in 3 and 41% were not in accordance with the current recommendations for indication and volume calculation, respectively. It should be emphasized that in none of the cases the use of specific subtypes of RBC would be indicated.

TABLE 2 Adequacy of red blood cell transfusion.

Variable		N (adequate)	% (adequate)
Clinical context (n=663)	Septic shock	240	83.6
	Acute respiratory failure	115	92.7
	Pneumonia	14	12
	Hemodynamic decompensation	52	94.5
	Mechanical ventilation	28	87.5
	Other	21	43.7
Trigger (n=814)	Adequate	532	65.3
Reason (n=814)	Clinical picture was considered	470	70.9
	Hb only	62	41
Pre-transfusion Hb (n=814)	< 7 g/dL	125	100
	7 to 10 g/dL	391	67.2
	> 10 g/dL	16	15
Volume adequacy (n=782)	Adequate	460	58.8
Subtype (n=837)	Plain RBC	805	100
	RBC with subtype(s)	0	0
	Filtered	0	0
	Irradiated	0	0
	Washed	0	0

Hb: hemoglobin; RBC: red blood cells.

TABLE 3 Comparison of the trigger, volume and subtype adequacy in relation to the site where red blood cell transfusion was performed.

	ER	Infirmary	pICU	p-value
Adequate trigger	121/188 (64.4%)	68/147 (46.3%)	343/479 (71.6%)*	<0.001
Adequate volume	119/180 (66.1%)*	66/131 (50.4%)	275/471 (58.4%)	0.020
Adequate subtype	191/201 (95.0%)	140/148 (94.6%)	474/488 (97.1%)	0.230

*Chi-square test significance level.
ER: emergency room; pICU: pediatric intensive care unit.

There was no difference between the male and female gender regarding the adequacy of the trigger, volume and subtype of the red blood cell concentrate. More than half of the transfusions occurred in children less than 1 year of age, data similar to those observed in a publication that included a similar population.[28]

In the trigger analysis, there was inadequacy mainly in transfusions based only on Hb values, without considering the clinical picture, with pre transfusion Hb ≥ 10 g/dL, performed in the infirmary ward and in patients with respiratory disease without respiratory failure or mechanical ventilation. The largest study ever published with a pediatric population has shown that the prescription of red blood cells based on current recommendations decreases the number of transfused RBCs by 44%.[7] However, the study included exclusively children hospitalized in the pICU and thus in a clinical scenario different from ours with more stable children.

With respect to the prescribed volume, attention was drawn to the request for volumes above the recommended level, which increases the risk of transfusion-related circulatory overload. This transfusion reaction is one of the most frequent, with a growing incidence in the past years and mortality of 12%.[20]

The prescription of a specific subtype of RBCs leads to a longer waiting time for RBC concentrates, which may influence the prognosis of an unstable patient. After analyzing the requisitions, no clear justification for prescribing these components was found.

The ER did not document the value of Hb in 6.5% of the transfusion requests, a fact that can be partly explained by the greater instability of the patients. The infirmary ward failed to record the weight in 1 out of 10 request forms. This fact may increase the risk of inadequacy of the prescribed volume. Failure to record the weight and/or type of Hb makes it impossible for the transfusion agency to detect if there is any indication or calculation error and thus act to improve the transfusion practice of the service.

Some hypotheses may be considered to justify the results obtained in our study. First, non-frequent updating of non-hematologic health professionals about proposed transfusion guidelines; second, the limited time available to address this issue in the medical undergraduate course and pediatric residency; and finally, the shortage of institutional continuing education programs on transfusion of blood components for the pediatric population.

Standardization of transfusion procedures according to current literature can reduce the cost of hospitalization, avoid waste of blood components and, especially, reduce the number of transfusion reactions.[29]

The implementation of continuing education in transfusion medicine should be emphasized at all levels (undergraduate, medical residency and professional) minimizing potential harm to the pediatric patient and the health care system. Emphasis should be given to the teaching of transfusion medicine in medical school and medical residency settings by both professor and preceptor, in addition to the updating of professionals by facilitating the provision of continuing education materials and courses, which could be done by hospital transfusion committees.

The results were reported to the hospital transfusion committee. Informative and up-to-date material on transfusional adequacy was prepared and is intended to be delivered to the pediatricians of the service, also available on the hospital's computers for consultation. Training for pediatricians who make RBC prescriptions at our institution was also proposed.

The strengths of this study include the number of transfusions analyzed, the analysis of requests made by pediatricians alone, a small percentage of loss (6.5%) and the availability of an official guide that has been continually updated to compare the results obtained.

Regarding the limitations, the retrospective design, a lack of more detailed data on the clinical characteristics of the patients and the absence of a control between prescribed vs. infused volume can be cited.

Conclusion

The results obtained in our study show that transfusion of RBC concentrates was more adequate when clinical status was taken into account. Also, there was a tendency to prescribe high volumes and subtypes of erythrocytes that cannot be justified according to current protocols.

Improving teaching of hemotherapy at medical undergraduate and residency levels as well as the implementation of a continuing education project for pediatricians who work with critically ill children are crucial.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Avaliação da prescrição de concentrados de hemácias na faixa etária pediátrica

Objetivo: Verificar a adequação na prescrição de concentrado de hemácias (CH) por pediatras em diferentes setores de um hospital pediátrico.
Método: Realizou-se estudo retrospectivo onde avaliamos 837/990 fichas de requisição de CH para crianças e adolescentes (0 a 13 anos), preenchidas entre janeiro de 2007 e abril de 2015 pelos médicos pediatras do pronto-socorro (PS), da enfermaria e da unidade de terapia intensiva (UTI). Excluíram-se as transfusões realizadas em portadores de anemia crônica, crianças com hemorragia aguda e requisições incompletas.
Resultados: Gatilho, volume prescrito e subtipo de concentrado de hemácias foram adequados em 532 (65,3%), 460 (58,8%) e 805 (96,2%) das transfusões, respectivamente. Quando foi considerado o quadro clínico, a adequação foi maior em comparação à prescrição pelo valor isolado da hemoglobina (70,9% vs. 41%). A UTI teve o maior percentual de acerto no gatilho (343 [71,6%]; p<0,001) e o PS, no volume prescrito (119 [66,1%]; p=0,020). A inadequação mais comum, em relação ao volume, foi a prescrição acima da recomendação (> 15 mL/kg, 309 [36,9%]). Foram solicitados 32 subtipos de CH e nenhum estava de acordo com as indicações atuais.
Conclusão: Os resultados obtidos mostram que a transfusão de CH aconteceu de forma mais adequada quando a situação clínica era levada em conta na solicitação. Houve uma tendência à prescrição de volumes elevados e de subtipos de hemácias não justificados segundo os protocolos atuais. É necessário melhorar o ensino de hemoterapia na graduação e residência médica.

Palavras-chave: Medicina Transfusional. Transfusão de Eritrócitos. Criança. Prescrições.

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Nonalcoholic steatohepatitis in posttransplantation liver: Review article

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Summary

Introduction: Nonalcoholic steatohepatitis (NASH) associated or not with cirrhosis is the third leading indication for liver transplantation (LT) around the world. After transplants, NASH has a high prevalence and occurs as both recurrent and de novo manifestations. De novo NASH can also occur in allografts of patients transplanted for non-NASH liver disease.
Objective: To evaluate recurrent or de novo NASH in post-LT patients.
Method: A literature review was performed using search engines of indexed scientific material, including Medline (by PubMed), Scielo and Lilacs, to identify articles published in Portuguese and English until August 2016. Eligible studies included: place and year of publication, prevalence, clinical characteristics, risk factors and survival.
Results: A total of 110 articles were identified and 63 were selected. Most of the studies evaluated recurrence and survival after LT. Survival reached 90-100% in 1 year and 52-100% in 5 years. Recurrence of NAFLD (steatosis) was described in 15-100% and NASH, in 4-71%. NAFLD and de novo NASH were observed in 18-67% and 3-17%, respectively. Metabolic syndrome, diabetes mellitus, dyslipidemia and hypertension were seen in 45-58%, 18-59%, 25-66% and 52-82%, respectively.
Conclusion: After liver transplants, patients present a high prevalence of recurrent and de novo NASH. They also show a high frequence of metabolic disorders. Nevertheless, these alterations seem not to influence patient survival.

Keywords: Nonalcoholic Fatty Liver Disease. Liver Transplantation. Fatty Liver. Metabolic Syndrome. Diabetes Mellitus.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) affects about a third of the Western population, being the largest cause of elevation of aminotransferases in the world.[1] It is a broad spectrum pathological condition that includes steatosis, steatohepatitis (NASH), fibrosis and eventually cirrhosis (Figure 1) and hepatocellular carcinoma (HCC).[2,3]

Steatosis may have a slow and asymptomatic course, but in 20% to 30% of cases it progresses to steatohepatitis, the stage of disease with the greatest potential for progression to cirrhosis and HCC (Figure 1).

Factors associated with the development of NASH include obesity, diabetes mellitus (DM), dyslipidemia and insulin resistance, which makes this disorder increasingly recognized as the hepatic component of metabolic syndrome (MetS).[4] Compared to the general population, NASH patients have increased cardiovascular risk and mortality.[5] The significant increase in morbidity and mortality due to the obesity epidemic caused NAFLD, especially NASH combined with cirrhosis, to become the 3rd largest cause of liver transplantation, with the estimate that it will be the leading cause in 20 years.[6,7]

After transplantation, some studies have observed up to 100% recurrence of NAFLD after 5 years.[8-10] The appearance of NAFLD in transplanted patients due to causes other than NASH, i.e. de novo NAFLD, was first described by Poordad et al.[11] in patients undergoing transplantation on account of hepatitis C. Due to better results after he-

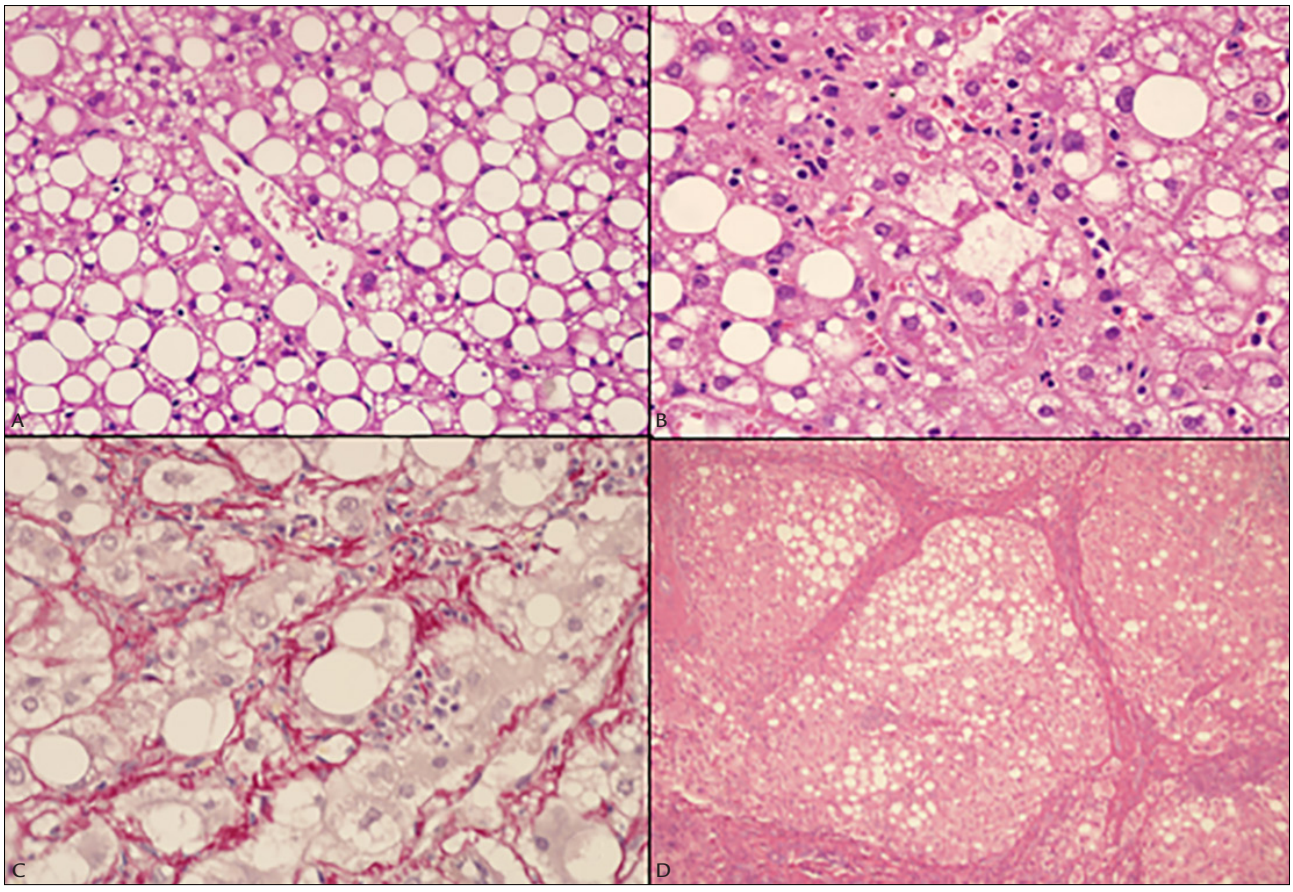

FIGURE 1 A. Steatosis: micro and macrovacuolar. B. Nonalcoholic steatohepatitis (NASH): steatosis, lobular inflammation and hepatocellular ballooning. C. Perisinusoidal fibrosis. D. Cirrhosis.
Courtesy of Professor Luiz Antônio Rodrigues Freitas.

patic transplantation, increased survival in the first year posttransplantation, and better control of chronic rejection,[12] an increased incidence of later changes such as de novo NAFLD and cardiovascular complications was noted.[13]

This review of the literature aimed to evaluate the relevance of recurrence or de novo NASH in liver transplant patients.

Method

Scientific articles indexed through PubMed, including Medline, SciELO and Lilacs, published in English and Portuguese, were used as search methods.

Prevalence, incidence, clinical characteristics, risk factors and survival in liver transplant patients were evaluated. The terms used in English were "NAFLD" or "NASH" or "steatosis" or "fatty liver" and "recurrency" and/or "liver transplantation." In Portuguese, we used as search terms "DHGNA" or "esteato-hepatite" or "esteatose" and/or "de novo", and/or "recorrência" and/or "transplante hepático." According to the study design, cross-sectional, longitudinal or descriptive investigations were included, with patients over 18 years of age, showing site and year of publication, prevalence and/or clinical characteristics of the patients, being published until August 2016.

Results

The initial search yielded 1,285 studies. We removed 423 duplicate articles and 752 after reading titles and abstracts, since they did not address the issue with relevance. Following the proposed theme, 110 articles were identified and 63 were selected. We excluded 47 articles because they were review studies or case reports. The selected studies were conducted in Europe, Asia and North America, and five were Brazilian.[14-17] Samples ranged from 7 to 10,204 patients and, due to the heterogeneity of the subject, the studies were grouped according to the following topics.

Survival

Sixteen (16) articles discussed the survival of patients transplanted by NASH (Table 1) and some of these articles

included in their statistics patients who were transplanted due to cryptogenic cirrhosis. No difference was observed in the mean survival of patients undergoing transplantation because of NASH compared to the survival of patients transplanted due to other etiologies. Only one study by Afzali et al.[18] showed survival at 5 years in NASH transplanted patients as higher than patients with alcoholic disease, hepatitis C (HCV) and hepatocellular carcinoma (HCC). Some studies failed to show differences in survival between patients transplanted due to NASH or other causes.[21,22,26,31] Malik et al.[31] found no difference in survival between patients who underwent transplantation due to NASH who relapsed compared to those who did not relapse.

Mortality and cardiovascular events are more common in patients transplanted due to NASH in the first few years after transplantation. We found 11 studies regarding cardiovascular mortality with a number of patients ranging from 21 to 5,653, totaling 7,662 patients evaluated with a follow-up period of 3 to 10 months. Cardiovascular mortality ranged from 7% to 26%.[18,22-24,26,27,31,33-36] Compared to transplanted patients due to other etiologies, the incidence is 15% higher in the first year[37] but does not increase the overall mortality after one year or in the long term compared to the other etiologies.[36,38]

TABLE 1 Survival of NASH patients undergoing liver transplantation.

Reference	Patients N	Survival 1 year (%)	Survival 3 years (%)	Survival 5 years (%)
Charlton et al.[6]	1,840	84	78	–
Afzali et al.[18]	1,810+3,843[cc]	87	81	75
El Atrache et al.[#19]	83	–	–	52
Dureja et al.[20]	11	78	–	–
Agopian et al.[21]	144	84	75	70
Kennedy et al.[22]	129	90	88	85
Barritt et al.[23]	21	76	76	–
Yalamanchili et al.[24]	18+239[cc]	86	–	71
Heuer et al.[25]	40	75	–	–
Bhagat et al.[26]	71	82	79	75
VanWagner et al.[27]	30	81	73	60
Houlihan et al.[28]	48	88	82	
Tanaka et al.[29]	7	100	100	100
Singal et al.[30]	1,368	86	82	80
Malik et al.[31]	98	79	74	72
Hejlova et al.*[32]	309	–	100	94

[#]Survival in a patient with metabolic syndrome.
*Evaluated the survival of patients with de novo NAFLD. In this study, the 10-year survival rate was 81%.
[cc]Cryptogenic cirrhosis was evaluated in conjunction with patients transplanted due to NASH in these studies.

Recurrence of NASH and de novo NASH

We selected 11 articles that addressed the recurrence of NASH, as shown in Table 2.

The studies of Contos et al.,[9] Ong et al.,[10] El Atrache et al.,[19] and Dureja et al.[20] found advanced fibrosis, greater than grade 3, in about 4% of the samples. Contos et al.[9] associate the increased recurrence of NAFLD with the use of corticosteroids. Charlton et al.,[39] in an earlier study conducted in 2001, showed 12.5% of cirrhotic patients, a percentage higher than the one found in more recent studies. It is possible that the higher frequency of recurrence in the older series, as well as the greater severity of the cases in that period, is related to the type of immunosuppression used at the time, more strongly based on corticosteroids.

We found eight articles reporting the presence of de novo NASH.

The onset of de novo NASH occurs as of the sixth month posttransplant, only after nutritional recovery from the immediate posttransplant.

As observed in Table 2, the incidence is high, and increases according to the follow-up time.[30,42] Hejlova et al.[32] found an increase from 30% after 1 year to 47% after 10 years. The series studied showed a low incidence of severe forms of the disease, at most 3%, except for Hejlova et al.[32] who showed 17% of advanced fibrosis, probably associated to the longer follow-up of the patients. Even so, there was no difference in the survival of patients with F3/F4 fibrosis compared to the others. There is no report of retransplantation or graft dysfunction.

The studies associate as factors related to de novo NASH the use of tacrolimus,[12] DM,[12] dyslipidemia,[12,30] high blood pressure (HBP),[12] alcoholic cirrhosis,[12] donor with a fatty liver[43] and weight gain after transplantation.[12,30,37]

Risk factors

Risk factors for NASH were found in 29 studies. Of these, eight reported on MetS. The authors observed that patients transplanted due to NASH have an incidence of MetS similar to those transplanted for other reasons, around 50% (Table 3). In the series evaluated by Laish et al.[35] and El Atrache et al.,[19] the population evaluated consisted exclusively of patients transplanted due to NASH. In the investigation by Seo et al.,[40] the population consisted of patients with de novo NASH. Despite the known relation between insulin resistance and metabolic syndrome, there are few articles evaluating posttransplant insulin resistance. The only studies, by Bianchi et al.[45], Anastácio et al.[14] and Veldt et al.,[59] showed a value of the HOMA index very close to that considered normal in the several populations and in the index study by Marchesini et al.[60] that considered 3

TABLE 2 Recurrence of NASH and de novo NASH in patients undergoing liver transplantation.

Reference	Patients N	Follow-up (months)	Recurrence		De novo	
			NAFLD (%)	NASH (%)	NAFLD (%)	NASH (%)
Yalamanchili et al.[24]	18	60	45	4		
Tanaka et al.[29]	7	120	14	–		
Bhagat et al.[26]	71	60	–	33		
Contos et al.[9]	27	>12	52	11		
Charlton et al.[39]	15	>12	60	33		
Dureja et al.[20]	88	>12	39	28		
El Atrache et al.[19]	83	45	–	24		
Ong et al.[10]	51	>24	25.5	16		
Vallin et al.[8]	11	>60	100	71.4		
Malik et al.[31]	98	60	–	25		
Agopian et al.[21]	144	60	15	8		
Seo et al.[40]	68	28			18	9
Sprinzl et al.[41]	129	24			34	5.4
Dumortier et al.[12]	421	>6			31	5.3
Kim et al.[43]	156	>12			27	6.7
Hejlova et al.[32]	546	>120			56.7	10
Lim et al.[37]	30	44			40	13
Vallin et al.[8]	80	>60			67	17.2
Finkenstedt et al.[42]	237	>60			32.6	

as cutoff point. Bianchi et al.[45] found a value of 3.1 in patients with MetS. Anastácio et al.[14] found 2.4 in a Brazilian population and Veldt et al.[59] 2.2 and 1.2 in diabetic and non-diabetic patients, respectively.

Posttransplant diabetes mellitus

Diabetes is often found in patients after liver transplantation. The population of pretransplant diabetics varies according to the etiology of the transplantation, most often NASH, and the characteristics of this population (obesity, age and ethnicity – more frequent among Westerners). Posttransplant diabetes (NODAT, New Onset Diabetes After Transplantation) is related to obesity, family history, glucose intolerance prior to transplantation, and hepatitis C as the etiology of transplantation, but it is also related to immunosuppressants. There are a number of studies arguing that the pathophysiology of NODAT is immunosuppressive toxicity in pancreatic B cells.[53,61,62]

As shown in Table 3, which includes 18 studies on diabetes, the longer the population follow-up, the higher the prevalence. Only one study associates NODAT with a lower frequency of sarcopenia and lower mortality in the first year posttransplantation. An explanation for this fact would probably be related to the better nutritional recovery seen in these patients.[57] There is no association of NODAT with graft dysfunction and decreased survival.[63] Even though studies evaluating patients with post-transplant NAFLD[8,19,40,45] yield prevalence rates for diabetes similar to those of the general population, there is an investigation by Stepanova et al.[64] including over 15,000 transplanted patients, some 3,000 of which transplanted due to NASH, which eventually concluded that the latter have a higher risk of developing DM.

Dyslipidemia, hypertension and obesity in liver transplant patients

It is known that transplanted patients have a higher incidence of dyslipidemia and hypertension. Currently, the basis of immunosuppressive treatment is performed with calcineurin inhibitors. Some studies compared patients who used different immunosuppressants. Bianchi et al.,[45] as well as other authors,[55,58] compared patients who used cyclosporine and tacrolimus, with an incidence of MetS of 52 vs. 60, HBP of 59 vs. 41, dyslipidemia of 57 vs. 38, and DM of 34 vs. 44, respectively. Although both favor metabolic disorders, cyclosporin is more associated with hypertension and dyslipidemia, whereas tacrollimus is associated with increased DM frequency (Table 3). The

TABLE 3 Frequency of metabolic disorders in patients undergoing liver transplantation.

Reference	Patients N	Follow-up (months)	MetS (%)	DM (%)	NODAT (%)	Dyslipid (%)	HBP (%)
Sprinzl et al.[41]	44	24	48				52
Seo et al.[40]	68	28		38		25	69
El Atrache et al.[19]	83	45	53	76			71
Hanouneh et al.[44]	148	60	53	59			60
Bianchi et al.[45]	296	38	45	38	29.4	50	52.7
Laryea et al.[46]	118	>60	58			48	62
Laish et al.[35]	252	>60	52				
Anastácio et al.[47]	148	>60	50				60
Yalamanchili et al.[24]	257	60		36.8			52
Lv et al.[48]	438	60		18			
Dumortier et al.[12]	421	>6		23.5		12	51.8
Marroni et al.[16]	75	>3		38			
Kennedy et al.[22]	129	>60		59			
Ong et al.[10]	13	>60		53			
Agopian et al.[21]	144	60		57			50
Vallin et al.[8]	80	>60		37.8			52
Parolin et al.[17]	82	20			18.9		
Mirabella et al.[49]	830	10			10.8		
Ling et al.[50]	10,204	30			24.3		
Carey et al.[51]	225	>12			17.3		
Saliba et al.[52]	211	24			22.7		
Moon et al.[53]	778	57			36.5		
Gisbert et al.[54]	85	>12				66	
Trotter et al.#[55]	57	>6				30	
Dehghani et al.*[56]	170	>12				70	
Marroni et al.[15]	75	> 3					14**
Darstein et al.[57]	255	>60					55
Hejlova et al.[32]	309	>120					67
Canzanello et al.¥[58]	158	>24					82

#The authors found 30% in patients who used cyclosporine and 6% with tacrolimus.

*The authors found 70% of hypertriglyceridemia and 15% of hypercholesterolemia.

¥The authors found 82% for cyclosporine and 64% for tacrolimus.

**Only new cases of posttransplant hypertension.

MetS: metabolic syndrome; DM: diabetes mellitus; NODAT: New Onset Diabetes After Transplantation; HBP: high blood pressure.

studies by Gisbert et al.[54] and Dehghani et al.[56] revealed that hypertriglyceridemia is the most frequent dyslipidemia in posttransplanted patients.

There are several investigations about obesity before transplantation and its influence on transplantation, graft dysfunction and mortality. Nevertheless, there are few studies evaluating posttransplant obesity. Seo et al.[40] found 10% weight gain in patients after transplantation. The statistics found vary from 20% to 36% of obese individuals in the population investigated.[38,46,65] Everhart et al.,[38] in a study assessing 774 patients, found the following risk factors for obesity: use of corticosteroids, genetic factors and recent marriage. Kouz et al.,[65] in turn, observed that obesity is more common in patients undergoing transplantation because of NASH compared to other etiologies. Regarding risk factors, obesity is associated with increased development of NODAT and de novo NASH.[12]

Discussion

The present review of the literature suggests that patients transplanted due to any etiology have a high incidence of NAFLD, mainly steatohepatitis (NASH), which is the phase with the greatest potential for progression of the disease in the posttransplant period. It occurs due to

recurrence of the disease or the onset of de novo NASH in transplanted patients due to other diseases. The frequency of both increases according to the time of follow-up. Higher recurrence is found in the older series, which may be related to the type of immunosuppression used at the time, more strongly based on corticosteroids.[9,30,39]

In the more detailed evaluations, the association between de novo NASH and use of tacrolimus,[12] DM,[12] dyslipidemia,[12,30] HBP,[12] alcoholic cirrhosis,[12] donor with a steatotic liver[43] and weight gain after transplantation[12,30,37] were observed. However, no differences were observed in the mean survival of transplant patients due to NASH compared to the survival of patients transplanted on the account of other etiologies even in the first year, when mortality associated with cardiovascular events is higher in patients transplanted due to NASH.

Similar to what is observed with NASH, there is a high prevalence of metabolic disorders in these patients, apparently related to the use of immunosuppressants.

When new cases of diabetes after transplantation (NODAT) are added to those of patients with diabetes prior to transplantation, prevalences of 50% can be found.[10,19,21,31] NODAT was observed in 10% to 36% of the population and was related to obesity, positive family history, glucose intolerance prior to transplantation and hepatitis C as the etiology of transplantation, in addition to immunosuppressants, especially calcineurin inhibitors.[53,62]

Numerous studies have demonstrated a higher incidence of dyslipidemia and hypertension in posttransplant patients. Some of them compared patients using different immunosuppressants. Among calcineurin inhibitors, currently the basis of treatment, cyclosporine has been shown to be more associated with hypertension and dyslipidemia, while tacrolimus is associated with increased DM frequency as previously mentioned.[45,55,58]

Although poorly studied in posttransplant patients, obesity was more commonly found in transplanted individuals due to NASH[65] compared to other etiologies, as well as association with NODAT and de novo NASH.[12] MetS was found in approximately 50% of patients after transplantation with no difference being found between patients transplanted due to NASH or other etiologies. A possible explanation for this fact should be the interference of immunosuppressants in the factors (DM, HBP, dyslipidemia and obesity) associated with MetS. In patients with non-transplanted NASH there is a strong correlation between MetS and insulin resistance; however, few studies have evaluated insulin resistance in this population. The few studies[14,45,59] evaluating insulin resistance based on the calculation of the HOMA index showed values very close to those considered normal. This aspect should be further evaluated in the future.

Our study has limitations, particularly its descriptive character, which does not allow conclusions based on strong scientific evidence. The heterogeneity of the studies regarding the topic addressed, the varied designs and the characteristics of the different populations hindered the performance of systematic analyses. Most of the studies evaluated were cross-sectional. Due to temporal differences related to the immunosuppressive regimen, many of these studies were not comparable, leading to biases in evaluation and clinical outcome.

Conclusion

Our review suggests that liver transplant patients have a high prevalence of steatosis and NASH, as well as post-transplant metabolic disorders. NAFLD/NASH after liver transplantation is usually not a serious disease and mortality is similar to that found in individuals who do not develop the disease.

Immunosuppressants appear to play an important role in the prevalence of NASH and its associated factors, as well as in the behavior of the disease. Further studies are still needed to better understand NAFLD/NASH after liver transplantation, especially its pathophysiology, treatment and prevention.

Resumo

Esteato-hepatite não alcoólica no pós-transplante de fígado: artigo de revisão

Introdução: A doença hepática gordurosa não alcoólica (DHGNA) é a terceira causa de transplante hepático no mundo. Tem elevada prevalência após transplante hepático (TH) e é representada pela recorrência da esteato-hepatite (NASH), ou por NASH *de novo*, que ocorre em pacientes transplantados por outra etiologia.
Objetivo: Realizar uma revisão da literatura para avaliar a relevância da recorrência ou do NASH *de novo* em pacientes transplantados de fígado.
Método: Realizada revisão da literatura através de artigos indexados no Medline, Scielo e Lilacs até 2016 publicados em inglês e português. Foram considerados elegíveis estudos que incluíram local e ano de publicação, prevalência e características clínicas dos pacientes.
Resultados: Foram identificados 110 artigos e selecionados 63, que avaliaram a recorrência de NASH, NASH *de novo* e sobrevida após o TH. A sobrevida foi de 90% a 100% em um ano e de 52-100% em 5 anos. A recorrência de

esteatose variou de 15-100% e a de NASH de 4-71%, enquanto esteatose e NASH *de novo* variaram de 18-67% e 3-17%, respectivamente. A frequência de síndrome metabólica, diabetes, dislipidemia e hipertensão variaram de 45-58%, 18-59%, 25-66% e 52-82%, respectivamente.
Conclusão: No pós-transplante de fígado, os pacientes apresentam elevada prevalência de recorrência, de NASH *de novo* e de distúrbios metabólicos. Entretanto, essas alterações parecem não influenciar a sobrevida dos pacientes.

Palavras-chave: Hepatopatia Gordurosa Não Alcoólica. Transplante de Fígado. Fígado Gorduroso. Síndrome Metabólica. Diabetes Mellitus.

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Pseudomyxoma peritonei in a pediatric patient: A case report and literature review

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Summary

Introduction: Pseudomyxoma peritonei (PMP) is a rare clinical condition, with an incidence of 1-2 cases per million, characterized by the dissemination of mucinous implants on the peritoneal surface and progressive gelatinous ascites. Although it usually presents an indolent behavior, its non-specific clinical presentation contributes to many cases remaining undiagnosed until a laparotomy is performed. With late diagnosis, performed after a long period of clinical deterioration and disease progression, it is common to find complications such as the formation of intestinal fistulas and obstruction.

Method: Review of the medical record and search for references in the Medline, Lilacs, SciELO and MD Consult databases.

Results: There are rare case reports found in the literature demonstrating atypical PMP presentations. Our report is that of a 17-year-old adolescent with a sporadic tumor diagnosed in a primary site in the transverse colon, contrary to data commonly found in the literature that mention a more frequent occurrence in women in the fifth decade of life and with a primary site in the ovary and appendix. The development of mucinous adenocarcinoma is rare in the pediatric population, and topography in the transverse colon and non-familial sporadic pattern are unusual.

Conclusion: The case reported not only raises awareness about the atypical presentations of the disease, but also emphasizes the use of imaging examinations for diagnosis, which has an important impact on prognosis and survival if performed timely.

Keywords: Pseudomyxoma Peritonei. Child. Tomography, X-ray Computed. Magnetic Resonance Spectroscopy.

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Introduction

Pseudomyxoma peritonei (PMP) is a rare clinical condition, with an incidence of 1-2 cases per million, and more frequent in women over 50 years (peak incidence at age 52). It is characterized by the dissemination of mucinous tumor implants on the peritoneal surface and the progressive development of gelatinous ascites throughout the abdominopelvic cavity, resulting in the so-called jelly belly.[1-4]

PMP has different forms of presentation and is classified into three subtypes: disseminated peritoneal adenomucinosis (DPAM), which includes histopathologically benign peritoneal lesions; peritoneal mucinous carcinomatosis (PMCA), which includes malignant lesions of a more aggressive course; and a third borderline subtype called peritoneal mucinous carcinomatosis, which exhibits intermediate features.[5-7]

It has an indolent behavior, with nonspecific clinical manifestations resulting from the compression of intra-abdominal structures, such as distension and pain, mechanical or functional intestinal obstruction, intestinal habit changes, nutritional failure and malnutrition secondary to increased pressure, fistulae, and infection.[1,2,8]

Although ovary and appendix are implicated as the most common primary sites, PMP may also originate

from other sites such as the ovarian tubes, pancreas, spleen and small intestine, while in some cases the primary site remains unknown.[1,2]

Imaging findings make an important contribution to the diagnostic elucidation, with computed tomography being the most used modality. Its main findings include ascites with low attenuation coefficient and the presence of heterogeneous mass with soft tissue density, which may or may not reveal gross calcifications or septations.[1,9]

To date, few cases of PMP in young patients with primary site located in the colon have been described in the literature. For this reason, we report this case of PMP in a 17-year-old pediatric patient evaluated using whole body CT and MRI.

Method

We performed the analysis of the medical record plus a bibliographic search in the Medline, Lilacs, SciELO and MD Consult databases.

Results

Clinical findings

A 17-year-old male patient, mixed race, medical student from the state of Amazonas, referred to the pediatric oncology department of this hospital complaining of four months of colic-type pain in the hypogastrium associated with dysuria and fever. The clinical picture progressed with weight loss, gastric fullness, postprandial vomiting and increased abdominal volume. On admission, the patient had a flat abdomen with a palpable abdominal mass of hardened consistency extending from the pelvis to the epigastric region, measuring approximately 20 cm.

He did not present previous comorbidities or family history of neoplasia. He denied having a habit of smoking or alcohol abuse. Laboratory results on hospital admission revealed left shift leukocytosis, platelet count at 768,000, CEA at 14.5 (RV up to 9.0) and CA 19.9 at 114.8. We observed a progressive increase in the levels of CEA and CA 19.9 over time.

Imaging findings

The patient brought an abdominal ultrasound from another service, which showed hypoechoic images with solid consistency, measuring about 8 cm in the epigastrium and mesogastrium, and also in the left iliac fossa, measuring 5 cm.

He underwent a CT scan of the abdomen and pelvis that revealed expansive lesions presenting soft tissue density, sometimes with foci of diffuse calcifications distributed in the abdominopelvic cavity, involving and displacing structures such as small intestine and colon loops towards the left flank, as well as surrounding the structures of the hepatic hilum, and causing scalloping of the liver capsule (Figure 1).

Whole-body magnetic resonance imaging was also performed, as it is a method that allows the visualization of the entire body with high resolution. The method has been gaining relevance in the evaluation of pediatric patients, since it does not use ionizing radiation, which has the potential to cause damage to the DNA with consequent increase in the risk of cancer. MRI showed multiple disseminated confluent lesions in the peritoneal cavity, with lobulated contour, exerting a compressive effect on the abdominal structures, especially on the hepatic surface, where the contours of the organ appeared scalloped, as well as compression and displacement of intestinal loops. These lesions showed low signal intensity on T1, and high intensity on Stir and diffusion weighted sequence (Figure 2).

Anatomopathological findings

A mass biopsy of the peritoneal cavity was performed, resulting in a histological study compatible with mesenchymal neoplasia, showing giant and signet ring cells. Immunohistochemical analysis compatible with high-grade mucoprodutant colon adenocarcinoma with loss of protein expression of the repair genes MLH1 and PMS2 (Figure 3).

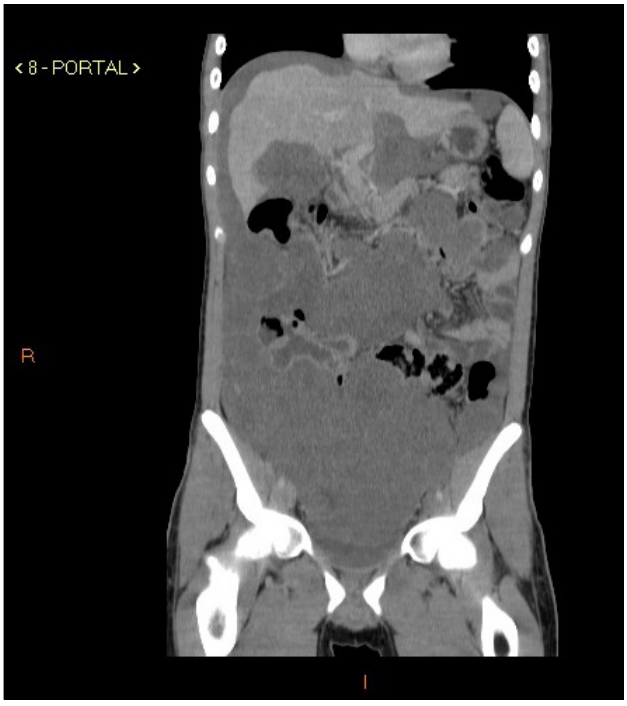

FIGURE 1 Multiple hypodense lesions throughout the peritoneal cavity, displacing intestinal loops and scalloping of the liver capsule.

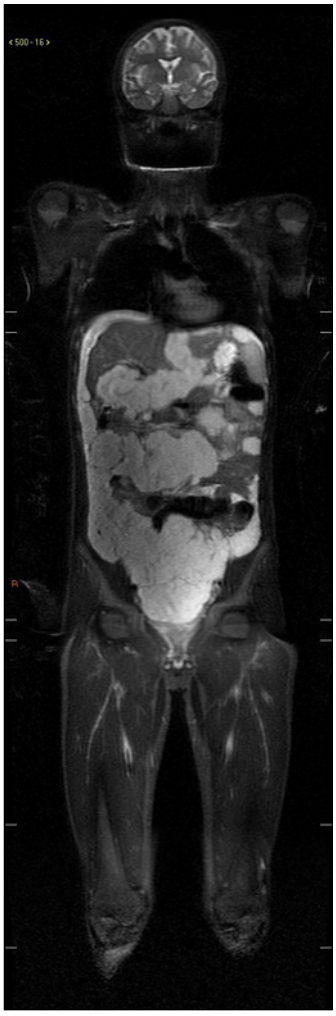

FIGURE 2 Coronal stir sequence demonstrating multiple disseminated peritoneal lesions with high intensity signal. No lesions were found elsewhere in this study.

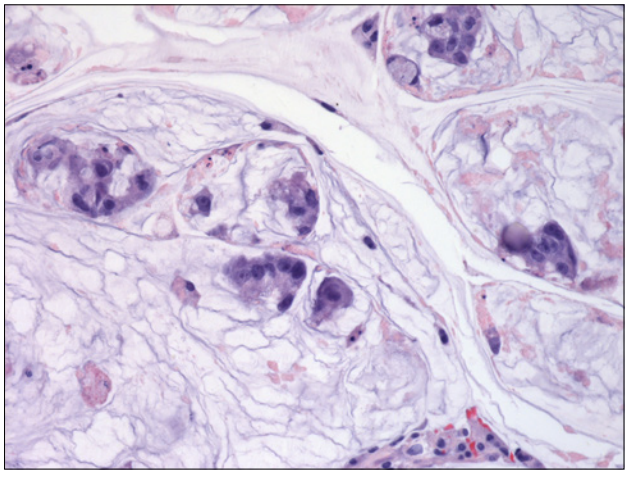

FIGURE 3 Slide demonstrating neoplasm with mesenchymal appearance, exhibiting giant and signet ring cells.

Treatment

The patient underwent surgery under general anesthesia with a xipho-pubic incision allowing extensive investigation of the entire cavity. We were able to visualize: ascites mucinous, voluminous mass in the mesogastrium involving the omentum, right and transverse colon, sparing the appendix, transverse mesocolon and mesenteric root, multiple peritoneal and pelvic implants and masses in the supra-mesocolic area involving the splenic and hepatic hila and the small gastric curvature. There was no evidence of involvement of the hepatic parenchyma and large vessels. We considered performing cytoreduction in two steps, with the infra-mesocolic approach performed first due to its greater extension and symptoms. Enterectomy, extended right hemicolectomy with colostomy at the level of the splenic flexure, anastomosis of the descending ileum, and resection of abdominal and pelvic mass were performed.

Follow-up

Patient presented disease progression, with inadequate response to oxyplatin chemotherapy. He underwent surgery for cytoreduction in the supra-mesocolic area, and a large amount of mucin was found in the abdominopelvic cavity, with diffuse infiltrative pattern carcinomatosis involving the mesenteric root, hepatic hilum and pelvis, with the disease progressing aggressively in the previously operated area. Due to the criteria of irresectability and intolerance to chemotherapy, the patient was treated with palliative care, evolving with septic shock and death about 15 months after the onset of symptoms.

Discussion

PMP is an uncommon clinical condition, with an incidence of 1 for every 5,000 laparotomies, characterized by the presence of ascites and diffuse mucinous neoplastic cells in the abdominal cavity. It is most evident in women after the fifth decade of life, with the ovary being the most frequent primary site, with a predominance of the cecal appendix in men.[2,3,5,6,10-12] The reported case refers to a male adolescent, aged 17 years at diagnosis, the primary site being the transverse colon, with histology compatible with sporadic mucinous adenocarcinoma, as opposed to reports commonly found in the literature. [2,3,5,6,10,11]

Although it usually presents an indolent behavior, its non-specific clinical presentation contributes to many cases remaining undiagnosed until a laparotomy is performed. With late diagnosis, performed after a long period of clinical deterioration and disease progression, it is common to find complications such as the formation

of intestinal fistulas and obstruction, consequent to the occupation of the whole cavity by mucinous masses.[5,11,13]

Imaging tests play an important role in diagnostic elucidation and therapeutic planning. Computed tomography (CT) is considered the imaging modality of choice, with findings that may be considered pathognomonic. Characteristic findings include the presence of amorphous areas of low attenuation with foci of hyperattenuation, which represent solid material with mucin, which may or may not be associated with foci of gross calcification or septation. Scalloping of the visceral surfaces, especially the spleen and liver, may also contribute by differentiating the mucinous ascites from other forms of ascites. The pattern of disease distribution initially at sites of limited peristalsis, progressing to occupy the entire abdominal cavity, also helps in the investigation.[1,5-7,11,14,15]

Contrast-enhanced tomography may provide information such as signs of obstruction in small bowel loops and intra-abdominal masses greater than 5 cm, indicating the risk of incomplete cytoreduction, which is critical for surgical programming.[11,16]

Although it is an innocuous and widely available imaging modality, ultrasonography cannot be used alone because mucinous ascites can resemble free intraperitoneal fluid. It can be used, however, to guide fine needle biopsies, providing a cytological diagnosis.[5]

Although the role of nuclear magnetic resonance still remains unclear, this method has shown promise for staging and treatment planning. In the case reported, classic findings guided the diagnosis of pseudomyxoma peritonei. Whole-body MRI also demonstrated masses with mucous appearance exerting compressive effect on the structures of the abdominal cavity scalloping of liver and spleen. There were no signs of distant metastases.[7,10,11,15]

Clinical evaluation of our patient with PMP included the investigation of tumor biomarkers, namely CEA and CA 19-9, generally found at high levels in situations such as this. These biomarkers are related to prognosis and, if levels are high, they are associated with a higher risk of relapse and lower overall survival, despite aggressive therapy.[10,17-19]

There is still no consensus on the best PMP treatment; the strategies vary widely, according to the clinical picture and extent of the disease. Cytoreductive surgery, which consists of the macroscopic removal of tumor masses, combined with intraperitoneal and systemic postoperative hyperthermic chemotherapy, are the strategy of choice for attempted cure. Patients eligible for the procedure cannot be older than 75 years, have severe or decompensated comorbidities and extensive disease affecting the mesentery and small intestine (with more than one point of stenosis), the hepatic hilum, pancreas, abdominal wall, retroperitoneum and extraperitoneal structures.

If the patient is unable to undergo the procedure, palliative resection of part of the disease can be performed to guarantee relief of symptoms. In some cases, palliative clinical treatment may also be performed with symptom control and clinical follow-up through physical examination and investigation of laboratory markers depending on the patient's conditions.[2,9,16,20,21]

Conclusion

Due to the rare occurrence and presence of nonspecific clinical manifestations, PMP remains a diagnostic challenge for both physicians and radiologists. It is important to recognize their forms of atypical presentation, which may include young patients with unusual primary sites such as spleen, pancreas, colon, urachus, and other organs. It is also essential that radiologists are aware of the specific imaging aspects, providing early diagnosis with a consequent impact on disease prognosis.

Resumo

Pseudomixoma peritoneal em paciente pediátrico: relato de caso e revisão de literatura

Introdução: O pseudomixoma peritoneal (PMP) é uma condição clinica rara, com incidência de 1-2 casos por milhão, caracterizada pela disseminação de implantes de natureza mucinosa pela superfície peritoneal e acúmulo progressivo de ascite gelatinosa. Embora apresente geralmente um comportamento indolente, a apresentação clínica inespecífica contribui para que muitos casos permaneçam sem diagnóstico até a realização de laparotomia. Com o diagnóstico tardio, realizado após um longo período de deterioração clínica e progressão de doença, é comum encontrar complicações, como a formação de fístulas e obstruções intestinais.
Método: Revisão do prontuário médico e pesquisa bibliográfica nas bases de dados Medline, Lilacs, SciELO e MD Consult.
Resultados: São raros os relatos de caso encontrados na literatura que demonstram apresentações atípicas do PMP. O presente estudo apresenta o caso de um adolescente com 17 anos ao diagnóstico e sítio primário no colón transverso com tumor esporádico, contrário aos dados comumente encontrados na literatura, que referem acometimento mais comum em mulheres na quinta década

de vida e com sítio primário em ovário e apêndice. O desenvolvimento de adenocarcinoma mucinoso é raro na população pediátrica e a topografia no cólon transverso e padrão esporádico não familial também são pouco usuais. **Conclusão:** O caso relatado alerta para as apresentações atípicas da doença e enfatiza o uso de exames de imagem para o diagnóstico, que, se realizado precocemente, impacta de maneira importante o prognóstico e a sobrevida.

Keywords: Pseudomixoma Peritoneal. Criança. Tomografia Computadorizada por Raios X. Espectroscopia de Ressonância Magnética.

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