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SUMMARY

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AMB Guidelines Program

Programa Diretrizes da AMB

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It has been 17 years of struggle, during which many have participated. Naming these individuals is not necessary, for they all continue to fight for the rights of patients, and their names are not hidden, they are public who take responsibility for what they think and write.

The struggle has been to keep the program running funded with AMB's own resources, without the support of those who, exercising an eminently political function, insist that there is a conflict of interest in the AMB guidelines. They are understandably unable to admit their own economic and political conflicts, and to critically appraise the fundamental elements of evidence-based guidelines.

The Guidelines Program is the space we have used to convey recommendations whose sole purpose is to increase benefits and reduce harm to patients. These recommendations express the thoughts of experts and are written primarily based on the best available evidence. Speaking on the basis of the best available evidence implies knowing how to obtain it, criticize it, synthesize it and translate it, considering the experience and expectations of both doctors and patients.

Many specialists are involved in the development of thousands of recommendations, distributed in more than 700 guidelines, which receive methodological guidance from a technical team of the AMB itself, with experience in systematic review and the language of guidelines.

The whole process begins with the elaboration of relevant clinical doubts by specialists (in Brazil, our program was the first to develop guidelines based on questions). These doubts are structured in a PICO (Patient, Intervention or Indicator, Comparison and Outcome) format, seeking to facilitate the organization of questions and the construction of search strategies. Searches are performed minimally on Medline, and usually on more bases. The selection of references is based on previously established eligibility criteria (the main ones being PICO and design), and this entire process is clearly displayed in the guideline's methodology section. After selection of evidence, data regarding the characteristics of the studies, their biases and outcomes of clinical interest are extracted. The strength of evidence is estimated using grading systems such as Oxford and GRADE. With such information in hand, the authors are able to develop the recommendations by estimating their level of uncertainty, and the magnitude and precision of benefit and/or damage effects.

The specialists from medical specialty societies that are part of AMB are not mere validators of a previously prepared text, but authors who, together with AMB's technical team, develop all stages of elaboration. After the guidelines are finalized, all AMB specialty societies that did not participate in the elaboration of that particular document are consulted so that they have the opportunity to contribute.

In Brazil, unfortunately, apart from the AMB Guidelines Program, "they" are always producing "booklets" with methodology for developing guidelines (true Portuguese versions of international manuals). Despite all the resources they have, very little has been done. Moreover, what has been done lacks a level of attention to evidence, medical experience and, worse, attention to the patient's needs, operating through two health systems (private or government-funded) divided into two guidelines that are NOT based in evidence: 1. Guidelines without limits, in which everything is accepted, and 2. Guidelines with strict limits, according to which almost nothing can be accomplished.

The AMB Guidelines Program, regardless of what "they" say, is reputable, very reputable, transparent, very transparent, exempt, has method, and contradicts many interests, including "theirs". But it never contradicts the interests of patients and, with all of its limitations resulting from these individuals' constant boycott and omission, it endures thanks to the willingness, dedication and selflessness of thousands of medical specialists. We are always open to all criticism and suggestions from those who have the interest and/or ability to do so.

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Ethical issues on the "synthetic" phosphoethanolamine clinical trial

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Summary

Notwithstanding its approval by the National Committee for Ethics in Research (Conep) on April 19, 2016, a trial of the so-called "synthetic" phosphoethanolamine (syn-phospho) pill in cancer patients raises ethical concerns. An analysis by a laboratory contracted by the Ministry of Science, Technology and Innovation (MCTI) revealed that syn-phospho contained a great amount of impurities and did not meet standards of pharmaceutical quality required for an investigational drug. Cytotoxicity against human tumor cell lines and in vivo rodent xenograft tumor assays consistently failed to demonstrate a potential anticancer activity of syn-phospho. Preclinical safety studies of syn-phospho were also insufficient to support a trial of this investigational drug in cancer patients. Moreover, the ethical approval decision apparently overlooked two previous findings that suggested a possible enhancement of mammary carcinoma cell proliferation by phosphoethanolamine, and an apparent increase in lung metastases (rat implanted tumor assay) by syn-phospho. The syn-phospho risk-benefit ratio is clearly unfavorable and, thus, this trial in cancer patients does not fulfill a key requirement to make a clinical research ethical. There are also concerns regarding whether the study design is robust enough (scientific validity), and the social value of the trial of syn-phospho in cancer patients is questionable.

Keywords: bioethics, clinical trial, investigational new drugs, neoplasms, preclinical drug evaluation, risk-benefit assessment.

Study conducted at the National School of Public Health, Fundação Oswaldo Cruz (Fiocruz), Rio de Janeiro, RJ, Brazil

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According to a nationwide registry of research in human subjects (www.saude.gov.br/plataformabrasil), the National Committee for Ethics in Research (Conep) cleared a clinical trial protocol entitled: "Evaluation of safety and efficacy of synthetic phosphoethanolamine in patients with advanced solid tumors" on April 19, 2016. A further search on the National Agency of Sanitary Surveillance (Anvisa) online registry of clinical trials (http://portal.anvisa.gov.br/consulta-de-ensaios-clinicos-autorizados) indicated that the agency did not authorize this new oncologic drug study in patients. As far as an investigational drug is concerned, for the sake of best protection of research subjects, clearance of clinical research by both Conep and Anvisa is required. It is of note that Anvisa is theoretically better equipped than Conep for a thorough analysis of preclinical data and clinical study protocols.

Furthermore, a bill that authorizes production, prescription and consumption of syn-phospho as an anticancer medication passed the Congress and the president signed it into law (Law 13,269/2016) on April 13, 2016. Since syn-phospho remains nearly untested for safety and efficacy, this law represents an unprecedented shortcut for a normally lengthy, costly and highly selective way to develop and approve a new drug for marketing. The syn-phospho law was challenged by a lawsuit (Direct Unconstitutionality Action) filed by the Brazilian Medical Association (AMB) and the full board of the Federal Supreme Court (STF) suspended its efficacy until a final decision by the court. The STF ministers who voted for a temporary suspension of syn-phospho law cited the lack of clinical studies in their declaration of vote.

Notwithstanding the approval by the Conep system, the syn-phospho trial in cancer patients does not fulfill at least three of seven key requirements to make a clinical research ethical. These requirements to protect the people participating in research (i.e., value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent and respect to enrolled subjects) are found in universally accepted codes,

declarations and other documents, and were clearly delineated by Emanuel et al.[1]

A first concern about the syn-phospho clinical study refers to whether its potential benefits for patients and the knowledge gained by society do in fact outweigh the risks for participants. One can always say that any clinical trial of a new drug or therapeutic intervention poses risks to subjects no matter how many nonclinical tests have preceded them. Owing to uncertainties regarding extrapolation between species and other methodological limitations of toxicity tests, preclinical safety evaluations can never rule out entirely the risks posed by a new medicine to patients. Nonetheless, regulators, bioethicists and most scientists agree that preclinical safety studies can disclose a number of potentially serious health hazards posed by a new and previously untested drug.[2] Therefore, the conclusion that an investigational drug is reasonably safe to be tested in humans must always stand on the best evaluation of data from nonclinical in vitro and in vivo studies.

Guidelines for clinical development of new pharmaceutical products issued by different regulatory agencies and international organizations are clear about this ethical requirement. The guidance by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (CIOMS-WHO), for instance, states explicitly (comments to guideline 8): "[...] clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk."[3]

The trial of syn-phospho in cancer patients does not comply with this ethical requirement because there are few preclinical studies on this compound and available data point towards an unfavorable risk-benefit ratio. Not only did laboratory and animal screening tests fail to demonstrate a potential anticancer activity, but also syn-phospho toxicity profile available at the time of ethical approval decision and trial onset were clearly insufficient to support test in humans. Moreover, Conep overlooked data from two experimental studies suggesting possible harm to cancer patients.

The first major problem with this clinical trial protocol is the poor characterization of the "new" drug under investigation.[4] Phosphoethanolamine ($NH_2CH_2OPO_3H_2$, syn phosphorylethanolamine, O-phosporylethanolamine; CAS Number 1071-23-4; Molecular weight 141.06) is an intermediate in the synthesis of phospholipids that serve as components of cell membranes. Within the cells, it is formed by ethanolamine kinase-mediated phosphorylation of ethanolamine. This primary amine can also be synthesized in the laboratory and a highly pure phosphoethanolamine (O-phosphoethanolamine ≥ 99.0% pure) is offered by a commercial supplier (Sigma-Aldrich Product Catalog Number # 27640). Phosphoethanolamine, irrespective of whether its origin is endogenous or exogenous, is a single molecule, thus receiving identical Chemical Abstract Service (CAS) Registry number.

Gilberto Chierice and coworkers, however, placed the adjective "synthetic" before phosphoethanolamine to label the chemical synthesized at their own laboratory (at the University of São Paulo, São Carlos campus). In six articles, Chierice and coworkers reported the effects of syn-phospho on cytotoxicity and xenograft tumor rodent assays.[5-10] It is of note that in five of these six studies the authors did not declare the purity of the test compound,[5-7,9,10] and in one study they informed that syn-phospho (analyzed by high-performance liquid chromatography) was 99% pure.[8] A Nuclear Magnetic Resonance (NMR) analysis conducted by an independent laboratory (University of Campinas – Unicamp) contracted by the Ministry of Science Technology and Innovation (MCTI), however, found that phosphoethanolamine accounted for only 32.2% of the so-called "synthetic" phosphoethanolamine.[4] The remaining constituents were impurities such as of Ca-, Mg-, Fe-, Mn-, Al-, Zn- and Ba-phosphates (34.9%), monoethanolamine (18.2%), pyrophosphates (3.6%) and phosphobisethanolamine (3.9%).[4] The diversity and amount of impurities in syn-phospho indicate that its effects on nonclinical and clinical tests may result from constituents other than phosphoethanolamine, or even to an interaction between constituents.

In any clinical trial application, regulatory agencies generally require from investigators and sponsors sufficient information regarding pharmaceutical quality, or the proper identification, quality, purity and strength of the investigational drug. The drug's pharmaceutical quality must also be uniform and consistent across batches used in preclinical and clinical studies to ensure that the preclinical safety evaluation and subsequent clinical trials tested essentially the same investigational drug product. Based on the results from the MCTI-contracted chemical analysis, syn-phospho is far from meeting standards of pharmaceutical quality required for investigational drugs.

In December 2015, the MCTI contracted a limited set of preclinical studies of syn-phospho consisting of in vitro assays (cytotoxicity, and genotoxicity tests) and in vivo rodent (acute toxicity, mouse bone-marrow micronucleus test, rodent xenograft tumor test, and 7 and 28 day repeated oral dose test in rats).[11] These preclinical studies were still in progress when the Conep approved the clinical trial protocol and thus it is unclear whether

their results influenced the Committee's decision-making. At any rate, this limited set of toxicity tests is clearly insufficient to support a clinical trial of an investigational drug. A sub-chronic/chronic toxicity study (longer than 28 days) in both rodent and non-rodent species, for instance, is missing. The fact that phosphoethanolamine is a natural substance and that syn-phospho pills are already in use by many cancer patients is not a valid argument for waiving a thorough preclinical safety assessment of this investigational drug. Drug adverse effects other than short-term toxicity generally remain unrecognized unless experimental and/or epidemiology observational studies are conducted.

The guidelines by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (e.g., ICH guidelines for non-clinical safety studies to conduct clinical trials)[2] clearly state that: "Nonclinical safety studies [...] should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported." According to the ICH recommendations and other guidelines, a nonclinical safety evaluation must include repeated-dose studies in two species (one non-rodent), the duration of which should be at least equivalent to that of the clinical trial to be supported (e.g., to support a 6-month clinical trial, durations of nonclinical repeated dose assays must be 6-month or longer). Repeated dose studies in two species with adequate duration to support a clinical study of syn-phospho in cancer patients were not available, nor were these studies in progress or even contracted by the MCTI at the time of research protocol approval and trial onset. Furthermore, a study by Kano-Sueoka et al.[12] found that phosphoethanolamine was a growth factor of rat mammary carcinoma cells in culture, while results from a study contracted by the MCTI suggested that syn-phospho may have enhanced the number of lung metastases in rats implanted with Walker 256 carcinosarcoma.[13]

It is noteworthy that experimental tests on a possible anticancer activity of syn-phospho or (pure) phosphoethanolamine yielded disappointing results. The studies by Chierice and coworkers[5-10] and those further contracted by the MCTI[12,13] showed consistently that syn-phospho has very low cytotoxicity. Syn-phospho was toxic to tumor and non-tumor cell lines only in the mM (10^{-3} M) concentration range while most oncologic drugs used in clinical practice (e.g., sunitinib, cisplatin, doxorubicin, and more) are toxic to cancer cell lines at μM (10^{-6} M) or even nM (10^{-9} M) concentrations. Moreover, the effects of syn-phospho on rodent xenograft tumor growth were modest and inconsistent across experiments.[11,13] Chierice et al.[6-8] used the intraperitoneal (ip) route (an unlikely route of administration for a human drug) to treat immunocompetent mice bearing transplanted tumors and thus indirect effects of ip administered syn-phospho (and its impurities) on tumor growth mediated by immune-stimulation cannot be ruled out.

In summary, not only preclinical safety studies are insufficient (and there exist concerns regarding a possible stimulation of cancer cell proliferation), but also experimental studies failed to find evidence that syn-phospho has an antitumor activity. In other words, there is no reasonable prospect that syn-phospho (or highly pure phosphoethanolamine) would bring concrete benefits to cancer patients and, in addition, the nonclinical toxicity profile is limited and unclear.

A second concern refers to the scientific validity of the clinical study. To be scientifically valid, a trial must be soundly designed and robust to demonstrate whether syn-phospho is an effective and safe oncologic drug. Unfortunately, contrasting to FDA clinical trial register system, Brazil's platform registry does not allow the public to learn about the study's design. It is unclear, for instance, whether this is a randomized trial. Random assignment and concealed allocation of trial participants are necessary to avoid systematic differences between baseline characteristics of groups that are being compared. Randomization is particularly complex in oncologic treatment trials. Although not providing details on the inclusion and exclusion criteria, the Brazilian platform registry informs that patients diagnosed with 11 different general ICD codes will be eligible. Taking into account that enrolled patients possibly are at different stages of the disease, that they underwent different prior therapies and are under different concomitant treatments, investigators will face a tremendous challenge in comparing drug effects on two groups of this highly heterogeneous population of patients. What are the clinical efficacy endpoints selected for this trial (overall survival, progression-free survival, time to progression, time to treatment failure, event-free survival, and so on)?[14] Moreover, how did investigators estimate the sample size needed to provide a statistically and clinically meaningful response to the central research question (anticancer efficacy and safety of syn-phospho)?

A third concern refers to the social value of this trial. As mentioned above, preclinical studies failed to demonstrate the antitumor activity of syn-phospho. In addition, no documented case report and no medical records corroborated the anecdotal reports saying that patients with cancer improved after taking syn-phospho pills. It is fair

to conclude, therefore, that there is nothing but unfounded rumors to support the syn-phospho clinical trial. Since the underlying hypothesis that syn-phospho would be an effective oncologic drug is weak, not to say very unlikely, on what grounds does the social value of this clinical trial stand? One could argue that there is a pressing need to respond to a "clamor by society" regarding the alleged anticancer effects of syn-phospho, and that this "clamor" would be sufficient to justify a clinical trial. From a medical ethics standpoint, this argument is questionable because it is not fair to expose patients to a novel drug with its inherent health risks – including a possible adverse impact on the patient's adherence to a well-established oncologic treatment – if there are no reasonable prospects of therapeutic benefits. In other words, it does not seem to be ethically acceptable to conduct a clinical trial just to put an end to an unfounded rumor. There is no doubt that there is a pressing need to respond to society's questions on this matter. The straightforward answer, however, should be that available scientific evidence indicates clearly that syn-phospho has no potential antitumor activity and thus there is no convincing rationale for conducting a clinical trial in cancer patients. Needless to reaffirm, for the sake of the patients' best protection and health benefits, that clinical research must conform to generally accepted scientific and ethical principles, as well as be supported by scientific literature and results from previous nonclinical laboratory and animal studies.

Resumo

Questões éticas sobre o ensaio clínico da fosfoetanolamina "sintética"

Não obstante a sua aprovação pela Comissão Nacional de Ética em Pesquisa (Conep) em 19 de abril de 2016, um ensaio da pílula de fosfoetanolamina "sintética" (sin-fosfo) em pacientes com câncer levanta preocupações éticas. Uma análise feita por um laboratório contratado pelo Ministério da Ciência, Tecnologia e Inovação (MCTI) revelou que a sin-fosfo continha grande quantidade de impurezas e não satisfazia os padrões de qualidade farmacêutica exigidos para um medicamento experimental. Os ensaios de citotoxicidade com linhagens de células originárias de tumores humanos e testes *in vivo* em roedores com tumores xeno-enxertados falharam consistentemente em demonstrar uma potencial atividade anticâncer da sin-fosfo. Os estudos pré-clínicos de segurança da sin-fosfo também foram insuficientes para apoiar a realização de um ensaio desse medicamento experimental em pacientes com câncer. Além disso, a aprovação ética aparentemente desconsiderou dois achados anteriores, sugerindo uma possível exacerbação da proliferação de células de carcinoma de mama pela fosfoetanolamina, e um aparente aumento de metástases pulmonares (ensaio de tumores implantados em ratos) pela sin-fosfo. A relação risco-benefício é claramente desfavorável para a sin-fosfo e, portanto, esse ensaio em pacientes com câncer não atende um requisito essencial para que uma pesquisa clínica seja ética. Há também preocupações quanto ao delineamento do estudo ser suficientemente robusto (validade interna), e o valor social do ensaio da sin-fosfo em pacientes com câncer é questionável.

Palavras-chave: bioética, ensaio clínico, novo medicamento experimental, neoplasias, avaliação pré-clínica de medicamentos, ponderação risco-benefício.

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Phototherapy with PUVA: Versatility and efficacy in dermatoses

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Introduction

Phototherapy is used in the treatment of several dermatoses, many with high prevalence and chronic progression.[1,2] Its classification is made according to the type of irradiation: ultraviolet A (UVA – between 320 and 400 nm wavelength) or ultraviolet B (UVB – between 290 and 320 nm).[1] The range of UVB between 311-312 nm is called narrow-band.

The immunological basis of phototherapy is the activation of immune-modulating cascades caused by the absorption of UV rays by chromophores of the skin. Cell membrane and DNA damage[3] occur due to photochemical reactions that have anti-inflammatory, immunosuppressive and antiproliferative effects.[1,4]

In order to determine the time and intensity of the sessions, a minimal erythematous dose (DEM), which is the minimum energy required to produce a uniform erythematous response within 24 hours, is calculated. Treatment is started with 75 to 90% of this dose. The energy is gradually increased to minimize adverse reactions and potentiate the treatment.[1]

PUVA treatment uses oral or topical psoralen followed by exposure to UVA irradiation.[4] Psoralens are tricyclic furocoumarins derived from plants and activated by UV rays.[4,5] The PUVA procedure with oral psoralens should be preceded by ophthalmologic evaluation and serum dosage of ALT, AST, gamma-glutamyltransferase (gamma GT), alkaline phosphatase, urea, creatinine, BHCG for women of childbearing age and antinuclear antibodies (ANA) to detect potential sensitivity to R-UVA. Topical PUVA, in turn, is indicated primarily for patients with hepatic or gastrointestinal dysfunction, cataract, drug interactions, and for children.[4,5]

The absolute contraindications for PUVA are xeroderma pigmentosum, some genodermatoses, systemic lupus erythematosus, dermatomyositis, previous history of melanoma and trichothiodystrophy. Relative contraindications include age less than 10 years, previous or current history of non-melanoma skin cancer, immunosuppressive treatment, gestation, cataracts, severe hepatic dysfunction, and history of systemic malignant tumors.[2]

Adverse effects include increased risk of melanoma and non-melanoma skin cancer, gastrointestinal changes, erythema, burns and pruritus. There may be conjunctival changes and early cataract, justifying ocular protection with sunglasses for at least eight hours after ingestion of psoralens. As a late manifestation there is photoaging.[1,4,6] Medical supervision and periodic laboratory evaluation are fundamental, as well as avoiding sun exposure with the use of physical and chemical barriers during treatment.[2]

This article aims to report three clinical cases, one of psoriasis, one of vitiligo and one of pityriasis alba, treated with PUVA with excellent response and, thus, show the diversity of dermatoses that can be treated with this therapeutic option. All the patients authorized in writing the use of their images as illustration of the cases by signing Free and Informed Consent Terms (FIC) forms.

Case reports

Case 1

Female patient, 21 years old, student. Diagnosis of vitiligo since 2007, treated in the past with topical and oral corticosteroids with no satisfactory response (Figure 1A). She denies any previous history of dermatoses or use of medications. We requested laboratory review and ophthalmologic evaluation as recommended, all within normal limits, before starting PUVA (8-methoxypsoralen 0.6 mg/kg) therapy twice weekly.

The patient progressed with xerosis and erythema in the lesions. We prescribe hydration and topical corticoid (0.1% mometasone furoate ointment) with good response and therefore without the need to discontinue treatment. After 44 sessions, the patient presented significant and satisfactory improvement of the lesions, with increased local pigmentation and improvement of achromic macules (Figure 1B). She is currently being treated with PUVA with gradual improvement of symptoms.

Case 2

Male patient, 48 years old, trader. Diagnosis of psoriasis 10 years ago (Figure 2A), with symptoms progressing. He has used unknown topical medications in the past. The patient denies other treatments, comorbidities, allergies and use of medications. PUVA therapy was indicated with 8-methoxypsoralen 0.6 mg/kg twice weekly. Laboratory review and ophthalmologic evaluation were requested before the start of treatment, in accordance with the protocol for phototherapy. After 14 sessions, the patient presented excellent results with significant improvement of psoriatic plaques (Figure 2B). Phototherapy was maintained as treatment.

Case 3

Male patient, aged 13 years, student, presenting hypochromic macules with indistinct margins and follicular papules located on the face (Figure 3A), compatible with pityriasis alba. He was being treated with hydrocortisone acetate 1% cream and moisturizer without satisfactory response. The patient denied having any comorbidities, other medications and allergies. Based on this information, we requested laboratory review and ophthalmologic evaluation, later recommending PUVA therapy with 8-methoxypsoralen 0.6 mg/kg twice weekly. After 21 sessions, the lesions showed complete improvement (Figure 3B).

Discussion

Biochemical exams and ophthalmologic evaluation were performed in all patients before PUVA treatment due to the

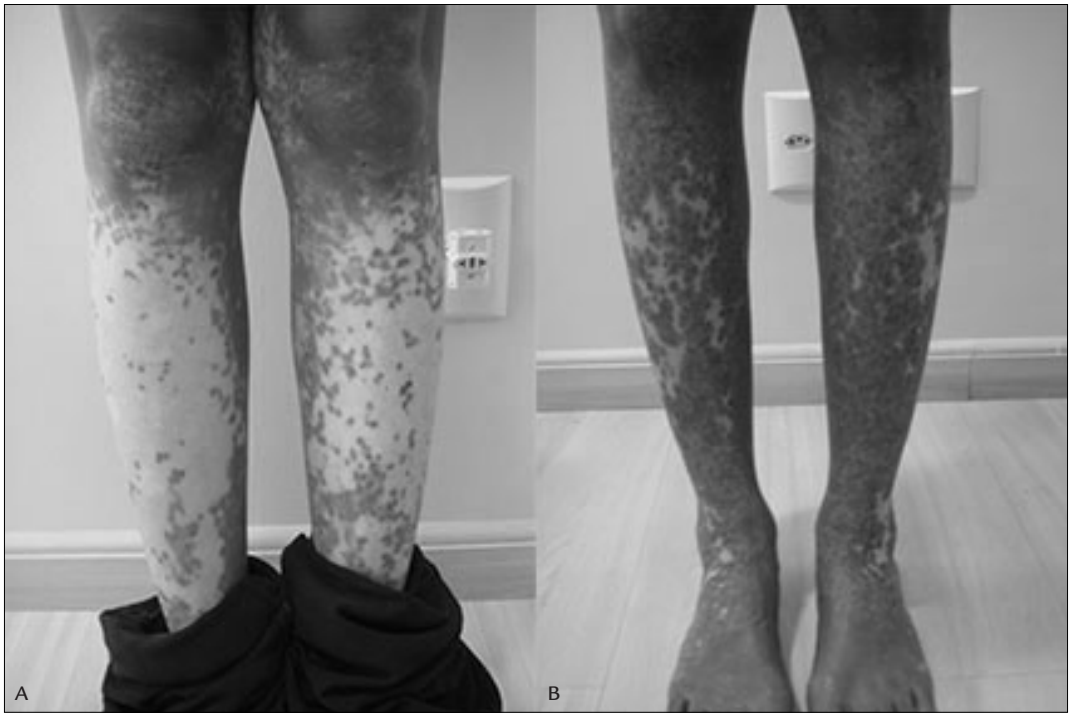

FIGURE 1 Achromic macules over the pre-tibial area before PUVA treatment, on the left. Increased pigmentation of vitiligo lesions after 44 PUVA sessions, on the right.

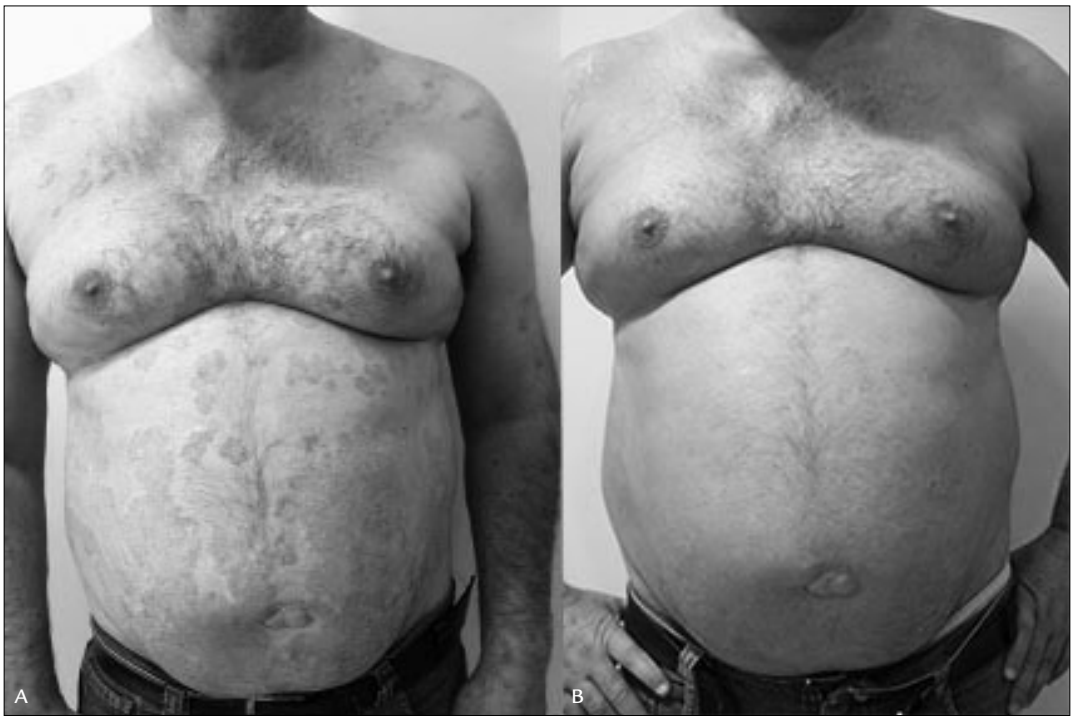

FIGURE 2 Extensive and confluent erythematous-scaling plaques, disseminated throughout the body prior to PUVA sessions on the left. Significant and satisfactory clinical improvement of psoriasis lesions after 14 sessions of PUVA, on the right.

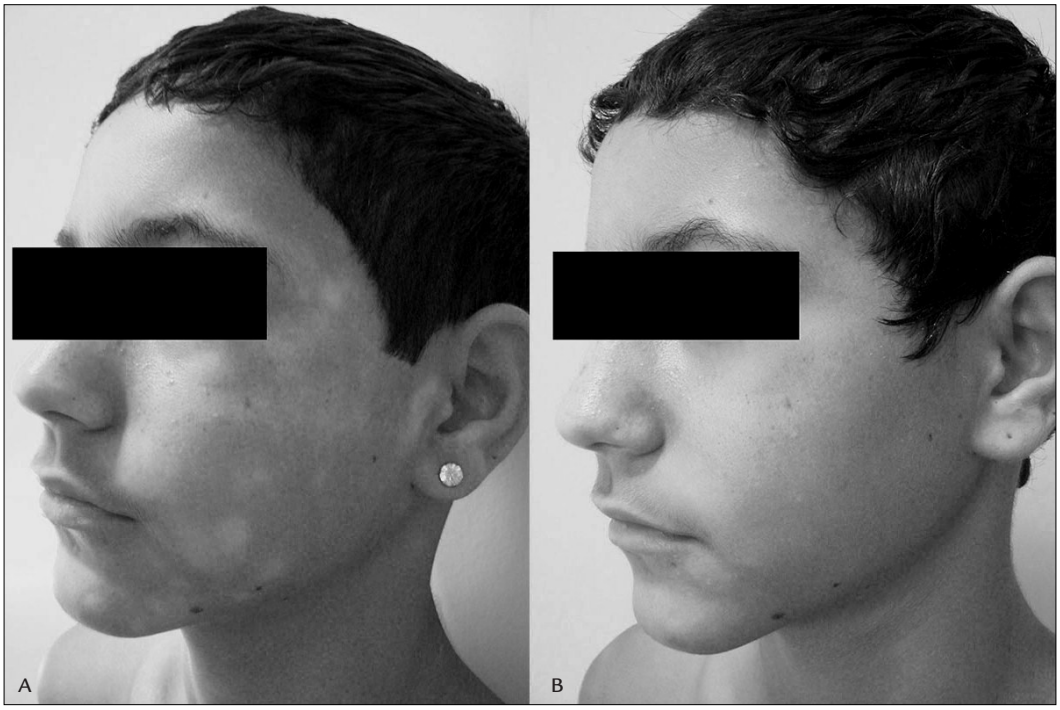

FIGURE 3 Hypochromic macules with poorly defined borders on the face compatible with pityriasis alba before PUVA, on the left. Satisfactory attenuation of pityriasis alba lesions after 21 PUVA sessions, on the right.

possible side effects and contraindications, so that the procedure could be safely performed.

In all modalities of UVB phototherapy or PUVA, complementary therapies such as topical vitamin D analogues, corticosteroids and topical or oral retinoids may be associated for better control of psoriasis and other dermatoses.[1,7,8]

One of the main indications of phototherapy is the control of psoriasis. According to the Brazilian Consensus of Psoriasis 2012, any form of phototherapy can be used in this dermatosis. UVB is the first line for psoriasis, as it is safer and more effective. It can be used in pregnant women and children, and poses less risk of photoaging and ophthalmological involvement, since it does not require psoralens as adjuvants.[7] On the other hand, PUVA is indicated as the best therapeutic option for extensive areas of involvement, thick psoriatic patches and patients with phototype III or greater.[1,5,9,10] In case 2, we chose PUVA because the patient had extensive psoriasis and thick plaques.

In vitiligo, repigmentation after treatment occurs due to migration of melanocytes from the hair follicles to the basal layer of the skin.[11] Phototherapy stimulates melanogenesis and interferes with the inflammatory process of the dermatosis.[1] In extensive vitiligo (as in the case presented) PUVA with oral psoralen is the best therapeutic option. Although many authors advocate UVB radiation as the safest method, others indicate it only when PUVA is contraindicated.[1,2] We opted for PUVA with oral psoralen because of its effectiveness in extensive vitiligo.

The etiology of pityriasis alba is unknown but appears to be related to xerosis and atopic eczema.[11] It mainly affects the face, back and outer side of the arms, sometimes posing a differential diagnosis with pityriasis versicolor.[11,12] The treatment of choice are emollients, sun protection and the use of topical corticosteroids. Refractory cases can be treated with PUVA.[13] The results of the sessions exceeded expectations with the disappearance of most of the lesions.

All three cases yielded excellent therapeutic results. Good tolerance to phototherapy should be emphasized without triggering relevant side effects. Thus, great psychosocial impact and self-esteem was obtained, with improvement in patients' quality of life.

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Spontaneous carotid dissection

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Summary

Carotid dissection is a rare occurrence but it is the main cause of stroke in individuals aged less than 45 years, and can be the etiology in up to 25% of strokes in young adults. We report a case with classic image of *ying yang* on vascular ultrasound, which was treated according to the best available medical evidence, yielding a favorable outcome.

Keywords: carotid artery internal dissection, evidence-based medicine, platelet aggregation inhibitors, stroke, Doppler ultrasonography.

Introduction

Carotid dissection (CD) accounts for only 1-2% of all ischemic strokes. In young individuals and middle-aged adults, however, this etiology accounts for 10-25% of these events.[1] Population incidence is around 1.7 to 3/100,000 per year, but it is the main cause of stroke in people aged less than 45 years.[2] Etiopathogenesis is still controversial but it is believed that an association of genetic predisposition (Ehler-Danlos syndrome, Marfan, fibromuscular dysplasia, osteogenesis imperfecta, etc.), environmental factors (recent infection, trauma or cervical manipulation) and risk factors (hypertension, migraine, low cholesterol levels, and body mass index) may lead to the development of CD.[1-9] Clinical presentation varies according to the artery involved. Ipsilateral headache and focal symptoms are often associated with the area of cerebral or retinal ischemia. After clinical suspicion, additional diagnostic tests are essential for diagnostic confirmation. Despite the good accuracy of Doppler ultrasonography, confirmation with magnetic resonance imaging (MRI) or computed tomography (CT scan) is still routine. Endovascular angiography, as a resource in the diagnostic stage, is used with caution due to the possibility of iatrogenic worsening.[1]

Case report

A 52-year-old female patient, caucasian, homemaker, complaining of left hemicranial headache and speech difficulty upon awakening three hours earlier. She denied previous episodes and other complaints such as paresis or paresthesia. She denied smoking, hypertension, diabetes, trauma, migraine, recent infection, dyslipidemia, use of oral contraceptives or any other significant personal or family history. On admission, she presented dysphasia with no motor or sensory deficits on neurological examination. No signs of intracranial hemorrhage were found on non-contrasted cranial CT scan, and the intravenous contrast phase showed no evident ischemic area. Cerebral angiography of supra-aortic trunks revealed a suggestive pattern of bilateral fibromuscular dysplasia in the distal third of the internal carotid arteries ("stacked coins" appearance) and dissection of the left internal carotid artery with stenosis of 70-80% of the lumen due to subintimal hematoma in left internal carotid artery (Figure 1). The patient was conservatively treated with acetylsalicylic acid (ASA) 100 mg/day and clopidogrel 75 mg/day. She showed favorable progression, without recurrence of stroke, and with progressive speech recovery six months after the event. Currently, the lesion area corresponding to language in the left cerebral hemisphere can be identified on gadolinium-enhanced magnetic resonance imaging (Figure 2). Color Doppler vascular ultrasound (CDUS) at six months after the event revealed that left internal carotid dissection with false lumen ending in a *cul-de-sac* remains. A bidirectional flow is observed: normal in the cranial direction and reverse in the central direction, with a classic image of *ying yang* on CDUS, which extended for about 4 cm from the carotid bulb and did not cause significant lumen stenosis (Figure 3). Systolic peak velocities were very

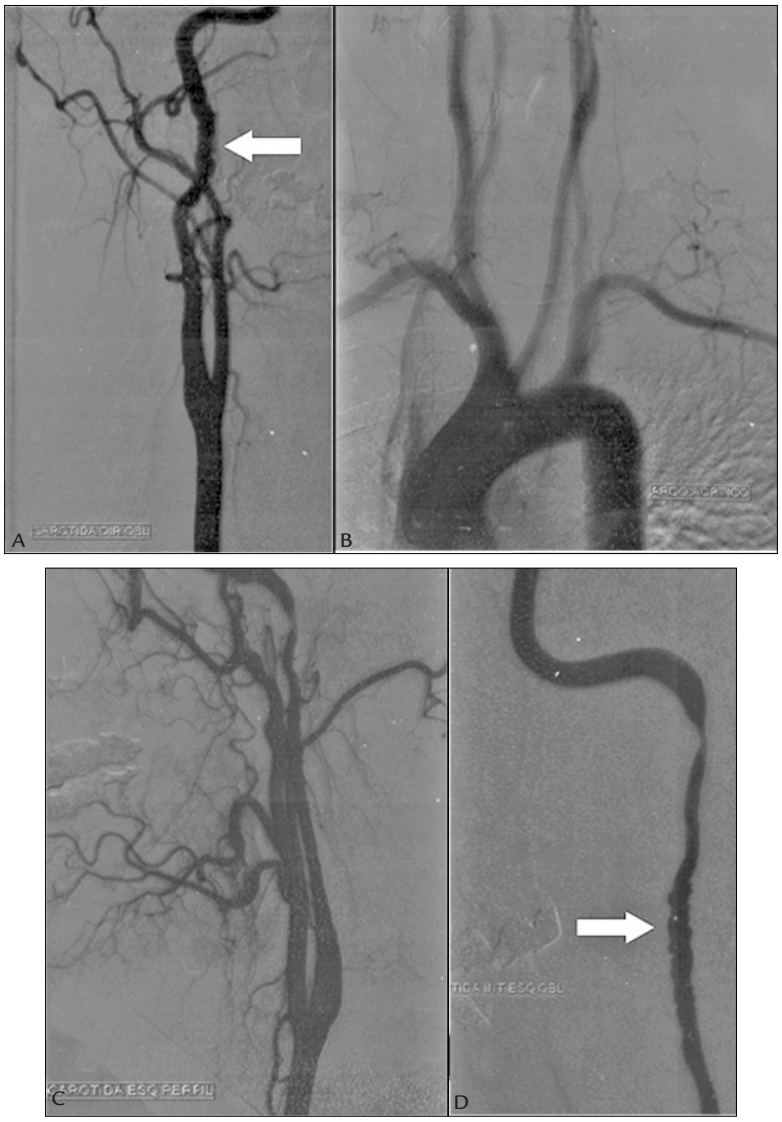

FIGURE 1 Digital fluoroscopy angiography. A. Right carotid, oblique view. B. Aortic arch, oblique view. C. Left carotid, lateral view (profile). D. Left internal carotid artery, oblique view. Arrows: "stacked coins" appearance.

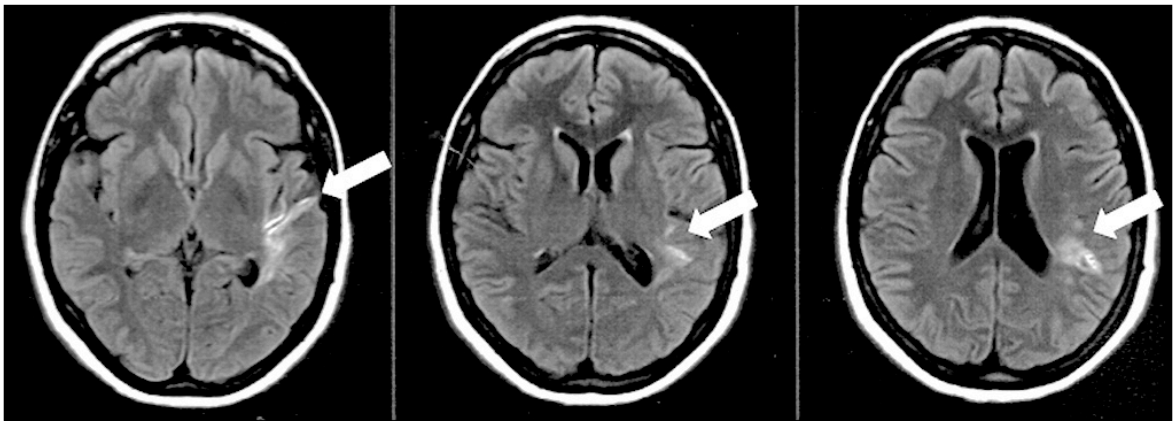

FIGURE 2 Gadolinium-enhanced T1-weighted cranial magnetic resonance imaging, six months after initial event. Arrows: area of ischemia.

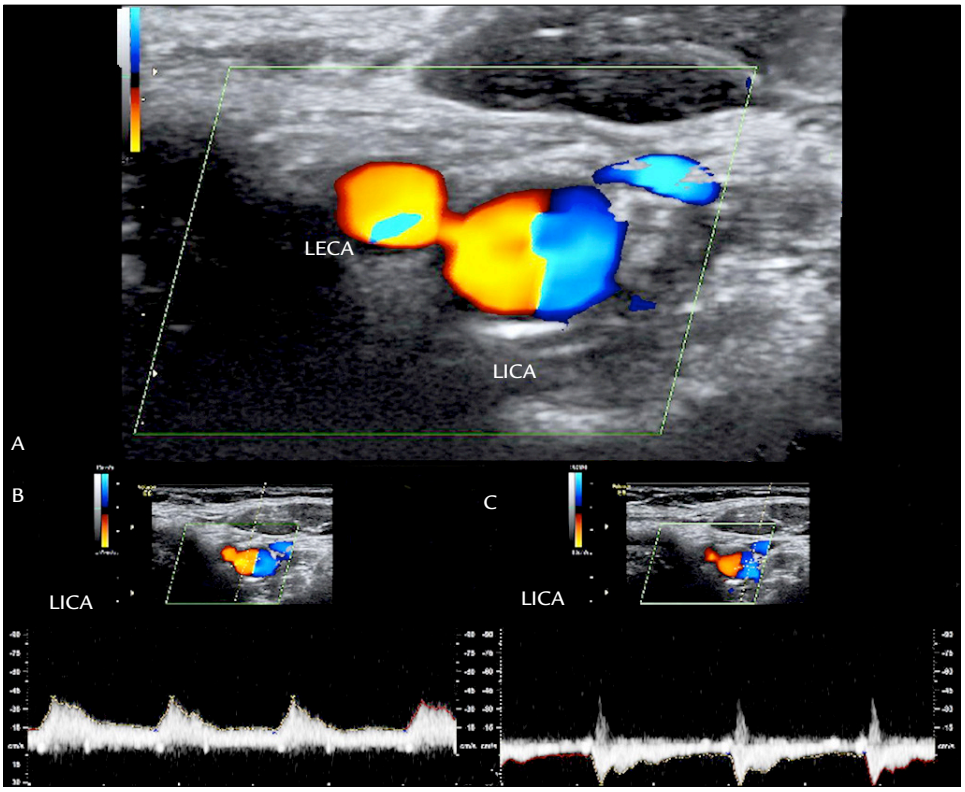

FIGURE 3 Doppler vascular ultrasound, six months after initial event. A. Color mode with *ying yang* image. B. Spectral mode, true lumen. C. Spectral mode, false lumen. LICA: left internal carotid artery; LECA: left external carotid artery.

similar (true lumen: 37 cm/s, and false lumen: 31 cm/s). This evidenced the high flow character in the false light, but without causing significant stenosis in the true light. No subintimal carotid hematoma was identified. The evaluation of renal arteries on CDUS did not confirm a typical pattern of fibromuscular dysplasia with a succession of dilatations and stenoses ("string of beads"). Then, clopidogrel was suspended, while ASA was maintained at a dose of 100 mg/day. The patient remained with no recurrence of stroke after one year of conservative treatment. She had complete remission of dysphasia and showed, on CDUS, a reduction in the extent of dissection to 1 cm, without hematoma or significant stenosis.

Discussion

The case corroborates the epidemiology of CD, having occurred in a young adult and affected the internal carotid artery hereafter the bifurcation as seen in up to 2.5% of all cases of stroke.[1] The only probable risk factor was the suggestive pattern of fibromuscular dysplasia on carotid endovascular angiography. The situation illustrates multifactorial etiopathogenesis and the difficulty in establishing a specific etiology. Currently, the main scientific evidence for clinical decision making is a systematic review of randomized clinical trials.[10,11] A Cochrane systematic review of randomized clinical trials on antithrombotic drugs for carotid artery dissection conducted in 2010 yielded no evidence in this regard.[2] In 2015, however, new evidence was produced. A randomized clinical trial found no significant difference between treatment with anticoagulants or antiplatelet agents to prevent death and stroke in symptomatic dissection of carotid or vertebral arteries.[12] In this clinical trial, recurrent events were much rarer than in previous observational studies, and the initial diagnosis of dissection was quite misleading after a thorough review of the images. This shows that radiographic criteria are not always correctly applied in clinical practice. Lower levels of evidence report that endovascular treatments, such as angioplasty with stenting or thrombolysis, may be superior to conservative treatment in selected populations.[13-16] The case presented is in line with the best scientific evidence available at the time. The patient underwent conservative treatment with antiplatelet agents and did not present recurrence of stroke or death within one year of follow-up.

Although rare, CD should always permeate the diagnostic suspicion in cases of stroke, especially in young patients and/or those with risk factors for developing the

disease. Diagnostic confirmation and follow-up should include non-invasive ancillary methods, with thorough collection and evaluation of these images. The best level of available evidence still recommends conservative treatment as a general measure, either with anticoagulation or anti-platelet aggregation.

Acknowledgments

We thank the patient for authorizing her case report.

Resumo

Dissecção espontânea de carótida

A dissecção de carótida é entidade rara, mas é a principal causa de acidentes vasculares cerebrais isquêmicos em menores de 45 anos e pode ser a etiologia de até 25% dos acidentes vasculares cerebrais em adultos jovens. Apresenta-se um caso com imagem clássica de *ying yang* à ultrassonografia vascular, que foi tratado de acordo com as melhores evidências médicas disponíveis e apresentou boa evolução.

Palavras-chave: dissecção da artéria carótida interna, medicina baseada em evidências, inibidores da agregação de plaquetas, acidente vascular cerebral, ultrassonografia Doppler.

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Clinical pharmacology profile of care in Hepatology clinic

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Summary

Since 2010, the Clinical Gastroenterology and Hepatology Division of the Central Institute of Hospital das Clínicas of the University of São Paulo Medical School (HC-FMUSP, in the Portuguese acronym) has been developing specialized electives assistance activities in the Outpatient Specialty Clinic, Secondary Level, in São Paulo NGA-63 Várzea do Carmo. The objective of this study was to analyze the pharmacotherapeutic profile of patients. This is a cross-sectional and retrospective study in which patients were seen at the Hepatology sector and the results were submitted to descriptive statistics. During the study period, 492 patients were treated at the clinic, with a mean age of 58.9 years and frequency of 61.2% female and 74.8% living in São Paulo. This population was served by various other medical specialties (cardiology and endocrine among others) and the major liver diagnoses were: chronic hepatitis B and C and fatty liver. Comorbidities were also identified, such as diabetes, hypertension and dyslipidemia. Most patients took their medication in the Basic Health Units. We found that 30% of patients use of more than five medications and the most prescribed were omeprazole 208 (42.3%), metformin 132 (26.8%) and losartan 80 (16.3%). Because it is an adult/elderly population, with several comorbidities and polymedication, it is important to be aware of the rational use of medication. The multidisciplinary team is important in applying correct conducts for the safe use of medicines, to reduce the burden on health spending and improving the quality of life of patients.

Keywords: hepatitis, drug, polypharmacy, ambulatory care, hematology, omeprazole.

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Introduction

The system of referral and counter-referral of the Unified Health System (SUS, in the Portuguese acronym) is the two-way referral of patients between the different levels of complexity of the services. The first means the referral of patients from a service of lower complexity to a service of greater complexity, assisting the patient and scheduling their procedure. Counter-referral, in turn, is when the patient can be sent back to their service of origin for treatment maintenance and follow-up.[1]

The referral and counter-referral network is developed on the basis of four components that function in an integrated manner. Primary Health Care (PHC) services are the patient's place of entry for the entire network; secondary care is made up of specialized outpatient clinics and hospitals of medium complexity; the tertiary network aggregates high-complexity hospitals. All are supported by logistics systems, regulation, health transport and electronic health records, as well as support systems, pharmaceutical assistance, diagnostic and therapeutic support.[2]

The Hospital das Clínicas of the University of São Paulo Medical School (HC-FMUSP, in the Portuguese acronym) has a Liver Care project that functions in line with the SUS referral and counter-referral system, in the NGA-63 Várzea do Carmo Outpatient Specialty Clinic, Health Assistance Management Center, in São Paulo.

This service unit has three pharmacies: one outpatient, one for specialized components and one for oncologic medication focused on the care of patients being treated for breast and prostate cancer.

The Hepatology sector in Várzea do Carmo has a database created from a questionnaire that records the drugs used by patients and the place where they collect their prescriptions. In this database, in addition to patient demographics, there is also information about diagnosis, medical specialties, use of medicines, facilities dispensing these patients' prescriptions, the possibility of acquiring them in the event they are not available for free, and data revealing their knowledge about the drugs they use.

The main services performed at Várzea do Carmo Medical Hepatology Outpatient Clinic are for viral hepatitis and hepatic steatosis. Therefore, it is important, in order to guarantee adequate assistance to the patient, to understand their profile in light of the concepts of polypharmacy. Polymedication, according to Bjerrum et al., is also known as minor polymedication, when the patient uses two to four drugs, and major polymedication, which is when there are five or more drugs of daily and continuous use.[3]

Our study, based on the database mentioned above, uses this concept to address the profile of patients seen at the Várzea do Carmo Hepatology Outpatient Clinic.

Objective

To analyze the pharmacotherapeutic profile of patients attended by the Clinical Hepatology sector in the Outpatient Specialty Clinic, Secondary Level, Várzea do Carmo, according to the definition of polypharmacy.

Method

Cross-sectional study, with retrospective data collection, from March to July 2015, in the Hepatology sector of the Outpatient Specialty Clinic, Secondary Level, São Paulo, State of São Paulo.

The study population included patients who were enrolled in the Hepatology database, aged 18 years or older. Patients whose data were non-existent or incomplete were excluded from the database. The research project was approved by the Research Ethics Committee of HC-FMUSP (CAPPesq) with CAAE: 53491816.1.0000.0068 - Opinion number 1.433.847 on March 2, 2016.

Information on demographics, diagnosis, specialties in which the patient is treated, medications, dosage, information on the patient's knowledge of the use of their medications, the facility dispensing the drugs and the possibility of each patient to acquire the medication in case that particular drug is not available in the network's pharmacies were transported to the REDCAP, a tool for Data Management in Scientific Research. The results were submitted to descriptive statistical analysis and expressed in tables and charts.

Results

Based on the database of the Hepatology and Gastroenterology Department of the Várzea do Carmo Outpatient Specialty Clinic, from March to July 2015, 492 patients were identified after visiting the Hepatology sector, totaling 1,931 consultations in the period. Of the patients treated, 304 (61.79%) were female and 188 (38.21%) were male. The mean age of the general population was 58.87 years, with a standard deviation of ± 13 years. As for place of residence, 368 (74.80%) patients resided in the city of São Paulo, while 124 (25.20%) resided in the greater São Paulo area.

The main liver diagnoses are shown in Table 1.

TABLE 1 The main liver diagnoses in 492 patients investigated.

Main liver diagnosis	Number of patients	Female n (%)	Male n (%)
Hepatitis C	172	89 (51.75%)	83 (48.25%)
Hepatic steatosis	112	77 (68.75%)	35 (31.25%)
Cirrhosis	72	30 (41.67%)	42 (58.33%)
Hepatitis B	35	19 (54.28%)	16 (45.72%)
Under investigation	62	40 (64.51%)	22 (35.49%)
Other diagnoses	78	42 (57.85%)	36 (46.15%)
Total	531*		

*39 patients were diagnosed with more than one condition.

These patients are also assisted by other specialties in the Várzea do Carmo outpatient clinic, at the Clinics Hospital of São Paulo, and in other primary, secondary or tertiary care centers. The most prevalent clinics were those of internal medicine 110 (22.35%), cardiology 98 (19.92%), endocrinology 79 (16.06%), gastroenterology 68 (13.82%), and rheumatology 62 (12.60 %) and ophthalmology 44 (8.94%).

As for the facilities where the patients collected their medications, we noted that: 317 (74.59%) would get them from Primary Health Units (UBS, in the Portuguese acronym), 110 (25.88%) from the Várzea do Carmo Outpatient Specialty Clinic and 36 (8.47%) from HC-FMUSP.

According to the information contained in the database, 373 (87.76%) patients correctly reported the name, quantity and purpose of all medications used daily, while 52 (12.24%) did not know how to give any of the requested information.

Regarding the possibility of acquiring the drug, 258 (60.8%) patients reported having the possibility of buying the medication if the drug was not available for free or when it was a drug that is not listed in the government-funded medication program on a federal, state or municipal level. Another 54 (12.5%) could buy it, depending

on the price of the medication, but 113 (26.7%) reported not being able to purchase the prescribed medication, regardless of the price.

Table 2 demonstrates that omeprazole, metformin, losartan, hydrochlorothiazide, simvastatin and enalapril were the medications most frequently cited by patients in a list of 33 spontaneous citations.

Of the drugs spontaneously reported by patients, treatment for hepatitis B was cited by 12 patients and treatment for hepatitis C by two.

TABLE 2 Distribution of patients according to their medication (n=425).

Medications	Total	Percentage (%)
Omeprazole	208	42.28
Metformin	132	26.83
Losartan	80	16.26
Hydrochlorothiazide	77	15.65
Simvastatin	67	13.62
Enalapril	62	12.60
Propranolol	60	12.20
Levothyroxine	53	10.77
Amlodipine	50	10.16
Atenolol	50	10.16
Acetylsalicylic acid	40	8.13
Insulin	35	7.11
Spironolactone	32	6.50
Captopril	26	5.28
Furosemide	25	5.08
Dipyrone	24	4.88
Glicazide	24	4.88
Calcium	23	4.67
Vitamin D3	23	4.67
Alendronate	18	3.66
Paracetamol	17	3.46
Glibenclamide	14	2.85
Domperidone	13	2.64
Pantoprazole	11	2.24
Prednisone	11	2.24
Bromopride	10	2.03
Fluoxetine	9	1.83
Lactulose	9	1.83
Tenofovir	7	1.42
Entecavir	4	0.81
Interferon	2	0.41
Ribavirin	2	0.41
Adefovir	1	0.20
Other	219	44.51

As for use of medication, we found that 425 (86.38%) patients used some medication, while only 67 (13.62%) did not use any. Therefore, 425 patients will be investigated for polypharmacy. Table 3 and Chart 1 show the patient's classification according to Bjerrum et al.[3]

TABLE 3 The pharmacotherapeutic profile according to the classification by Bjerrum et al. with the five drugs most often prescribed to patients on minor polymedication and the ten most often prescribed to patients on major polymedication.

Drug	Minor polymedication n=425	Major polymedication n=425
Omeprazole	154 (36.23%)	86 (20.23%)
Metformin	72 (16.94%)	62 (14.58%)
Losartan	43 (10.11%)	44 (10.35%)
Hydrochlorothiazide	43 (10.11%)	34 (8.00%)
Enalapril	38 (8.94%)	34 (8.00%)
Amlodipine	–	33 (7.76%)
Simvastatin	–	33 (7.76%)
Acetylsalicylic acid	–	32 (7.52%)
Propranolol	–	25 (5.88%)
Levothyroxine	–	24 (5.64%)

Discussion

The sex and age distribution found in our study is in line with what we expected. Likewise, the distribution of diagnoses among the population served is in accordance with the distribution of these conditions in the general population.

The study demonstrates that a patient can be treated simultaneously at the primary, secondary and even tertiary level of care. The factor keeping a particular patient in tertiary care is the medicines he or she uses, that is, if they are not available in primary or secondary care.

Within this scope, where it is observed that these patients will continue to require specialized or ultra-specialized services, i.e. tertiary care, we are able to say that the concern for rational use of medicines is of note.[2]

Our patients collect their medication from different facilities such as Primary Care Units, the Várzea do Carmo Outpatient Specialty Clinic and the FMUSP Hospital das Clínicas. For the same reasons cited above, dispensing centers are also classified according to complexity and not all medicines are available from the same location.

From a viewpoint of the safe and rational use of medication, there is control over the use of medical prescriptions, because each dispensing facility indicates in

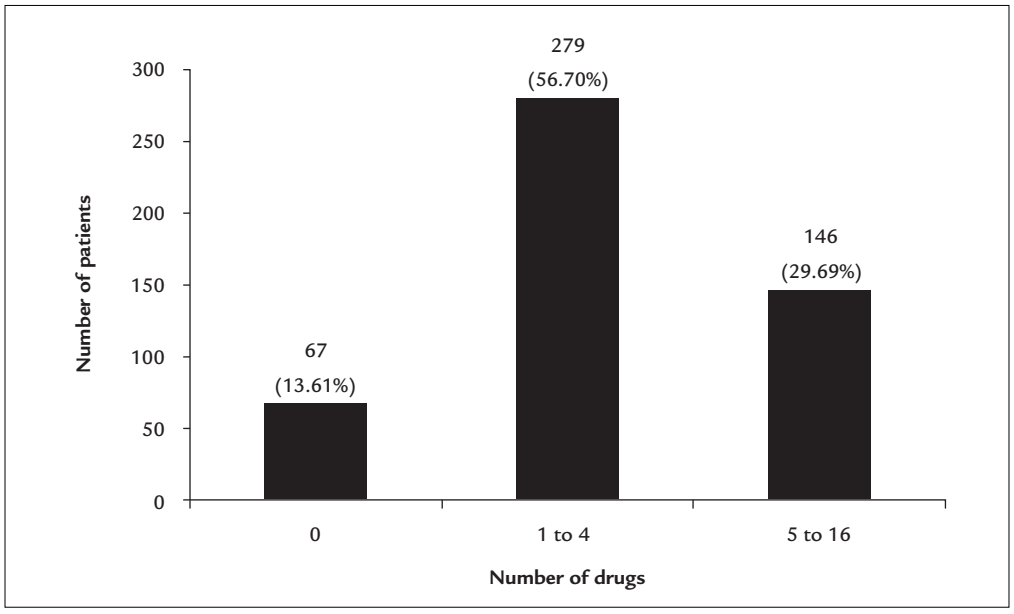

CHART 1 Number of patients vs. number of drugs (n=492).

the prescription that the drug was delivered. However, a patient who consults with more than one prescribing physician can have the same prescription repeated and, with different prescriptions, receive more medication than needed.

Comparing the above data with the information obtained in the database about the patients' lack of knowledge about their medications, misuse is a possibility. In addition, too much medication in a patient's possession can lead to self-medication, either through overuse or sharing.

Considering also that some patients mentioned the impossibility of acquiring prescription items if these drugs were not available for free, care about rational use is even more justified as a measure to avoid shortage and waste that can burden the public service.

Omeprazole is one of the drugs most frequently mentioned by patients, which, outside the scope of gastroenterology, raises the question of whether the drug is being used rationally. Omeprazole may alter the metabolism of other drugs by enhancing or reducing their effects, exposing patients to unnecessary side effects and drug interactions without proper monitoring.[4-6]

Regarding the findings of medication use, the 67 patients who do not use any medication are those that are still under investigation, through laboratory tests. There were still no medical prescriptions for these patients at the time of the study and therefore they were excluded from the analysis.

Comparing the drugs most often mentioned with the diseases for which they are indicated, we found:

- Type 2 diabetes mellitus: biguanine (metformin).
- High blood pressure: diuretics (hydrochlorothiazide), angiotensin converting enzyme inhibitor (enalapril), angiotensin receptor antagonists (losartan).
- Dyslipidemia: hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (simvastatin).

Diabetes is growing worldwide; it is estimated that 382 million people have the disease and that it should reach 471 million people by 2035.[4] Systemic hypertension showed prevalence > 30% in Brazilian cities in recent years, which means blood pressure (BP) levels ≥ 140/90 mmHg.[7]

Dyslipidemia, a growing disease in Brazil and the world, is one of the risk factors for overweight, along with diabetes. Without medical follow-up, dyslipidemia and obesity may directly affect hepatic steatosis, the second most frequently cited diagnosis. Steatosis can progress to hepatitis and cirrhosis.[8-17]

Comparing the mean age of patients (58 years) and their comorbidities (compatible with the age of these patients and the need for chronic medication use), we found justification for the observation of polypharmacy in all patients.

Based on the classification by Bjerrum et al., we were able to correlate medications and diagnoses. Among the cases of minor polymedication, we found diabetes mellitus and systemic hypertension, while major polymedication was also found in cases of diabetes mellitus and hypertension but with additional drug treatment, which indicates

worsening of the disease.[3] In some cases, there is also the possibility of complications caused by liver disease, such as portal hypertension with the use of propranolol and problems related to hepatitis C and its treatment, including hypothyroidism, which requires levothyroxine.[18]

The observation that only 12 of the 35 patients with hepatitis B virus cite medications for the treatment of this disease is suggestive that inactive diseases may be present in the remaining patients.

A patient with an inactive disease requires specific tests such as normal alanine aminotransferase (ALT) and serum HBV DNA levels below 2,000 IU/mL. The serological profile observed is HBeAg-negative in patients with chronic inactive hepatitis. To confirm the diagnosis of inactive disease over time, it is necessary to perform periodic examinations such as ALT, on a quarterly basis, and measurements of HBV DNA and serum HBsAg levels every 12 months to confirm viral elimination. Given these criteria, pharmacological treatment is not recommended, but medical follow-up of these patients is of paramount importance,[19,20] maintaining them in the secondary care system.

Only two patients out of 172 cited pharmacological treatment for hepatitis C, which may be due to the risk-benefit assessment of drugs available at the time, given their adverse reactions, such as anemia, thrombocytopenia, rash, neutropenia and more. The therapeutic arsenal for the treatment of chronic hepatitis C (ICD-10: 18.2) in the study period was: alpha-interferon 2b, alpha-2 interferon 2a and 2b, ribavirin, epoetin alpha, filgrastim, telaprevir and boceprevir, according to the Clinical Protocol and Therapeutic Guidelines for Chronic Viral Hepatitis C and Coinfections, published in 2013.[21]

With the proposed inclusion of new drugs (sofosbuvir, daclatasvir and semiprevir), which have proven efficacy and minimal adverse reactions, we chose in most cases to await the release of the new drugs. These drugs are currently part of the Clinical Protocol and Therapeutic Guidelines for Chronic Viral Hepatitis C and Coinfections published in 2015, and patients who meet the criteria of this protocol may already benefit from treatment.[22,23]

Conclusion

The results demonstrated that the study population is adult or elderly, with several comorbidities and, therefore, users of polymedication. The fact that patients in general have access to several prescribing physicians and thus the possibility of duplicity of prescriptions is important to ensure rational use of the drug in a multiprofessional team.

The patients treated have diagnoses that are consistent with the Hepatology sector, demonstrating that the referral and counter-referral system can remove this patient from the tertiary health system, but this does not make his or her care less complex, since the patient remains allocated in the three levels of attention.

Resumo

Perfil clínico farmacológico dos atendimentos no ambulatório de Hepatologia

Desde 2010, a Divisão de Gastroenterologia e Hepatologia Clínica do Instituto Central do HC-FMUSP tem desenvolvido atividades assistenciais eletivas especializadas em Hepatologia no Ambulatório de Especialidades Nível Secundário de São Paulo no Estado de São Paulo NGA-63 Várzea do Carmo. O objetivo do estudo é analisar o perfil farmacoterapêutico dos pacientes. Trata-se de um estudo transversal e retrospectivo, no qual pacientes foram atendidos pelo setor de Hepatologia e os dados encontrados foram submetidos à estatística descritiva. Os resultados demonstraram que 492 pacientes foram atendidos nesse ambulatório durante o período do estudo com a média de idade de 58,9 anos, frequência de 61,2% do sexo feminino e 74,8% residindo na capital paulista. Essa população foi atendida por outras diferentes especialidades médicas (cardiologia e endócrino, entre outras), e os principais diagnósticos hepáticos foram hepatite crônica B e C e esteatose hepática. Também foram identificadas comorbidades como diabetes, hipertensão arterial e dislipidemia. Boa parte da população tende a retirar a sua medicação nas Unidades Básicas de Saúde. Foi verificado que 30% dos pacientes fazem uso de mais de cinco medicamentos, sendo os mais prescritos o omeprazol (208; 42,3%), metformina (132; 26,8%) e losartana (80; 16,3%). Por se tratar de uma população adulta/idosa, com diversas comorbidades e com polimedicação, é importante estar atento ao uso racional do medicamento. O atendimento da equipe multiprofissional é importante para aplicar tomadas de condutas corretas para a segurança no uso de medicamentos e diminuir a oneração em gastos em saúde, melhorando a qualidade de vida do paciente.

Palavras-chave: hepatites, medicamento, polifarmácia, assistência ambulatorial, hepatologia, omeprazol.

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Impact of biological therapy on body composition of patients with Chron's disease

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Summary

Introduction: Protein-energy malnutrition in Crohn's disease (CD) has been reported in 20 to 92% of patients, and is associated with increased morbidity and mortality and higher costs for the health system. Anti-TNF drugs are a landmark in the clinical management, promoting prolonged remission in patients with CD. It is believed that the remission of this disease leads to nutritional recovery. The effect of biological therapy on body composition and nutritional status is unclear.

Method: Prospective study of body assessment by bioelectrical impedance method in patients with moderate to severe CD undergoing treatment with infliximab. The main outcome was the body composition before and after 6 months of anti-TNF therapy.

Results: There was a predominance of females (52%) with a mean age of 42±12 years. Most patients were eutrophic at baseline and remained so. There was an increase in all parameters of body composition after anti-TNF treatment: BMI (22.9±3.2 versus 25±3.8; p=0.005), waist circumference (88.1±6.7 versus 93.9±7.7; p=0.002), lean mass index (17.5±2.2 versus 18.2±2.3; p=0.000) and fat mass index (5.5±2.3 versus 6.8±2.3; p=0.000). Phase angle remained unchanged (6.2 versus 6.8; p=0.94).

Conclusion: After therapy with IFX, all components of body composition increased, except for phase angle. The substantial increase in fat mass index and waist circumference led to concern regarding cardiovascular risk and, thus, to the need for further studies.

Keywords: Crohn's disease, body composition, biologics.

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Introduction

Crohn's disease (CD) is a chronic, transmural, immune-mediated condition that affects the gastrointestinal tract with a potential for involvement of various organs with extra-intestinal manifestations. The etiology of CD remains unclear, but it is believed to be multifactorial with associated environmental, genetic and immunological factors. The overall prevalence is 5 to 50 cases per 1,000 inhabitants, with a predominance of Caucasians.[1] An estimate of the prevalence in the city of São Paulo, Brazil, reported the occurrence of 14.8 cases per 100,000 inhabitants.[2]

Protein-calorie malnutrition (PCM) has been reported in about 20 to 92% of patients with CD.[3-7] Many factors contribute to PCM and deficiency of macro-nutrients, vitamins and minerals in this group of patients. Changes directly related to disease activity, such as inflammatory changes in the intestinal epithelium, as well as previous intestinal resections, may be responsible for malabsorption of nutrients and vitamins (such as vitamins A, D, E, K and B12). Pain, present at times of disease exacerbation, and increased inflammatory mediators, such as tumor necrosis factor, are associated with anorexia and cachexia.[8] In addition to these factors, the therapy used in the

treatment of CD can be associated with certain side effects that negatively affect the nutritional profile of these patients.[9] Also, increased nutritional requirements as a consequence of inflammatory activity and complications of the disease may corroborate for weight loss.[10]

It is well-known that weight loss, low body mass index (BMI) and PCM predominate in patients with moderate to severe CD, especially those admitted to hospital, being associated with higher mortality, longer hospitalization and increased health costs.[11] Zhang et al. showed that the BMI is inversely related to intra-abdominal infectious complications in patients with CD undergoing an elective surgical procedure.[12]

Location, phenotype, severity and disease activity appear to be directly related to impairment of nutritional status. Disease activity is related to increased basal energy expenditure, weight loss and anemia.[13,14] In addition to malnutrition, changes in body composition such as the occurrence of sarcopenia have been described in patients with CD.[15-18] Schneider et al. describe the occurrence of sarcopenia in 60% of patients with CD even during clinical remission.[18] Loss of lean mass (LM) has been associated with worsening of bone mineral density, increased morbidity, loss of muscle strength, and increased risk of infectious complications.

Traditionally, nutritional status has been evaluated based on objective parameters (anthropometric measures, skinfolds, clinical questionnaires, laboratory tests) and complementary methods already well-established for the evaluation not only of nutritional status, but also of body composition (dilution methods, dual-energy absorptiometry and electrical bioimpedance). Bioelectrical impedance analysis (BIA) is a method widely used to estimate body composition and nutritional status in several clinical populations because it is a simple, fast, noninvasive method with reproducible results.[19] Not only does it determine the fat mass (FM) and the fat-free mass (LM), the four-part model also allows the evaluation of the degree of cellular damage by determining a phase angle (PA), which has been considered a promising tool to assess the nutritional status and indicate prognosis.[19-21]

Biological therapy has dramatically changed the treatment of inflammatory bowel diseases (IBDs). This therapy is based on a monoclonal antibody that acts directly by blocking tumor necrosis factor alpha (TNF-α) and is effective in reducing inflammation, improving symptoms and inducing intestinal mucosa healing in a significant portion of patients.[22-24] Anti-TNF therapy is associated with a lower rate of complications of CD in the short and long term, reduction of rates of hospitalization and surgery, and a significant improvement in quality of life.[22,24] On the other hand, some studies have demonstrated an association between biological therapy and changes in metabolic profile (e.g. hypertriglyceridemia, change in LDL composition, increase in HDL), and weight gain, mainly at the expense of increased abdominal and visceral fat.[25]

Since anti-TNF therapy controls the inflammatory state and induces remission in moderate to severe CD, it is possible that after this intervention an increase in body weight, LM and PA of these patients may be observed. In this context, our study was designed to evaluate the impact of anti-TNFα therapy on body composition and PA in patients with active CD.

Method

In the period from April 2013 to August 2015, patients with moderate to severe CD with indication of anti-TNF therapy (infliximab – IFX) from the Intestinal Inflammatory Disease Outpatient Clinic of the Federal University of Juiz de Fora were included consecutively in our prospective study for the evaluation of body composition using BIA.

The study protocol was defined in accordance with the Declaration of Helsinki and approved by our Institutional Ethics Committee. All patients signed the informed consent form, before being accepted in the study.

The diagnosis of CD was established based on clinical, endoscopic, histopathological or imaging data.[24] Patients aged between 18 and 65 years with moderate to severe CD, refractory or dependent on corticosteroids were included. Exclusion criteria were: severe comorbidities, gestation and/or concomitant infection. All patients underwent induction therapy with IFX (5 mg/kg at weeks 0, 2 and 6) followed by maintenance every 8 weeks. Patients who did not respond to anti-TNF therapy were excluded from the analysis.

At baseline, medical history and eligibility criteria were assessed. Relevant data such as age, gender, BMI and smoking habit were noted. Variables associated with the disease included duration, location and phenotype according to the Montreal Classification,[26] therapy and previous history of surgery.

Disease activity was established according to the Harvey-Bradshaw Index (HBI). Moderate to severe cases were considered as active disease if HBI > 8, either associated or not with the presence of extensive and profound ulcers on colonoscopy, complications (e.g., stenosis, fistulas or abscess) and/or complex perianal disease. Biochemical parameters such as complete blood count, ESR,

lipid profile, triglycerides, blood glucose, ferritin and albumin were evaluated.

Anthropometry and body composition

Patients should wear light clothing and be barefoot for the measurement of anthropometric data. Height was measured in centimeters (cm) rounded to the nearest 0.5 cm, and weight was measured in kilograms (kg) rounded to the nearest 0.1 kg. LM, FM and PA were obtained by electrical bioimpedance (Quantum BIA-101Q, Detroit, MI). Impedance measurements were performed on the right side, with the patient in the supine position, and the limbs apart from each other. We used a previously validated regression equation to analyze LM.[19,27] The LM and FM indexes are calculated by dividing the LM and FM by the squared height, respectively. PA is a derived measure obtained from the relation between the direct measures of resistance and reactance. It is calculated directly from reactance and resistance:[28]

$$PA = \text{arc tangent}\,(\text{reactance} / \text{resistance}) \times 180° / \pi$$

PA occurs when a portion of the electric current is stored by the cell membranes, creating a phase shift.[29] In a healthy individual, PA can range from 4 to 10 degrees.[8,30]

Physical Activity Assessment Questionnaire

The level of habitual physical activity (HPA) in daily life was assessed using the questionnaire activity described by Baecke et al.,[27] and validated for the Brazilian population.[28] This instrument is composed of 16 questions that cover three components of physical activity: 1) occupational physical activity score (Q1 to Q8); 2) leisure-time physical activity score (Q9 to Q12); and 3) leisure-time activities and locomotion score (Q13 to Q16). Together, these three domains, work, sports and non-sporting leisure, result in a global physical activity score. Scores ranging from 9 to 16 indicate a moderate level of daily physical activity, while scores < 9 are observed in sedentary individuals.[31]

Statistical analysis

Sample size was calculated considering a type I error set at 0.05 and a sample power at 0.9 to detect a 1.5 kg LM difference in patients with CD before and after treatment with anti-TNFα. Thus, 25 patients would be needed for the study.

The collected data were analyzed using specific statistical software (SPSS- Statistical Package for the Social Sciences™, v. 13.0). For intra-group comparison in the active disease (baseline) and remission phases (in the 6th month), paired Student's t-test or Wilcoxon test were performed. Pearson or Spearman correlation was used to assess the degree of association between variables. The type I error probability was assumed to be 5% in all tests.

Results

Of the 26 patients selected for the study, three were excluded: one did not attend the reevaluation visit, one had morbid obesity and one did not respond to IFX induction therapy.

Table 1 shows the demographic and clinical characteristics of patients with CD.

TABLE 1 Demographic and clinical characteristics of our patients with Crohn's disease (n=23).

Characteristic	n (%)
Sex	
Female	12 (52.2)
Age (years)*	42.0±12.0
Location of CD	
Upper GI tract	2 (7.5)
Ileum	6 (26.1)
Colon	4 (17.4)
Ileum and colon	11 (49)
Phenotype of CD†	
B1	12 (52.2)
B2	7 (30.4)
B3	4 (17.4)
Disease duration (years)#	7.48 (1-20)
Previous surgeries	9 (39.2)
Smoking habit	4 (17.4)

*Mean and standard deviation; #mean and range; †B1: non-stricturing, non-penetrating; B2: stricturing; B3: penetrating.

Six months after IFX therapy, there was a significant reduction in HBI score (7 versus 2; p<0.0001), as well as complete withdrawal of corticosteroids (35% versus 0%; p<0.0018).

Table 2 shows the laboratory data, anthropometric values and body composition. Based on BMI, most patients were classified as having normal weight both at baseline and after 6 months, despite an increase in BMI observed after treatment with IFX (22.9 versus 24.9; p=0.000).

In the analysis of body composition, we observed an increase in all parameters, except PA (Figure 1). Although baseline and post-intervention PA values were similar, they were significantly lower than the predicted values (predicted PA: 6.8°; baseline PA: 5.6° and post-intervention PA: 6.1°).

TABLE 2 Anthropometric and body composition indicators at baseline and 6 months after treatment with IFX in patients with Crohn's disease.

	Baseline	Post-intervention	p
Hemoglobin	13.2±1.0	13.9±1.6	0.082
Leukocytes	6,978±4,040	6,529±3,336	0.595
Triglycerides	121±55	120±72	0.809
Total cholesterol	183±43	175±39	0.393
HDL	49±12	52±12	0.916
LDL	104±15	96±38	0.373
Albumin	4±0.5	4±0.3	0.430
Weight (kg)	62.6±9.5	68.4±13.2*	0.006
BMI (kg/m^2)	22.9±3.2	25.0±3.8*	0.005
WC	88.1±6.7	93.9±7.7*	0.002
Lean mass (%)	75.8±7.2	72.0±6.5*	0.008
LMI	17.5±2.2	18.1±2.3	0.000
Fat mass (%)	24.3±7.4	27.5±6.1*	0.008
FMI†	5.5±2.3	6.8±2.3	0.000
Phase angle (degrees)	5.9 (4.2-7.5)	6.1 (4.5-7.5)	0.153

Data presented as mean and standard deviation or median and interquartile range; WC: waist circumference; * LMI: lean mass index, lean mass (kg) divided by squared height; †FMI: fat mass index, fat mass (kg) divided by squared height.

In relation to the level of habitual physical activity of the patients, low levels of habitual physical activity were observed in the baseline evaluation and after the intervention, even after achieving disease remission (6.2 vs. 6.8; p=0.94).

Discussion

Biological therapy is a milestone in the treatment of IBDs. Anti-TNF agents have become drugs of choice in the treatment of patients with moderate to severe CD who do not tolerate the usual therapy. TNF-α is an inflammatory cytokine with catabolic power and a lipolytic and apoptotic effect that plays a significant role in lipid and glucose metabolism.

The efficacy of anti-TNFα agents in controlling the inflammatory process of IBD is indisputable. However, its effects on the body composition of patients with CD are still controversial. In our study, 20 (87%) of 23 patients had an increase in total body weight and, in 9 (39.1%), BMI values increased above 24.9, which is indicative of overweight/obesity. With regard to body composition, an increase in the LM (17.5±1.2 versus 18.1±2.3; p=0.000)

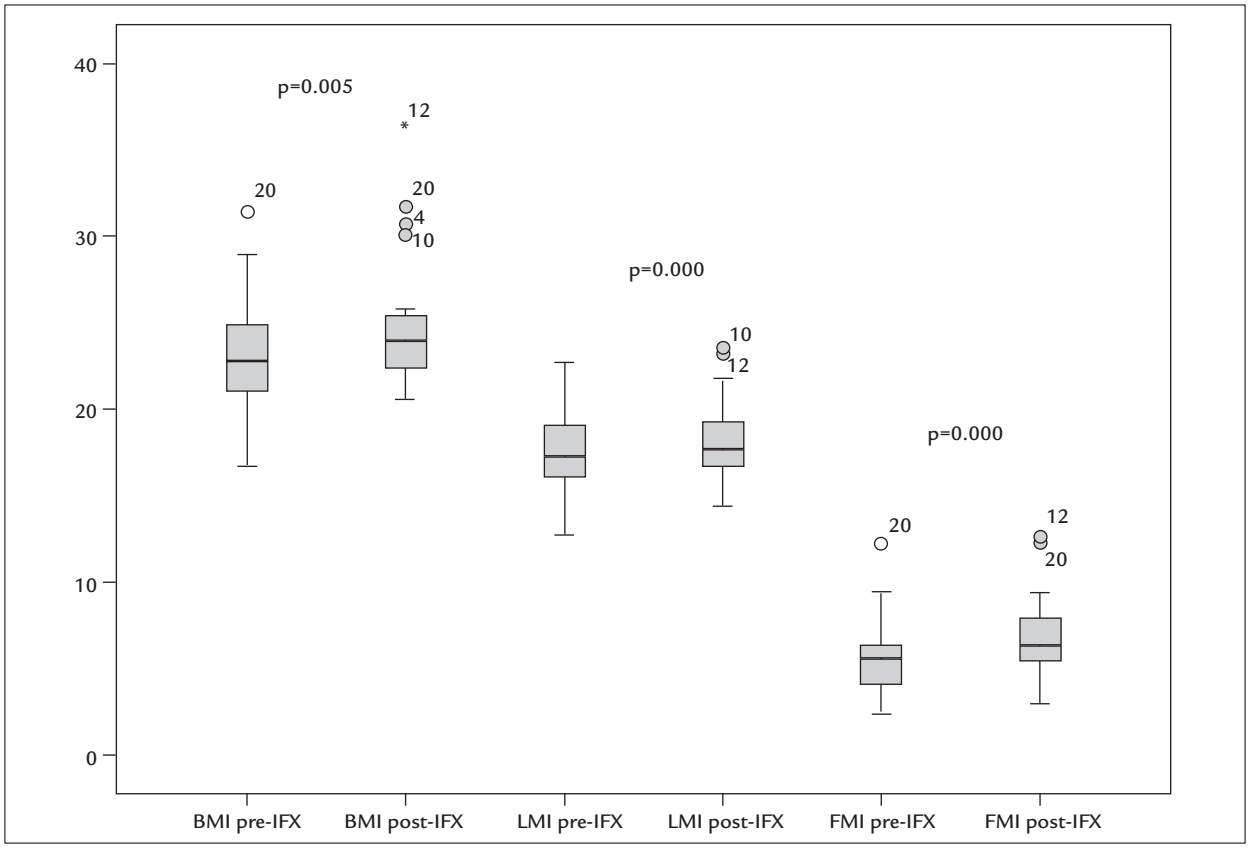

FIGURE 1 Evaluation of body composition before and after 6 months of treatment with infliximab.

BMI: body mass index; LMI: lean mass index (lean mass in kg divided by squared height); FMI: fat mass index (fat mass in kg divided by squared height); IFX: infliximab.

and FM indexes (5.5±2.3 versus 6.8±2.3; p=0.000) was observed. Vandan et al. evaluated 30 patients with CD undergoing IFX therapy and observed weight gain and change in nutritional status, the latter associated with clinical remission of the disease.[29] Weight gain after biologic therapy has also been observed in other studies in patients with autoimmune diseases, suggesting that this therapy, and not simply the remission of CD, is associated with these changes in weight.[30,32,33]

Our results demonstrated that there was a substantial increase in FM after the use of IFX. It should be noted that all patients had the body water percentage within normal values, so that FM and LM could not be affected by disturbances in the patients' hydration status.[21] Increased FM after treatment with anti-TNF in patients with CD has also been reported in the study by Wiese et al.[34] The gain of FM in patients who achieved clinical remission after biological therapy can be explained by factors such as improvement in the quantity and quality of food intake due to absence of symptoms, less catabolism secondary to reduction of inflammation and, last, TNF-α blockade. TNF is a mediator of cachexia induced by inflammation.[31] In addition, inhibition of TNF-α may trigger an increase in the number of adipocytes by facilitating adipogenesis, resulting in increased FM.[8]

It should be noted that IFX therapy resulted in increased waist circumference (88.1±6.7 vs. 93.9±7.7 cm; p<0.05) in our patients with CD. This finding makes us speculate whether the increase in waist circumference should be attributed to visceral or subcutaneous adiposity. Some studies using magnetic resonance imaging have shown an increase in abdominal fat volume in patients treated for 8 weeks with IFX, with homogeneous fat distribution between the visceral and subcutaneous compartments.[35,36] Interestingly, the accumulation of mesenteric fat in patients with CD has been observed and demonstrated to be independent of steroid use.[29,37]

A low level of physical activity leads to the disuse of skeletal muscle and consequent atrophy, which may be a factor present in patients with CD. All of our patients had a low level of habitual physical activity at baseline, with no change after induction and maintenance of CD remission.

Data regarding the metabolic profile of patients with CD undergoing anti-TNF therapy are controversial.[35,38-40] Popa et al. observed reduced levels of triglycerides after six months of anti-TNFα therapy in patients with rheumatoid arthritis.[38] Similar to the findings of Parmantier-Decreucq et al., despite weight gain, we did not observe changes in our patients' profile after anti-TNF therapy.[35] It is believed that a good control of the inflammatory state can positively influence the lipid concentration.[41]

Some studies have suggested that in different chronic clinical conditions, the PA can be considered a marker of general health, nutritional status and prognosis.[42,43] Reduced PA values are associated with unfavorable disease progression and poor prognosis. In our study, the values found for PA were significantly lower than the reference values, even after treatment with IFX. This lack of improvement after 24 weeks of IFX therapy may be explained by the time of intervention, which may not have been sufficient to produce substantial gain in the cell compartments of which PA is representative. Another factor to be considered is that PA decreases the greater the FM and the lower the LM. Although our patients gained LM, FM gain was even more substantial.

Our study has some limitations. First, although the electrical bioimpedance method is valid and reliable for body composition analysis, it consists of a bi-compartmental model, unable to measure visceral fat and subcutaneous fat. Although the method was influenced by the state of hydration (e.g., chronic or cirrhotic renal patients), our patients maintained healthy hydration and, therefore, there was no impact of this factor on CD. Second, the sample size, although modest, was based on sample calculations, and was able to detect significant differences. And finally, the lack of a control group with healthy individuals did not allow comparisons with the patients.

Important clinical implications can be highlighted in the present study. In patients with active CD who achieved remission, there was a gain in LM and FM. However, fat gain was more significant with consequent nutritional disorder despite CD remission. In addition, considerable fat gain, the persistence of sedentary lifestyle even with disease in remission, and a significant increase in waist circumference suggest a possible increase in cardiovascular risk in these patients.

In conclusion, in patients with moderate to severe CD who achieved remission after 24 weeks of anti-TNF therapy, body weight gain was observed, attributed mainly to gain of FM, increased waist circumference and unchanged PA. Future studies should seek to assess the impact of fat gain on cardiovascular outcomes and overall health, as well as evaluate the effects of nutritional and physical activity interventions simultaneously with anti-TNFα treatment.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Impacto da terapia biológica em portadores de doença de Crohn: Um estudo prospectivo

Introdução: Desnutrição proteico-calórica em pacientes de doença de Crohn (DC) tem sido relatada em 20 a 92% dos casos associando-se a maior morbimortalidade e maiores custos para o sistema de saúde. Agentes anti-TNF são um marco no controle clínico, promovendo remissão prolongada em portadores de DC. Acredita-se que a remissão da doença leve à recuperação nutricional desses pacientes. O efeito da terapia biológica na composição corporal e no estado nutricional é pouco conhecido.
Método: Estudo prospectivo de avaliação corporal por método de bioimpedância em portadores de DC moderada a grave submetidos a terapia com infliximabe (IFX). O desfecho principal foi a composição corporal antes e após 6 meses de terapia anti-TNF.
Resultados: Houve predomínio do sexo feminino (52%), com média de idades de 42±12 anos. A maioria dos pacientes era eutrófica na inclusão do estudo e assim permaneceu. Houve aumento de todos os parâmetros da composição corporal após o tratamento anti-TNF: IMC (22,9±3,2 *versus* 25±3,8; p=0,005), circunferência abdominal (88,1±6,7 *versus* 93,9±7,7; p=0,002), índice de massa magra (17,5±2,2 *versus* 18,2±2,3; p=0,000) e índice de massa gorda (5,5±2,3 *versus* 6,8±2,3; p=0,000). O ângulo de fase manteve-se inalterado (6,2 *versus* 6,8; p=0,94).
Conclusão: Após terapia com IFX, observou-se aumento de todos os componentes da composição corporal, exceto no ângulo de fase. O aumento substancial do índice de massa gorda e da circunferência abdominal levantam a preocupação de aumento nos riscos cardiovasculares e necessidade de estudos complementares.

Palavras-chave: doença de Crohn, composição corporal, biológicos.

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Sexual addiction in drug addicts: The impact of drug of choice and poly-addiction

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Summary

Objective: To compare the risk of comorbid sexual addiction in a sample of individuals with a diagnosis of substance dependence, stratifying the sample by drug of choice as well as by mono versus polysubstance addiction.
Method: All data were collected at Santa Casa de São Paulo, Brazil. The study sample comprised all alcohol or drug dependents admitted to the Addiction Treatment Unit between November 2013 and August 2014. A generalized linear model with a binomial distribution was performed to compare the odds of having a Sexual Addiction Screening Test (SAST) score greater than 6 points in the subgroups analyzed.
Results: A total of 133 participants were included in our analysis, all reporting cocaine/crack and/or alcohol as drug of choice. Polysubstance addicts had a significant higher risk of a positive screening for sexual addiction compared to monosubstance addicts, age-sex adjusted odds ratios of sexual addiction being respectively 2.72 (95CI 1.1-6.71) and 0.37 (95CI 0.15-0.91). The odds of a SAST score greater than 6 was not statistically different between the cocaine/crack and alcohol groups, respectively 0.38 (95CI 0.14-1.02) and 2.67 (95CI 0.98-7.25). We found a significant relation between stronger drug addiction and greater levels of sexual addiction in the cocaine/crack group (p=0.0012), but not in the alcohol group.
Conclusion: Our study reinforces the importance of assessing sexual behavior of drug addicts in clinical practice, especially considering users of multiple substances or with severe dependence.

Keywords: substance-related disorders, sexual behavior, observational study as topic.

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Introduction

The condition known as sexual addiction, sexual compulsion or hypersexuality is associated with a number of negative outcomes such as psychological distress, risky sexual behaviors, impairment in interpersonal relationships, and decreased professional performance. Although some authors point to a high prevalence, estimated rates being 2% in young adults, there is scarce scientific evidence on the underlying nature of this condition.[1] This lack of knowledge justifies the controversy over the nomenclature, each label implying different assumptions on etiological mechanisms.[2] Due to similarities with substance addictions, many authors consider sexual addiction as the most appropriate denomination. In this article, we use the terms addiction and dependence interchangeably.[3,4] Also in support of this concept, sexual addiction is highly frequent in alcohol or drug dependents, prevalence of a dual diagnosis being reported as 25%.[5] Despite the previously described connections between the conditions and potential treatment implications, few studies have assessed the risk of sexual addiction among individuals with substance addiction, specially when it comes to different drugs of choice or usage patterns.

Sexual addiction has been characterized as the engagement in excessive, repetitive sexual activities, including sex-related thoughts, masturbation and pursuing new sexual partners. The use of pornographic material to obtain sexual arousal is also very frequent, as well as seeking professional sex workers. Although this disorder is common and might lead to severe adverse consequences, there is no conclusive evidence on the underlying theoretical framework. Authors who support a sexual addiction-model point to similar clinical features between sexual and chemical addictions, including the escalating pattern, persistence despite adverse consequences, and repeated and unsuccessful efforts to reduce these behaviors.[6] There is also growing evidence on a common etiologic basis for the reinforcement effect of drugs and sex, with studies supporting the contribution of the same neurophysiological structures and similar patterns of neuroplasticity over time.[7,8] Furthermore, many therapeutic approaches for sexual addiction incorporate elements of addiction-based treatments such as relapse prevention-focused psychotherapy and mutual-help programs with a 12-step format.[9] Previous reports also suggested that topiramate and naltrexone, medications used for the treatment of some types of substance addiction, may have a therapeutic effect in sexually addicted patients.[10]

Of prognostic relevance, studies with substance addicts have described that sexual addiction is associated with increased relapse rates. One possible explanation is that both addictions are often complementary, many addicts reporting the simultaneous use of substances and sex to experience an enhanced effect. Another common pattern is the shifting between different addictive behaviors during treatment, or using one dependence to counteract withdrawal symptoms from the other. There are also reports on patients using alcohol and drugs to either facilitate sexual behavior or to handle feelings of shame and guilt derived from their sexual practices.[8,11] Importantly, both sexual addiction and drug use have been associated with increased risk of HIV transmission and other sexually transmitted diseases (STDs).[12,13] Although more studies are needed to estimate the rates of STDs among individuals concomitantly addicted to substances and sex, this population presents several vulnerability factors, making their study of interest since they will require public health strategies specific for each condition.

Considering the concepts of sexual and substance addiction as an integrated paradigm may support the development of more effective treatment approaches for individuals with both diagnoses. Prior to the implementation of targeted strategies, however, it is important to determine which specific substances or usage patterns might be associated with a higher risk of sexual addiction. Although previous studies have been conducted describing the rates of substance addiction among sexually addicted subjects, few authors have compared the risk of comorbid sexual addiction in users of different substances, or among mono versus polysubstance users.

In face of this gap in the literature, our study was designed to assess the risk of comorbid sexual addiction in a sample of substance addicts, stratifying individuals by drug of choice as well as mono versus polysubstance addiction.

Method

Study design

This is an observational study to assess the risk of sexual addiction in a sample of individuals diagnosed as having alcohol or substance dependence, stratified by drug of choice and mono versus polysubstance addiction. Our study is described in accordance with the Reporting of Observational Studies in Epidemiology (STROBE) statement.[14]

Setting

Data were collected at the Addiction Treatment Unit of Santa Casa de São Paulo, a tertiary care teaching hospital located in central São Paulo, Brazil. Our system is a referral center for the metropolitan area of São Paulo, a city with over 20 million inhabitants, while also providing care for patients from the entire state and country. Patient recruitment and data collection processes occurred over a period of nine months, from November 2013 to August 2014.

Ethics

Our study was approved by the Institutional Review Board of Santa Casa de São Paulo School of Medicine (protocol number CAAE: 15723813.5.0000.5479), informed consent being offered to all potential participants and subsequently signed prior to any study protocol being implemented. Patients did not receive any form of compensation for participating in the study.

Participants

The study sample comprised all patients consecutively admitted to the Addiction Treatment Unit at Santa Casa de São Paulo. Inclusion criteria were age over 18 years and a diagnosis of alcohol or substance dependence according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revision (DSM-IV).[15] A total of 139 patients were initially part of the analysis.

Variables

The outcome of interest was that of SAST scores. Our main predictors were the diagnosis of alcohol and/or substance dependence, the identification of mono or polysubstance usage (i.e., addiction to more than one substance, including alcohol) and the severity of dependence according to the Short Alcohol Dependence Data (SADD) Questionnaire or the Drug Abuse Screening Test (DAST), as applicable. Nicotine addiction was not included in the polysubstance concept. Potential confounders were selected based on evidence from previous literature combined with clinical judgment. Specifically, we selected age and sex.[16]

Data sources/measurement

Data collection was performed by the main researcher, assisted by Psychiatry residents specifically trained for this protocol. Initially, a 40-minute psychiatric interview was conducted to investigate the necessary criteria in the DSM IV. Participants were then evaluated through the following self-reported instruments: (1) SAST, which is a 20-item dichotomous scale providing an initial assessment of sexual addiction, previously validated in the Brazilian population, with a suggested cut-off score of six points to account for appropriate sensitivity. This is a lower score compared to the 13-point threshold recommended for the original scale version.[17] In the Brazilian study, the instrument achieved good sensitivity (0.83), specificity (0.75) and internal consistency (Cronbach's alpha = 0.89[18]). (2) SADD Questionnaire, a 15-item scale developed to indicate the severity of alcohol dependence, graded as: I) 0-9 = mild; II) 10-19 = moderate; III) 20-45 = severe. This scale was tested among Brazilian patients, presenting adequate internal reliability with Cronbach's alpha coefficient = 0.79.[19] (3) DAST, a 20-item scale designed to evaluate the severity of drug-related problems in the last year, according to the following classification: I) 0 = no problems; II) 1-5 = mild; III) 6-10 = moderate; IV) 11-15 = substantial; V) 16-20 = severe. This instrument includes questions concerning abuse, dependence, withdrawal (signs and symptoms), social impairment, family relationships, legal implications and medical problems. Satisfactory psychometric measures of reliability and validity were reported, with a Cronbach's alpha coefficient of 0.92. This test, however, has not yet been validated for the Brazilian population.[20,21]

Statistical methods

Our exploratory analysis started by evaluating distributions, frequencies and percentages for each of the numeric and categorical variables. Categorical variables were evaluated for near-zero variation.[22] Extensive graphical displays were used for both univariate analysis and bivariate associations, accompanied by broader tests such as Maximal Information Coefficient[23] and Non-negative Matrix Factorization[24] algorithms for numeric variables. Missing data were explored using a combination of graphical displays involving univariate, bivariate and multivariate methods. Imputation was performed using a k-nearest neighbors algorithm (n=5).[25]

A generalized linear model with a binomial distribution (logistic regression) was performed to assess the impact of each predictor variable on the risk of sexual addiction, ultimately assessing the odds ratio of having an SAST score greater than six among individuals with different drugs of choice, as well as between mono versus polysubstance addicts. We also measured the impact of different severity levels of drug dependence using the Pearson's Chi-square test. Results are reported as odd ratios for Boolean outcomes, and predicted means for numeric outcomes, along with 95% Confidence Intervals (95CI). All analyses were performed using the R language[26] and the following packages: ggplot2,[27] rmarkdown.[28]

Results

Sample characteristics

An initial sample size of 139 subjects participated in this analysis. Of these, six individuals who had marijuana as their drug of choice were excluded because of the small sample size, thus leading to a final sample size of 133 subjects. Most of our subjects were single, heterosexual, unemployed males (84.2%), in their late 30s, with a high-school education level. Regarding drug of choice, 59 subjects indicated preferential use of alcohol (44.4%), while 74 were primarily users of cocaine/crack (55.6%). We had no other substances referred to as drugs of choice, though 39.1% of our sample size comprised polysubstance addicts, smoking being reported by 38.3% of our subjects (Table 1).

Comparing individuals with different drugs of choice, those in the alcohol group were older and had higher rates of unemployment. The majority in this group was classified as having severe addiction through the Alcohol Addiction Scale (50.8%), with most individuals (84.7%) being monosubstance addicts. In contrast, most individuals in the cocaine/crack group had substantial drug-related problems, and polysubstance dependence was frequent (58.1%).

Considering a SAST cut-off of six points as recommended for the Brazilian population, polysubstance addicts had a significantly higher risk of a positive screening for

TABLE 1 Sample characteristics stratified by drug of choice.

Variable [Missing]	Total (133)	Alcohol (59)	Cocaine/crack (74)
Age [1]	37.15 (±9.61)	40.69 (±10.47)	34.38 (±7.9)
Gender female [0]	21 (15.8%)	9 (15.3%)	12 (16.2%)
Currently working [16]	52 (44.4%)	17 (32.7%)	35 (53.8%)
Marital status [2]			
Divorced/separated	26 (19.8%)	9 (15.5%)	17 (23.3%)
Married	19 (14.5%)	15 (25.9%)	4 (5.5%)
Single	74 (56.5%)	26 (44.8%)	48 (65.8%)
Common law partner	12 (9.2%)	8 (13.8%)	4 (5.5%)
Race [9]			
Black	15 (12.1%)	5 (9.1%)	10 (14.5%)
Mixed	35 (28.2%)	17 (30.9%)	18 (26.1%)
White	74 (59.7%)	33 (60%)	41 (59.4%)
Sexual orientation [6]			
Bisexual	4 (3.1%)	0 (0%)	4 (5.6%)
Heterosexual	113 (89%)	51 (92.7%)	62 (86.1%)
Homosexual	10 (7.9%)	4 (7.3%)	6 (8.3%)
Income (Brazilian reais) [15]			
No income	10 (8.5%)	4 (8.2%)	6 (8.7%)
Up to minimum income	28 (23.7%)	18 (36.7%)	10 (14.5%)
Minimum to 2,000	56 (47.5%)	15 (30.6%)	41 (59.4%)
2,000–5,000	20 (16.9%)	12 (24.5%)	8 (11.6%)
More than 5,000	4 (3.4%)	0 (0%)	4 (5.8%)
Education level [1]			
No formal education	2 (1.5%)	2 (3.4%)	0 (0%)
Primary school	12 (9.1%)	4 (6.9%)	8 (10.8%)
High school	63 (47.7%)	28 (48.3%)	35 (47.3%)
Mid school	25 (18.9%)	9 (15.5%)	16 (21.6%)
University	30 (22.7%)	15 (25.9%)	15 (20.3%)
SAST – Total [34]	5.26 (±4.03)	4.11 (±3.33)	5.95 (±4.27)
SAST higher than 6 [34]	32 (32.3%)	7 (18.9%)	25 (40.3%)
SAST higher than 13 [34]	5 (5.1%)	0 (0%)	5 (8.1%)
SADD – Total [31]	17.54 (±9.67)	20.22 (±9.85)	13.86 (±8.18)
SADD – Category [1]			
Does not apply	32 (24.2%)	0 (0%)	32 (43.8%)
Mild (0–9)	26 (19.7%)	10 (16.9%)	16 (21.9%)
Moderate (10–19)	33 (25%)	19 (32.2%)	14 (19.2%)
Severe (20–45)	41 (31.1%)	30 (50.8%)	11 (15.1%)
Type of addiction [0]			
Mono-addiction	81 (60.9%)	50 (84.7%)	31 (41.9%)
Poly-addiction	52 (39.1%)	9 (15.3%)	43 (58.1%)
DAST – Total [42]	12.27 (±3.89)	9.76 (±4.48)	12.85 (±3.53)
DAST – Category [0]			
Does not apply	42 (31.6%)	42 (71.2%)	0 (0%)
Mild (1–5)	4 (3%)	4 (6.8%)	0 (0%)
Moderate (6–10)	24 (18%)	4 (6.8%)	20 (27%)
Substantial (11–15)	37 (27.8%)	7 (11.9%)	30 (40.5%)
Severe (16–20)	26 (19.5%)	2 (3.4%)	24 (32.4%)

sexual addiction compared to monosubstance addicts (Figure 1), the age and sex-adjusted odds ratio of sexual addiction being respectively 2.72 (95CI 1.1-6.71) and 0.37 (95CI 0.15-0.91). We also found a significant relationship between the severity of drug addiction and the risk of sexual addiction in the cocaine/crack group using the Pearson's Chi-squared test (p=0.0012) (Figure 2), but a similar trend was not observed in the alcohol group.

An SAST score higher than six was present in 18.9 and 40.3% of the individuals, respectively, in the alcohol and cocaine/crack groups. Only five individuals had an SAST score higher than 13, all in the cocaine/crack group. The age-sex adjusted odds for SAST scale higher than six demonstrated no statistically different results between the cocaine/crack and alcohol groups, respectively calculated as 0.38 (95CI 0.14-1.02), and 2.67 (95CI 0.98-7.25). We, however, found no significant differences in the risks of sexual addiction when stratifying the alcohol or cocaine/crack groups between mono and polysubstance dependence.

Discussion

To the best of our knowledge, this is the first study comparing the risk of sexual addiction among substance addicts and alcohol or cocaine/crack as their drugs of choice, as well as between mono and polysubstance addicts. Based on the SAST, we found that polysubstance addicts had a higher risk of sexual addiction than monosubstance addicts. There was no significant difference in the risk of sexual addiction of individuals who reported cocaine/crack versus alcohol as their drug of choice. More severe dependence was a risk factor for sexual addiction only among individuals reporting cocaine/crack as their drug of choice. In our sample, no subjects reported other substances as their drug of choice.

The distribution of drugs of choice in our sample is consistent with studies reporting alcohol and cocaine as popular drugs of abuse in the Brazilian population. Another characteristic reported in the Brazilian population is the infrequent use of heroine, consistent with our analysis in this sample. However, the previously described use of marijuana and solvent inhalants in Brazil was not verified in our sample.[29] Our findings may reflect differences in the access to health care services among addicts to different substances.

As expected, the prevalence of sexual addiction in our study was higher than the corresponding estimated rates in the general population. Our results are also in agreement with the literature demonstrating that polysubstance addicts have higher rates of psychiatric comorbidities compared with individuals addicted to one substance.[30,31]

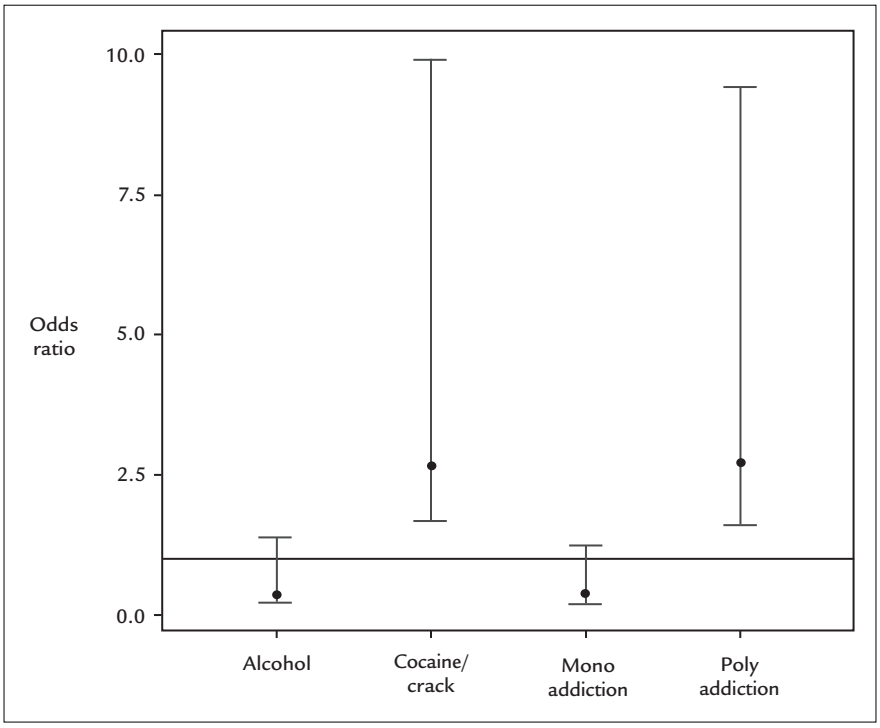

FIGURE 1 Age and sex adjusted odds ratio of having an Sex Addiction Screening Test score higher than six according to drug of choice and mono versus polysubstance addiction, São Paulo, 2013-2014.

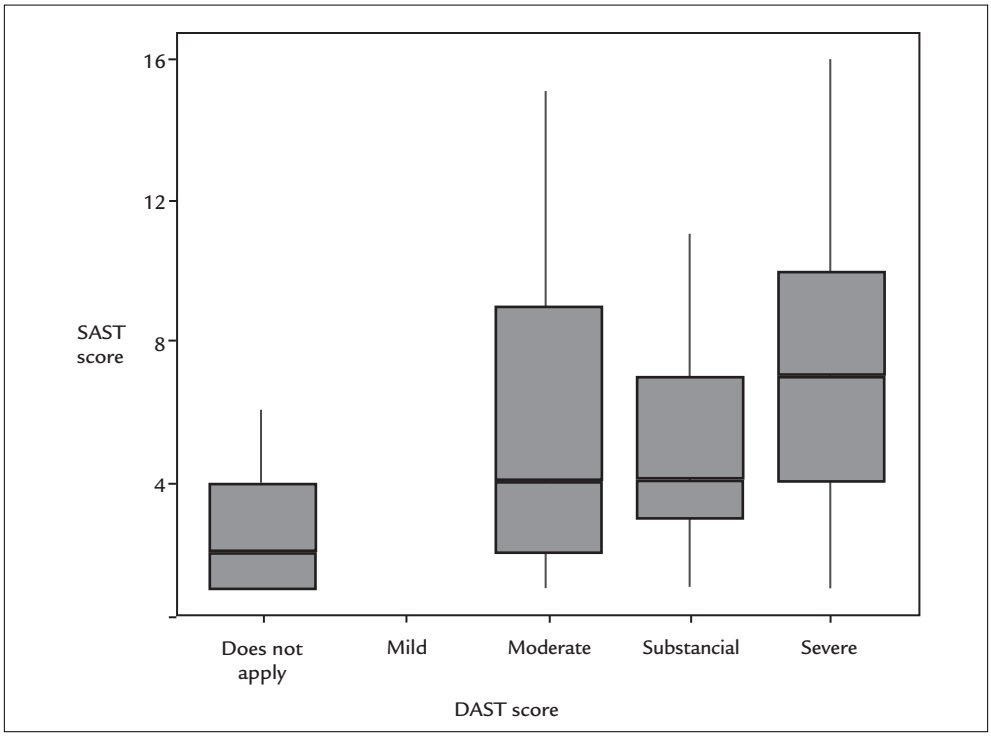

FIGURE 2 Severity of drug-related problems according to the Drug Addiction Screening Test (DAST) and risk of sexual addiction according to the Sex Addiction Screening Test (SAST), São Paulo, 2013-2014.

Furthermore, comparisons of personality profiles among drug addicts demonstrated an increased disturbance pattern when polysubstance addiction is involved.[32] Considering our findings in this context, it is possible that pre-morbid personality traits associated with polysubstance addiction such as novelty-seeking may predict sexual addiction.[33]

Another possible explanation for the association between polysubstance and sexual addiction might be the influence of socio-cultural contexts where sex, drugs, and alcohol are connected. For instance, dance clubs and circuit parties are environments where the use of multiple substances and the seeking of new sexual partners are common behaviors, possibly eliciting a mutually reinforcing pattern.[34] Contextual factors might also have a role in the association between severity of drug addiction and increased sexual activity. Heavy substance users might be more vulnerable to the exchange of sex for money or drugs while craving drugs, resulting in a higher number of sexual partners.[35,36]

Interpretations of our results based on the effects of each drug on sexual response must be viewed with caution. According to popular beliefs, cocaine and alcohol are considered aphrodisiac, often being used with the intent of enhancing sexual activity.[37] Among mild alcohol and cocaine/crack users, increased sexual desire might be caused by transient drug-induced increases in dopaminergic activity, disinhibitory effects and non-pharmacological factors, such as learned behavioral responses and expectations about the sexual effects of drugs.[38,39] As for the chronic abuse of these substances, the literature demonstrates an association with decreased libido, impairment on sexual performance and sexual dysfunction.[40] Further research is needed to better understand the direct and indirect impact of each substance on sexual behavior. Several variables should be contemplated, including but not limited to dosage, chronicity of use, gender and psychosocial factors.

Despite filling a gap in the literature, our study does have limitations. First, given that our sample was small and not randomly drawn from a larger patient population, its external validity can be questioned. Nevertheless, our sample is not atypical for its setting, making our conclusions valid for similar populations. Second, our data did not establish the dose-response impact of each type of drug use on the risk of sexual addiction. However, this is a sample of individuals with high levels of substance addiction, thus supporting our results in this context. Finally, although our data have demonstrated that sexual addiction is a significant problem in our sample, we did

not compare it to a control group of non-substance addicts in our comparison. Although the rates of sexual addiction in our sample are higher than that reported for the general population, future research should address this question.

Conclusion

Our study reinforces the importance of assessing the sexual behavior of alcohol and drug addicts in clinical practice, especially considering polysubstance users and severe drug addicts. Sexual addiction must be systematically evaluated and addressed within drug rehabilitation programs, given that concurrent treatment may lead to better outcomes. Moreover, substance addicts should be targeted for public health programs focused on the prevention of risky sexual behavior. More studies are needed to understand the neurobiological basis of sexual addiction and its connection to other chemical and behavioral addictions, which may lead to more comprehensive treatment programs.

Resumo

Dependência sexual em dependentes químicos: o impacto de diferentes drogas de escolha e de polidependência

Objetivo: Comparar o risco de dependência sexual em uma amostra de indivíduos com diagnóstico de dependência química, estratificados por droga de escolha e por dependência única ou de múltiplas substâncias.
Método: Todos os dados foram coletados na Santa Casa de São Paulo, Brasil. A amostra estudada correspondeu a todos os indivíduos dependentes de álcool ou outras substâncias admitidos no Ambulatório de Dependência Química entre novembro de 2013 e agosto de 2014. Modelos lineares generalizados com distribuição binomial foram utilizados para comparar o risco de escores maiores que seis na Escala de Rastreamento para Dependência de Sexo (SAST) nos subgrupos analisados.
Resultados: Foram analisados os dados de 133 pacientes usuários de cocaína/*crack* e/ou álcool. Usuários de múltiplas substâncias apresentaram risco significativamente maior de um *screening* positivo para dependência sexual comparados com usuários de uma única substância. Os *odds ratios* de dependência sexual ajustados por sexo e idade obtidos nos dois grupos foram, respectivamente, 2.72 (IC95% 1.1-6.71) e 0.37 (IC95% 0.15-0.91). O risco de dependência sexual entre usuários de cocaína/*crack* e álcool foi estimado, respectivamente, em 0.38 (IC95% 0.14-1.02) e 2.67 (IC95% 0.98-7.25), não indicando diferença significativa. Foi encontrada uma relação significativa entre severidade de dependência química e maiores níveis de dependência sexual entre dependentes de cocaína/*crack*, mas não de álcool.
Conclusão: Nosso estudo reforça a importância de avaliar o comportamento sexual de dependentes químicos na prática clínica, especialmente considerando usuários de múltiplas substâncias, ou casos de maior severidade.

Palavras-chave: transtornos relacionados ao uso de substâncias, comportamento sexual, estudos observacionais como assunto.

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Treatment of digital ulcers in systemic sclerosis: Case series study of thirteen patients and discussion on outcome

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Summary

Introduction: In systemic sclerosis (SSc), digital ulcers (DU) are debilitating and recurrent. They are markers of prognosis and are associated with disability and mortality. Treatment strategies have been developed to block the proposed mechanisms of this complication.
Objective: Clinical description of a population of SSc patients with DU, treatment, complications and outcome.
Method: Analysis of 48 SSc patients meeting 2013 ACR-EULAR criteria, followed between 1999-2015; 13 patients had DU. Treatment protocol applied included cycles of 21 days of alprostadil, which can be repeated in the absence of DU healing. After DU healing, bosentan was initiated.
Results: DU healing was achieved with intravenous prostanoid in 12 patients; seven patients required repeated treatment for DU healing. Twelve patients were later treated with bosentan; three of them experienced recurrence of DU, while one was anti-B2-GPI positive. Four patients had soft tissue loss and three other suffered digital amputation, these being late diagnosis.
Conclusion: Younger patients and early referrals had better outcomes. Endothelin receptor antagonist toxicity should be monitored, particularly in patients previously exposed to hepatotoxic drugs.

Keywords: systemic sclerosis, digital ulcers.

Study conducted at Hospital Distrital de Santarém, Santarém, Portugal

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Introduction

Systemic sclerosis (SSc) is a rare and progressive disease that affects the connective tissue. It is characterized by a diffuse vasculopathy that is accompanied by cutaneous and visceral fibrosis. Digital ulcers (DU) are one of the main complications derived from SSc-associated microvasculopathy, which is recurrent and incapacitating. They occur in 30% of patients with limited SSc and 58% in diffuse forms.[1-3]

Its etiology is multifactorial; however, two triggers have been described as responsible for the development of DU: one is related to the structure of the vascular wall, which leads to a proliferation of the intima and an increased production of vasoconstrictors; the other is related to the existence of a variable degree of intraluminal thrombosis.[1,4-6]

Among the mechanisms considered to be responsible for the development of DU, endothelial injury results from a decrease in the caliber of the intravascular lumen caused by the secretion of collagen and other components of the extracellular matrix, which in turn leads to fibroblast activation, hindering blood flow and causing chronic ischemia of tissues. Endothelial injury is accompanied by increased levels of endothelin-1 (ET-1), a potent vasoconstrictor peptide. The actions of ET-1 are mediated by two types of receptors: endothelin type A (ETa) and type B (ETb). Activation of type A leads to vasoconstriction and vascular remodeling, whereas type B leads to vasodilation. This leads to an imbalance between the production of vasoconstricting (ET-1) and vasodilating (prostacyclin and nitric oxide) substances.[3,4,7,8]

Another proposed mechanism is the presence of autoantibodies that produce direct damage on endothelial cells. Secondarily, platelet activation occurs by the release of thromboxane and then intraluminal thrombosis.[3,4,7,8]

The treatment of DU was developed from the blockade of these proposed etiopathogenic principles,[1,4-6] which are inseparable from those that contribute to Raynaud's phenomenon, since both constitute a similar microvascular dysfunction occurring at different stages. Standard treatment is described in evidence-based European clinical practice guidelines, and there is a need for systematic and rigorous research to better define and structure new treatments for this complication.[9]

The results of previous studies suggest that intermittent cycles of iloprost improve the progression of DUs and prevent new episodes of digital ischemia. Also, treatment with endothelin receptor antagonists (bosentan) may have some efficacy in preventing new DUs as well as in improving the functionality of the hand.[2]

The objective of our review is to describe a population of patients with SSc and DU, their treatment, complications and clinical results, implementing the protocol of our Center.

Method

A case series including 48 patients with SSc, of whom thirteen had associated DU. In the sample studied, there was a predominance of the female sex (69%), and the mean age was 61.8 years ranging between 49 and 81 years (Table 1). The DUs presented by all included patients were distal or cardinal. They were followed between 1999 and 2015, in a doctor's office for Autoimmune Diseases, in our area of influence (which covers about 200,000 inhabitants). All of them met the criteria of the ACR-EULAR 2013 classification.[3,10]

The protocol applied included 21-day cycles of daily 60 mcg of alprostadil (the only prostacyclin available in our Center) that could be repeated if there was no scarring. In response, bosentan was initiated in increasing doses, starting with 62.5 mg twice daily up to 125 mg twice daily. After completing each cycle of alprostadil, patients were referred to the Day Hospital for observation, and in the case of those who were treated with bosentan, the control was performed every three months in the Specialty Consultation. As a defining characteristic of clinical improvement of the DU, the following elements were considered: decrease in extension, absence of inflammation, healing and absence of recurrence.

The clinical records, data from the Computer Registry of Autoimmune Diseases of Portugal (RIDAI) and the international registry DUO (Digital Ulcers Outcome) were reviewed. Statistical analysis was performed using Microsoft Excel 2007®, after obtaining Informed Patient Consent.

Results

Thirteen patients with SSc and DU (Figure 1) were diagnosed, of whom twelve had a form of limited SSc, and four also had associated calcinosis.

Regarding markers, anticentromere antibodies (ACA) were positive in ten patients, anti-B2-GPI in two, other two had anti-Ro/SSA and anti-La/SSB, and anti-Scl 70 was found in one case. It should be noted that a single case that was diagnosed with diffuse SSc was ACA positive without anti-Scl-70 positivity. Antiphospholipid antibodies (APLA) were investigated in nine of the cases, with two being positive.

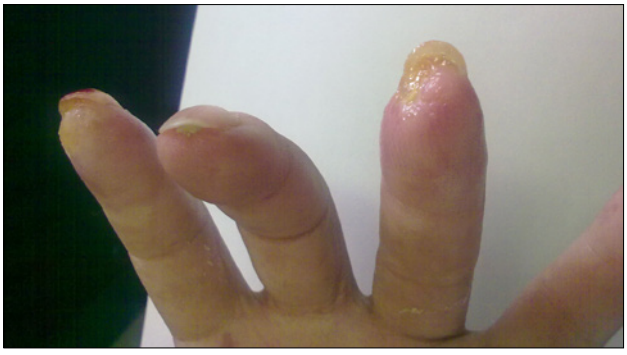

FIGURE 1 Example of digital ulcers in the left hand of patient number 4 prior to treatment with bosentan.

All patients were medicated with calcium channel antagonists (CCA) for Raynaud's phenomenon. Healing was achieved with prostanoids in twelve of the patients in the first cycle, with a need to repeat treatment in seven of them. Twelve subsequently underwent treatment with bosentan (Figure 2), with one case of recurrence of DU in three of them, one of which was anti-B2-GPI positive.

There was also recurrence of DU in a patient who had not yet started treatment with bosentan due to a delay in medication approval and dispensing.

After healing, there was residual Raynaud's phenomenon in six patients, with a need to adjust vasodilator therapy in all of them.

An alteration of the liver enzymes was observed in four patients, persisting in one individual with a history of alcoholism and relapsing DU, and therefore the treatment with bosentan was stopped.

In three patients there was previous exposure to methotrexate, with normalization of the transaminase values after taking folinic acid.

Eleven patients were medicated with antiplatelet agents and four with oral anticoagulants, two of them

TABLE 1 Patients characteristics and clinical outcomes.

Patient ID/Sex	1 /F	2/F	3/M	4/F	5/F	6/M	7/M	8/F	9/F	10/F	11/M	12/F	13/F
Age	76	68	62	63	57	49	51	67	55	69	81	63	60
Cause of death	Digestive bleeding		Liver failure										
SSc subtype	Limited	Limited	Limited	Limited	Limited	Limited	Limited	Limited	Diffuse	Limited	Limited	Limited	Limited
Calcinosis				Yes						Yes	Yes	Yes	
Antibodies	Anti-centromere, anti-scl70,	Anti-centromere	Anti-centromere	Anti-centromere, anti-B2-GPI IgM	Anti-centromere	0	Anti-centromere	Anti-centromere	Anti-centromere	0	0	Anticentromere, anti-SSA, anti-SSB, anti-B2-GPI IgM	Anti-centromere, anti-SSA, anti-SSB
Prior use of methotrexate				Yes			Yes		Yes				
Alcoholism			Yes				Yes						
Smoker			Yes			Yes	Yes						
Treatment with prostacyclin (PC)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
New cycle of PC				Yes	Yes	Yes				Yes	Yes	Yes	Yes
Residual Raynaud's phenomenon after treatment		Yes		Yes	Yes					Yes	Yes	Yes	
Treatment with bosentan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes
Transaminase alteration due to bosentan use			Yes	Yes			Yes		Yes				
Ulcer recurrence			Yes	Yes							Yes		
Scarring				Yes	Yes					Yes		Yes	
Amputation			Yes			Yes						Yes	
Antiaggregation	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Anticoagulation				Yes		Yes						Yes	Yes
Admission for digital ulcers	Yes	Yes	Yes			Yes	Yes						

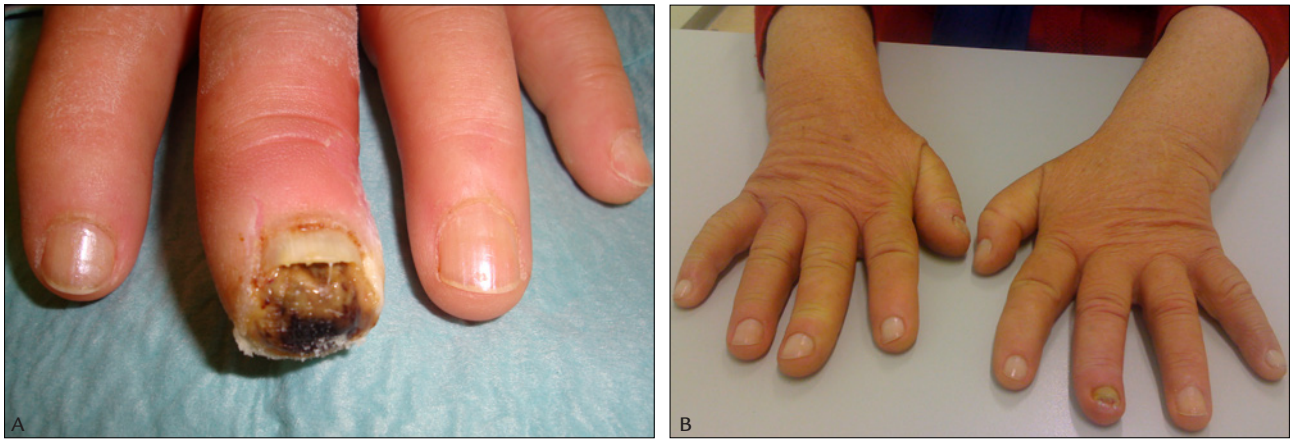

FIGURE 2 Digital ulcer of the third finger of the left hand with loss of substance in patient number 10, prior to treatment (A) and after treatment (B).

were anti-B2-GPI positive, with an improvement in the healing process. Two patients were already anticoagulated, one of them due to pulmonary hypertension prior to the diagnosis of SSc and another because of the presence of mitral valve prosthesis.

Four patients had scarring, and digital amputation was necessary in three other cases that were diagnosed very late (one of them had actually undergone the procedure before the diagnosis of SSc).

Two patients died, one of liver failure and the other of digestive hemorrhage. Three patients remained active and only one of the eleven retired due to peripheral vasculopathy.

Discussion

DUs are a prognostic marker of SSc, which is associated with functional disability of the hand, leading to a lower quality of life and greater morbidity and mortality.[4,11]

The treatment of DU involves screening for complications, promoting healing and preventing recurrences. Optimal treatment is a challenge and includes non-pharmacological, pharmacological and surgical measures. The intravenous use of CCAs and prostanoids has a high level of scientific evidence.[9] Endothelin receptor antagonists are approved for the prevention of DU recurrence with improved hand functionality and better functional and vital prognosis based on the results of the RAPIDS-1 and RAPIDS-2 trials.[2,4,6,12,13] Other studies have shown that bosentan treatment increased the fingertip blood flow in patients with low perfusion in its initial stages, helping in the process of remodeling the capillary microcirculation.[2,5]

Short-acting antiplatelet and anticoagulant therapy should be considered, although there is no strong evidence of its efficacy.[4] There is strong theoretical support for the use of antiplatelet agents in SSc and a consensus on the practical approach for prescription, being recommended in all patients with chronic digital ischemia.[4,14]

The role of statins is noteworthy, as they have proven useful in some studies for increasing the levels of nitric oxide and reducing ET-1. This improvement in endothelial dysfunction may be attributable to its anti-inflammatory and immunomodulatory properties.[4] The benefit of long-term anticoagulation is probably achieved in patients with APLA and severe or recurrent digital ischemia.[4,11]

Conclusion

In this small series, the most favorable progression was observed in young patients, which we admit is due to early diagnosis and beginning of the treatment. Conversely, the evolution was unfavorable in older patients, with prolonged disease progression, late diagnosis and presence of lesion in a target organ.

It was necessary to monitor the toxicity of endothelin receptor antagonists in individuals previously exposed to alcohol and hepatotoxic drugs, which may require discontinuation of bosentan.

Treatment with bosentan helped to prevent recurrences with new ulcers, but a significant number of patients presented residual Raynaud's phenomenon, leading to a necessary intensification of vasodilating therapy. In the treatment of DU, one always has to resort to several drugs simultaneously or sequentially, always looking for a synergy.[15] Registering information is essential for further progress in this area, to increase available evidence.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Tratamento de úlceras digitais na esclerose sistêmica: série de casos de 13 doentes e análise crítica dos resultados

Introdução: As úlceras digitais (UD) são complicações incapacitantes e recorrentes, associadas a menor qualidade de vida e maior mortalidade na esclerose sistêmica (ES). O tratamento baseia-se em antagonizar os mecanismos fisiopatológicos em causa.
Objetivo: Descrever uma amostra de doentes com diagnóstico de ES e UD, o tratamento, as complicações e os resultados clínicos.
Método: Série de 48 casos diagnosticados com ES, critérios de classificação ACR-EULAR 2013, seguidos entre 1999 e 2015, dos quais 13 apresentavam UD. O protocolo aplicado incluía ciclos de 21 dias de alprostadil podendo ser repetidos no caso de não existir cicatrização. Nos casos em que houve cicatrização foi iniciado bosentano.
Resultados: No tratamento das UD, 12 doentes realizaram prostaciclina endovenosa, com necessidade de tratamentos repetidos em sete doentes. Doze doentes foram posteriormente tratados com bosentano, com recorrência de UD em três doentes, um deles com presença de anti-B2-GPI. Quatro doentes ficaram com cicatrizes e em três houve amputação digital, sendo casos de diagnóstico tardio.
Conclusão: Os doentes mais jovens tiveram melhores resultados, possivelmente em razão de melhorias globais nos cuidados de saúde prestados e de referenciação precoce. A toxicidade dos antagonistas dos receptores da endotelina deve ser monitorizada, sobretudo em doentes com exposição prévia a drogas hepatotóxicas.

Palavras-chave: esclerose sistêmica, úlceras digitais.

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Cardiac remodeling indicators in adolescent athletes

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Summary

Objective: The idea that different sports and physical training type results in different cardiac adaptations has been widely accepted. However, this remodelling process among different sport modalities is still not fully understood. Thus, the current study aims to investigate the heart morphology variation associated with a set of different modalities characterized by distinct models of preparation and different methods and demands of training and completion.
Method: The sample comprises 42 basketball players, 73 roller hockey players, 28 judo athletes and 21 swimmers. Anthropometry was assessed by a single and experienced anthropometrist and the same technician performed the echocardiographic exams. Analysis of variance was used to study age, body size and echocardiograph parameters as well as different sport athlete's comparison.
Results: Basketball players are taller (F=23.448; p<0.001; ES-r=0.553), heavier (F=6.702; p<0.001; ES-r=0.334) and have a greater body surface area (F=11.896; p<0.001; ES-r=0.427). Basketball and hockey players have larger left auricle diameters compared with judo athletes (F=3.865; p=0.011; ES-r=0.316). Interventricular end-diastolic septal thickness (F=7.287; p<0.001; ES-r=0.347) and left ventricular posterior wall thickness (F=8.038; p<0.001; ES-r=0.362) of the judokas are smaller compared to the mean values of other sports participants. In addition, relative left parietal ventricular wall thickness is lower among swimmers compared with judokas (F=4.127; p=0.008; ES-r=0.268).
Conclusion: The major contributors to changes in heart morphology are for the most part associated with sport-specific training and competition and the specific dynamics and adaptive mechanisms imposed by each sport.

Keywords: sports modalities, young athletes, echocardiography, left ventricle mass, body size, growth.

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Introduction

The practice of sports offers a field of application to understand left ventricular (LV) cardiac remodeling, and is addressed in several studies[1-3] pointing to the occurrence of concentric or eccentric hypertrophy depending on the modality practiced. However, athletes of the same modality, exposed to apparently similar training methodologies, evidence different cardiac remodeling processes,[4] which implies the need to systematize knowledge across the vast spectrum of sports modalities and, within each of them, sex and age group by competitive level. Complementarily, no evidence of dichotomous cardiac adaptation was found among athletes of modalities with predominance of strength in the performance structure.[5] The level of demand for the upper limbs is considered relevant in the process of cardiac remodeling.[6]

The average heart rate during a basketball game is around 171 beats per minute (bpm), although basketball

is characterized by the existence of multiple and repeated episodes of high intensity and short duration exertion,[7] and therefore is naturally regarded as a modality in which short-term energy demands predominate. Roller hockey, like most general sports games, has a complex structure, and it has been estimated that 71% of playing time (n=14, 20-32 years) includes intermittent high intensity activities, with an average heart rate of 163.5 bpm and a reference lactate concentration of 4.20±0.95 mmol/L.[8] Despite some similarity between collective sports games in relation to the intermittent nature of the effort, roller hockey players are characterized by a predominance of musculoskeletal structures,[9] as opposed to basketball, which attracts and promotes players of high stature. Modalities such as basketball, roller hockey and swimming were classified as sports with a low or moderate static component and high dynamic component, unlike judo,[10] a modality in which repeated application of force and resistance is fundamental.[11]

Cardiac dimensions in children and young people were assumed to be directly proportional to height.[12] In adolescent athletes, the available studies describe LV morphology and function as well as other cardiac parameters,[1,13] but it is not always the interpretation of results relating to the relationships between sporting modalities, cavity dimensions and wall thickness that consider the additional effect attributable to body size, proportionality between trunk and limbs, and components of body composition. Our study examines the variation in the morphology of the heart associated to a set of sports modalities that are characterized by distinct long-term preparation models, different training and competition methodologies, and unique processes of selection and promotion of the most talented athletes. Our objective is to complement the studies that only proceed to the comparative analysis of athlete and non-athlete adolescents.

Method

Study design and population

Our study has a cross-sectional design and comprises young male athletes of various modalities (n=164, 15.28±0.76 years): 42 basketball players (including 24 international players with participation in European championship games in their respective age groups), 73 hockey players (including 12 international and European champions in their respective age groups), 28 judokas (recruited to train with the national team in their respective age groups) and 21 swimmers (classified among the best swimmers of the Central Region of Portugal in their respective age groups). Several groups were formed according to age: 14.0-14.9 years (n=41); 15.0-15.9 years (n=100) and 16.0-16.9 years (n=23). All athletes were involved in federated sports for at least five years. None of the participants had evidence of organic disease or were under the effect of any active substance (medication or ergogenic supplementation). The study was approved by the Research Ethics Council and the Scientific Council of the FCDEF, University of Coimbra, and later by the Portuguese Foundation for Science and Technology (SFRH/PROTEC, process no. 67972/2010), in accordance with the principles of the Declaration of Helsinki. Participants and their representatives signed free and informed consent terms, ensuring the voluntary nature of the participation, as well as the confidentiality of the data.

Whole body anthropometric measures

Stature, body mass, and triceps subcutaneous and subscapular fat folds were evaluated by a single experienced anthropometrist, following the procedures described by Lohman et al.[14] Stature was measured using a Harpenden stadiometer (model 98.603, Holtain Ltd, Crosswell, UK) and body mass using a SECA scale (model 770, Hanover, MD, United States). The folds of subcutaneous fat were measured using a Lange Skinfold Caliper adipometer (Beta Technology, Ann Arbor, MI, United States). Technical errors of measurement for height, body mass and folds of subcutaneous fat were 0.27 cm, 0.47 kg, and 0.47-0.72 mm, respectively. Percentage of fat mass was estimated according to the protocol by Slaughter et al.[15] Subsequently, the absolute values for fat and lean mass were determined, in kilograms.

Echocardiographic evaluation

Echocardiogram is a noninvasive imaging test that allows information on cardiac structure and function to be obtained. It is the main source of information about cardiac adaptation in response to intensive training in athletes.[16] To evaluate the cardiac morphology, a GE Vivid 3 echocardiograph was used, with a 1.5-3.6 MHz multifrequency probe (GE Vingmed Ultrasound, Horten, Norway). M-mode images were recorded from a parasternal long-axis view under direct visualization of the respective two-dimensional image. Dimensions and thicknesses were recorded at rest and parameters matching those of other similar studies performed with young athletes and adult athletes were selected.[3,17] All echocardiographic examinations were performed by the same operator according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Echocardiography.[18] The following diameter measure-

ments were obtained: aortic root (AoR), left auricle (LA), left ventricular end-diastolic and end-systolic (LVED and LVES, respectively) diameters, and interventricular septal wall (IVSW) and left ventricular posterior wall (LVPW) thicknesses. Based on the previous dimensions, we calculated LV mass (LVM) using the ASE cube formula modified by Devereux et al.[19] and measures of the predictors (IVSW, LVED and LVPW) expressed in millimeters:

$$LVM\ (g) = 0.8 \times [1.04 \times ((IVSW + LVED + LVPW)3 - LVED3)] + 0.6$$

(Equation 1)

LVM was adjusted for body surface area (BSA, equation 2), allowing the calculation of the LV mass index (g/m^2). Subsequently, left ventricular relative wall thickness (LVRPT) was determined as described by equation 3 to distinguish an LV concentric (≥0.44) or eccentric (<0.44) profile:[1,13]

$$BSA\ (m^2) = 0.007184 \times [body\ mass\ (kg)]^{0.425} \times [height\ (cm)]^{0.725}$$

(Equation 2)

$$LVRTP = [(IVSW + LVPW) / LVED]$$

(Equation 3)

LV systolic function is translated by calculating the LV shortening (LVSF) and ejection fraction (LVEF). The shortening fraction uses the end-diastolic (LVED) and end-systolic (LVES) diameters, while the ejection fraction uses the end-diastolic (LVEDV) and the end-systolic (LVESV) volumes, respectively, according to equations 4 and 5:[18]

$$LVSF = [(LVED - LVES) / LVED] \times 100$$

(Equation 4)

$$LVEF = [(LVEDV - LVESV) / LVEDV] \times 100$$

(Equation 5)

Data quality was assessed by determining the intraobserver variability using a random subgroup of 20 individuals (basketball players, n=5; hockey players, n=5; non-athletes, n=10) who were evaluated and reevaluated after one week by the same investigator, using the same equipment and following the procedures described above. The difference and percentage of difference between the two measurements were determined considering a 95% confidence interval for the dimensions of the cavities and cardiac thicknesses (0.02-0.17 mm, 95CI -1.95–2,28 mm). The parameters resulting from the evaluation of the previous measurements had a percentage of intraobserver variability ranging from 0.3 to 0.8% (95CI -4.1–8.1%).

Statistical analysis

Minimum, maximum, mean and standard deviation values were calculated for all variables. The absolute frequencies of adolescents divided by age group were calculated, considering also their classification by sport modality. We then used variance analysis (ANOVA) to study the age-related variation in body size measurements and parameters resulting from the echocardiographic evaluation, considering the entire sample. Finally, we used ANOVA once again to obtain a new comparison between athletes in different sports modalities, and covariance analysis (ANCOVA) adjusted for the additional effect of age, height and body mass. For the two analyzes of variance, we calculated the magnitude of the correlation effect (ES-r) estimated by the square root of the ratio of the *t* value squared and the difference between *t* value squared and the degrees of freedom. The level of significance was maintained at 5%, as established for social and behavioral sciences. For statistical analysis of the data, we use Statistical Program for Social Sciences – SPSS software, version 19.0 for Windows.

Results

The characteristics of the study's total sample are shown in Table 1. The dispersion measures given by the range of variation are quite high, that is, 52 cm for height and 72.9 kg for body mass. The central tendency values found for the echocardiographic parameters show a slight increase in left ventricular cavity diameter (54.5 mm) for these age groups, suggesting a markedly eccentric profile (LVRPT=0.28).

The age-related variation for the entire sample of athletes is shown in Table 2. Understandably, the groups of athletes aged 15 and 16 years had higher mean values for height (F=5.039; p<0.01; ES-r=0.243) and BSA (F=3.984; p<0.05; ES-r=0.217). Although this trend also occurs in relation to body mass, the values are not statistically significant. Additionally, in relation to the echocardiographic parameters, those in the groups of 15 and 16 year-old athletes, compared to their 14-year-old peers, had higher means in left ventricular end-diastolic (F=4.211; p<0.05; ES-r=0.223) and end-systolic (F=5.215; p<0.01; ES-r=0.247) diameters, as well as IVSW thickness (F=3.197; p<0.05; ES-r=0.195). Also, LA diameter (F=6.881; p<0.01; ES-r=0.281) and LVM (F=4.432; p<0.05; ES-r=0.228) were higher in the 16 year-old group.

Anthropometric characteristics and echocardiographic variables were sensitive to the type of modality practiced. As expected, basketball players were taller (F=23.448; p<0.001; ES-r=0.553), heavier (F=6.702; p<0.001; ES-r=0.334) and had greater BSA (F=11.896; p<0.001; ES-r=0.427) than

TABLE 1 Characteristics of the total study sample (n=164).

Variable	Unit measured	Abbreviation	Amplitude		Mean		Standard deviation
			Minimum	Maximum	Value	(95CI)	
Age	years		13.31	16.66	15.28	(15.19-15.39)	0.76
Height	cm		143.6	195.6	172.7	(172.1-174.7)	8.4
Body mass	kg		38.4	111.3	65.2	(63.7-67.5)	12.6
Body surface	m²	BSA	1.24	2.32	1.77	(1.75-1.81)	0.19
LV end-diastolic diameter	mm	LVED	44.2	65.0	54.9	(54.3-55.6)	4.2
LV end-systolic diameter	mm	LVES	24.9	45.5	34.7	(34.2-35.3)	3.4
Interventricular end-diastolic septal wall thickness	mm	IVSW	5.8	10.6	8.1	(7.9-8.2)	0.8
LV end-diastolic posterior wall thickness	mm	LVPW	5.5	10.0	7.6	(7.5-7.7)	0.8
LV ejection fraction	%	LVEF	42.0	76.0	65.4	(64.7-66.1)	4.5
LV shortening fraction	%	LVSF	29.8	45.3	36.7	(36.2-37.1)	3.1
Aortic root diameter	mm	AoRD	19.6	34.0	27.5	(27.1-27.9)	2.7
LA diameter	mm	LAD	20.0	47.9	36.2	(35.6-36.9)	4.2
LA diameter:aortic root ratio	mm/mm	LAD/AoRD	0.77	2.00	1.33	(1.30-1.35)	0.17
Left ventricular mass	g	LVM	83.1	258.1	157.3	(152.1-162.4)	33.6
Left ventricular mass index	g/m²	LVMI	54.6	136.1	87.9	(85.7-90.2)	14.9
LV relative parietal thickness		LVRPT	0.22	0.36	0.29	(0.28-0.30)	0.03

Note: 95CI: 95% confidence interval; LV: left ventricle; LA: left auricle.

TABLE 2 Descriptive statistics (mean ± standard deviation) and age-related variation for the entire sample of athletes.

	Sub-15 14.0–14.9 (n=41)	Sub-16 15.0–15.9 (n=100)	Sub-17 16.0–16.9 (n=23)	F	p	Magnitude		Comparisons Post hoc*
						ES-r	(qualitative)	
Height (cm)	170.2±9.5	174.0±7.3	176.5±9.2	5.039	0.008	0.243	(small)	S17>S15; S16>S15
Body mass (kg)	62.6±13.5	65.9±11.7	69.9±11.8	2.723	0.069	0.181	(small)	
Body surface area (m²)	1.72±0.22	1.79±0.17	1.85±0.19	3.984	0.020	0.217	(small)	S17>S15
LVED (mm)	53.5±4.4	55.2±3.8	56.5±4.5	4.211	0.016	0.223	(small)	S17>S15; S16>S15
LVES (mm)	33.4±3.7	35.0±3.1	36.0±3.3	5.215	0.006	0.247	(small)	S17>S15; S16>S15
IVSW (mm)	7.8±1.0	8.1±0.8	8.2±0.7	3.197	0.044	0.195	(small)	S17>S15; S16>S15
LVPW (mm)	7.4±1.0	7.6±0.7	7.7±0.8	1.454	0.237	0.133	(small)	
LVEF (%)	66.2±6.1	65.1±4.0	64.9±4.4	0.865	0.423	0.103	(small)	
LVSF (%)	37.5±3.4	36.4±2.9	36.1±3.4	2.171	0.117	0.162	(small)	
AoRD (mm)	26.8±2.7	27.8±2.7	27.8±2.6	2.035	0.134	0.157	(small)	
LAD (mm)	34.6±4.1	36.5±4.1	38.4±4.0	6.881	0.001	0.281	(small)	S17>S16>S15
LAD/AoRD (%)	1.30±0.18	1.32±0.18	1.39±0.15	1.865	0.158	0.150	(small)	
Left ventricular mass (g)	145.9±38.5	158.9±29.8	170.3±33.6	4.432	0.013	0.228	(small)	S17>S16>S15
LVMI (g/m²)	83.8±14.4	88.8±14.8	91.5±13.2	2.544	0.082	0.175	(small)	
LVRPT	0.28±0.03	0.29±0.02	0.28±0.02	0.121	0.886	0.039	(trivial)	

LVED: left ventricular end-diastolic diameter; LVES: left ventricular end-systolic diameter; IVSW: interventricular end-diastolic septal wall thickness; LVPW: left ventricular end-diastolic posterior wall thickness; LVEF: left ventricular ejection fraction; LVSF: left ventricular shortening fraction; AoRD: aortic root diameter; LAD: left auricle's diameter; LAD/AoRD: LA diameter/aortic root ratio; LVMI: left ventricular mass index; LVRPT: left ventricle's relative parietal thickness.

hockey players, judokas and swimmers. The variation associated with sports modality for echocardiographic parameters was only significant for some variables of cardiac morphology. Basketball players, hockey players and swimmers had higher values for IVSW thickness (F=7.287; p<0.001; ES-r=0.347) and LVPW thickness (F=8.038; p<0.001; ES-r=0.362) compared to the judokas. The same happens in the test of comparison of means having as dependent variables the LVM (F=7.015; p<0.001; ES-r=0.341) and left ventricular mass index (F=9.463; p<0.001; ES-r=0.388). Basketball players and hockey players have a larger left atrial cavity, compared to judokas (F=3.865; p=0.011; ES-r=0.316). Finally, the data points to a higher LVRPT in swimmers compared to judokas (F=4.127; p=0.008; ES-r=0.268), being swimmers characterized by a markedly eccentric left ventricular profile (Table 3). Table 3 also shows the results of covariance analysis. Covariates included: chronological age, stature and body mass, allowing to verify that, in general, the differences between the size of the cavities and thickness of the heart tissue structures, as well as composite measures, confirm the main conclusions previously described. In fact, it suggests that the results found are mainly due to chronic adaptations to the effects of training and competition and not so much to the sport selection factor that associates particular morphological archetypes to each of the modalities, particularly, tall adolescents to basketball. The results presented in Table 3, adjusted for mean values of age equal to 15.30 years, height equal to 173.4 cm and body mass equal to 65.6 kg, allow us to conclude that judo athletes have less increase in IVSW (F=7.876; p<0.01; ES-r=0.362) and LVPW (F=9.794; p<0.01; ES-r=0.397) thicknesses. As for the latter variable, after adjustment for age and body size, it is still possible to distinguish swimmers, who present significantly higher values compared to basketball players and hockey players. The smaller dimensional development of a judoka's heart is also noted with respect to the left atrial cavity (F=3.338; p<0.05; ES-r=0.245). Finally, in agreement with the previous points and after controlling a number of additional effects, the comparison between modalities, with respect to the mean values of the left ventricular mass, presents the swimmers positively and the judokas negatively.

Discussion

Recognizing the complexity derived from difficulties in distinguishing the effects of sports training, growth and biological maturation, our study analyzed the effects of age and sports modality on the remodeling process of the heart cavities of young athletes in their late teens. Manolas et al.[20] refer to this age group as the period of greatest increase in cardiac chambers. In our study, the mean LV end-diastolic diameter was 1.7 mm greater in 15-year-old athletes compared to the mean value determined for athletes at an immediately younger age, i.e., 14 years. Likewise, a mean difference of 1.3 mm was found between the 15 and 16 year olds, with the highest values among the older athletes. This direct variation between age and measures of LV end-diastolic diameter coincides with the increase in height and body surface of younger adolescents compared to the older ones.

Recently, a longitudinal study[21] with healthy adolescents aged 11 to 15 years determined that sports participation for 3.1±1.2 hours per week plus one match per week was not associated with increased LV growth, after statistical adjustment for individual differences in growth and biological maturation. However, it has been widely accepted that different modalities of physical training result in diverse patterns of cardiac adaptation in athletes.[17] The association established between anthropometry of the whole body and the generalities of the echocardiographic parameters should also be recognized.[21-23] It is true that higher values for body size translate into higher values for the dimensions of aortic root, left atrium, ventricular cavities and LV wall thickness.[16] Recently, a study with male hockey players aged 14.5 to 16.5 years determined correlations between left ventricular mass and several indicators: 0.36 with chronological age, 0.50 with skeletal age, 0.52 with height, 0.61 with seated height, 0.56 with lean mass.[22]

After organizing the analysis of the means by sports modality, we found that the basketball players were taller, heavier and consequently presented greater body surface compared to their peers in the remaining three sports modalities. In fact, basketball players are recognized and consensually among the groups of athletes with larger body size and are also those with higher values for LA diameter, IVSW and LVPW thickness, LVM and left ventricular mass index.[24] In this particular aspect, the results of our study are similar to those of Madeira et al.,[1] which also included 15-16 year-old participants. Variations of heart dimensions cannot be attributed solely to the adaptive effect to training.

Based on the results of our study, we found that the judokas presented lower values for IVSW and LVPW thickness, left ventricular mass and mass index in comparison with all other athletes, and an LA diameter lower than that presented by basketball and hockey players. Other studies[23] that included athletes from a single age group stated that swimmers have smaller ventricular cavities,

but higher values for IVSW and LVPW thickness compared to young hockey players. Although we have also found a trend towards slightly higher mean values in our study, the differences are not statistically significant.

Swimmers, compared to control groups, often present higher values for cardiac cavity diameters and LV wall thickness.[25] Future studies should have a mixed longitudinal design with samples derived from a single modality or, desirably, sub-samples extracted from more than one modality, associating measures capable of describing the volume and weekly intensity of training and competitions to the longitudinal predictors. Regarding LVRPT, all modalities studied have a markedly eccentric profile, although in the judokas this profile is significantly more pronounced than in swimmers. While some authors mention that the enlargement of the left atrium is also a component of the athlete's heart,[26] we did not find significant changes in the other echocardiographic variables between

TABLE 3 Descriptive statistics (mean ± standard deviation) for the groups of athletes organized by sport modality and ANOVA to test the variation associated to the modality practiced, followed by ANCOVA with adjustment for age (centered in 15.30 years), height (centered in 173.4 cm) and body mass (centered at 65.6 kg).

	Basketball (n=42)	Roller hockey (n=73)	Judo (n=28)	Swimming (n=21)	ANOVA		Magnitude		Comparisons
					F	p	ES-r	(qualitative)	Post hoc*
Age (years)	15.32±0.64	15.29±0.73	15.23±0.49	15.35±0.43	0.147	0.931	0.053	(trivial)	
Height (cm)	181.1±7.8	169.9±6.9	171.4±7.4	172.8±5.0	23.448	<0.01	0.553	(wide)	B>H; B>J; B>N
Body mass (kg)	72.4±11.0	63.9±11.3	63.6±16.2	60.7±6.0	6.702	<0.01	0.334	(moderate)	B>H; B>J; B>N
BSA (m²)	1.92±0.17	1.74±0.17	1.74±0.23	1.72±0.09	11.896	<0.01	0.427		B>H; B>J; B>N
LVED (mm)	56.0±3.9	55.0±4.6	53.3±3.5	55.1±3.3	2.561	0.057	0.214	(small)	
LVES (mm)	35.1±3.3	35.1±3.6	33.4±3.2	34.7±2.6	1.825	0.145	0.182	(small)	
IVSW (mm)	8.2±0.8	8.1±0.8	7.5±0.7	8.4±0.8	7.287	<0.01	0.347	(moderate)	B>J; H>J; N>J
LVPW (mm)	7.8±0.9	7.6±0.7	7.0±0.6	8.0±0.8	8.038	<0.01	0.362	(moderate)	B>J; H>J; N>J
LVEF (%)	66.9±4.6	64.5±4.3	64.9±6.0	66.0±3.2	2.710	0.057	0.220	(small)	
LVSF (%)	37.2±3.5	36.3±3.1	36.7±3.2	37.0±2.4	0.831	0.479	0.124	(small)	
AoRD (mm)	28.2±2.7	27.5±2.6	26.4±2.2	27.8±3.2	2.596	<0.05	0.215	(small)	
LAD (mm)	37.3±4.4	36.7±4.5	34.1±3.6	35.6±2.8	3.865	<0.01	0.260	(small)	B>J; H>J
LAD/AoRD	1.33±0.18	1.34±0.19	1.30±0.14	1.30±0.19	0.723	0.540	0.116	(small)	
LVM (g)	167.5±35.4	157.5±32.5	134.3±23.7	166.6±29.8	7.015	<0.01	0.341	(moderate)	B>J; H>J; N>J
LVMI (g/m²)	86.8±13.7	90.2±14.7	77.1±8.6	96.5±14.9	9.463	<0.01	0.388	(moderate)	B>J; H>J; N>J
LVRPT	0.29±0.03	0.29±0.02	0.27±0.03	0.30±0.03	4.127	<0.01	0.268	(small)	N>J
	Adjusted means (controlled for age, height and body mass)				ANCOVA		Magnitude		Comparisons
					F	p	ES-r	(qualitative)	Post hoc*
LVED (mm)	54.5	55.4	53.8	56.0	2.733	0.046	0.223	(small)	
LVES (mm)	33.9	35.4	33.8	35.4	3.803	<0.01	0.260	(small)	H>J
IVSW (mm)	8.1	8.1	7.5	8.5	7.876	<0.01	0.362	(moderate)	B>J; H>J; N>J
LVPW (mm)	7.5	7.7	7.1	8.1	9.794	<0.01	0.397	(moderate)	N>B; H>J; N>H; N>J
LVEF (%)	67.6	64.2	64.6	65.8	3.635	<0.01	0.255	(small)	B>H
LVSF (%)	37.5	36.2	36.5	36.8	1.239	0.298	0.152	(small)	
AoRD (mm)	27.2	27.9	26.7	28.0	2.135	0.098	0.198	(small)	
LAD (mm)	36.9	36.6	34.4	36.4	3.338	<0.05	0.245	(small)	B>J; H>J
LAD/AoRD	1.36	1.32	1.29	1.32	0.777	0.509	0.121	(small)	
LVM (g)	154.5	161.1	138.5	174.5	10.576	<0.01	0.410	(moderate)	N>B; H>J; N>J
LVMI (g/m²)	86.0	90.1	77.7	98.0	10.855	<0.01	0.414	(moderate)	N>B; H>J; N>J
LVRPT	.29	.29	.27	.30	4.013	<0.01	0.267	(small)	N>J

Note: Only comparisons with statistically significant differences are identified.
BSA: body surface area; LVED: left ventricular end-diastolic diameter; LVES: left ventricular end-systolic diameter; IVSW: interventricular end-diastolic septal wall thickness; LVPW: left ventricular end-diastolic posterior wall thickness; LVEF: left ventricular ejection fraction; LVSF: left ventricular shortening fraction; AoRD: aortic root diameter; LAD: left auricle's diameter; LAD/AoRD: LA diameter/aortic root ratio; LVM: left ventricular mass; LVMI: left ventricular mass index; LVRPT: left ventricle's relative parietal thickness.

the groups, so it is possible that there are more differences between athletes and non-athletes than between athletes of different modalities.

The study of systolic function, performed by calculating the shortening and ejection fractions of the left ventricle, confirms the results reported in the literature,[27] that is, no significant differences were found between groups. This fact demonstrates that the increase of the cavities and the thickness of the walls of the LV represents for the athletes an increase in cardiac performance, without any impairment at functional level, like other (pathological) situations that can progress to increased cardiac dimensions. In this case, the increase in dimensions is due to the sports training and is performed in a harmonic way, in accordance with the proportion with the body weight.[28]

Limitations

Four sporting modalities have been taken into account, making it difficult to obtain statistically significant results with so many groups. Therefore, it is possible that the choice of only two clearly contrasting modalities would result in greater association. Magnetic resonance imaging is the most appropriate method to determine LVM, although echocardiographic examination is still the most used methodology, particularly in the context of clinical practice and, especially, in the child and adolescent population. Future studies should consider female athletes and other age groups coinciding with periods of greater sporting specialization, i.e., 17-19 years. Variability of measures resulting from echocardiographic examination with measures of body composition should also be considered.

Conclusion

Briefly, modalities such as basketball and roller hockey tend to attract, respectively, tall and short adolescents, due to different aspects of performance structure, namely airspace dispute in basketball and skills related to fast movements with the ball next to the ground in roller hockey. It seems that differences in cardiac morphology between athletes of different modalities should also be understood in the light of adapting to the chronic effects of exertion. This is supported by the analyzes in our study, both in relation to the treatment of absolute values and the control of additional effects related to age, stature and body mass. The differences found between judokas and swimmers corroborate the effect of the sports modalities on the process of cardiac remodeling. While the judokas practice an acyclic modality, with great peripheral resistance and less development of ventricular mass, cavities and walls of the ventricle, swimmers are exposed to cyclical movements facilitating the ejection fraction and cardiovascular return. Swimmers training and competition loads are also characterized by less intermittent heart rate regimens, which contributes to the existence of higher mean values both for cardiac mass and cavities, and thickness of the walls limiting them.

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Indicadores de remodelagem cardíaca em atletas adolescentes

Objetivo: Os efeitos decorrentes da prática de diferentes modalidades desportivas resultam em padrões divergentes de adaptação cardíaca. A presente pesquisa procura estudar a variação da morfologia do coração associada a um conjunto de modalidades desportivas distintas quanto à natureza do esforço e aos modelos de preparação, incluindo metodologias de treino e sistemas de competição.
Método: Foram estudados 42 basquetebolistas, 73 hoquistas, 28 judocas e 21 nadadores. A antropometria foi avaliada por um único e experiente antropometrista e os exames ecocardiográficos foram realizados pelo mesmo operador. Recorreu-se à análise da variância para estudar a variação associada a idade, medidas de tamanho corporal e parâmetros ecocardiográficos, bem como para a comparação entre os atletas de diferentes modalidades desportivas.
Resultados: Os basquetebolistas são os atletas mais altos (F=23,448; p<0,001; ES-r=0,553), mais pesados (F=6,702;

p<0,001; ES-r=0,334), com maior superfície corporal (F=11,896; p<0,001; ES-r=0,427) e, com os hoquistas, apresentam um diâmetro da aurícula esquerda superior ao dos judocas (F=3,865; p=0,011; ES-r=0,316). A espessura telediastólica do septo interventricular (F=7,287; p<0,001; ES-r=0,347) e da parede posterior do ventrículo esquerdo (F=8,038; p<0,001; ES-r=0,362) dos judocas é inferior à dos outros atletas, mesmo quando controlado para o tamanho corporal. Os nadadores apresentam uma espessura parietal relativa do ventrículo esquerdo superior à dos judocas (F=4,127; p=0,008; ES-r=0,268).

Conclusão: As diferentes fontes de variação da morfologia cardíaca prendem-se com as dinâmicas do processo de treino, competição e correspondentemente com os mecanismos adaptativos, sobrepondo-se ao processo de formação desportiva a longo prazo.

Palavras-chave: modalidades desportivas, jovens atletas, ecocardiografia, massa do ventrículo esquerdo, tamanho corporal, crescimento.

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Effect of rhubarb on extravascular lung water in patients with acute respiratory distress syndrome

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Summary

Objective: The aim of this study was to evaluate the effect of rhubarb on extravascular lung water (EVLW) in patients with acute respiratory distress syndrome (ARDS).

Method: A total of 80 patients with ARDS were randomly divided into a treatment group (40 cases) and control group (40 cases). Patients in the treatment group received rhubarb (30.0 g/d) and patients in the control group received conventional therapy for seven consecutive days. Extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI) were determined using pulse contour cardiac output (PiCCO) technology, and the oxygenation index was measured by blood gas analysis at baseline and on days 3, 5 and 7 after treatment.

Results: The oxygenation index was higher and the levels of EVLWI and PVPI were lower after treatment in the two groups; however, these indexes showed significant differences on the 5th and 7th days after rhubarb treatment compared with the results in the control group ($p<0.05$).

Conclusion: Rhubarb can decrease EVLWI and PVPI, and improve oxygenation in patients with ARDS.

Keywords: rhubarb, ARDS, EVLWI, oxygenation index.

Introduction

The mortality rate in acute respiratory distress syndrome (ARDS) is as high as 40%,[1] and is a major cause of death in intensive care unit (ICU) patients.[2] Therefore, research on the pathogenesis of ARDS and the development of effective new drugs for the treatment of ARDS are very important. Although the causes of ARDS are complex, the basic mechanism in the development of ARDS involves the alveolar capillary epithelium (ACM) and alveolar epithelial injury caused by abnormal inflammatory responses.[3,4] In the treatment of the primary disease, almost all measures used to inhibit the inflammatory response, including the use of cytokine monoclonal antibodies and free radical scavenging agents, failed in clinical trials.[5,6] Few effective drugs have been found to improve alveolar capillary permeability, reduce extravascular lung water (EVLW), and improve oxygenation.[7-9] Studies using traditional Chinese medicine and traditional Chinese and Western Integrative Medicine have explored methods for the effective treatment of ARDS.[10,11] The effect of rhubarb on EVLW in patients with ARDS has not been reported (Zhejiang Science and Technology Information Research Institute. Science and Technology Novelty Search Report, No. 201533B2108291), but the study provided a theoretical basis for the clinical use of rhubarb in the treatment of ARDS. Moreover, the pulse contour cardiac output (PiCCO) technology used in the project to monitor hemodynamics was mature, low-risk and less expensive.[12] Timely monitoring of EVLW dynamics can quantitatively reflect ACM injury and pulmonary edema, and was helpful in the observation and assessment of ARDS; EVLW monitoring is easily implemented in clinical settings.[12]

Our randomized controlled study examined the effect of rhubarb on EVLW and the oxygenation index at dif-

ferent time points in patients with ARDS. Effective means of treating ARDS using Chinese medicine were explored, with the expectation of further improvement in the success rate through the application of Chinese and Western Integrative Medicine.

Method

Selection of cases

Eighty patients with ARDS who met the inclusion criteria in our department from January 2012 to June 2014 were randomly divided into a treatment group (rhubarb + conventional treatment, 40 cases) and a control group (conventional treatment, 40 cases); there were 47 males and 33 females aged 22-79 years, with mean age of 58.4 years. Of these, six had severe pancreatitis, 15 had pulmonary infections, 13 had abdominal infections, ten had multiple injuries, and 36 had sepsis. Our study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Yiwu Central Hospital. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

Inclusion criteria were based on the 2011 Berlin consensus definition of ARDS:[13,14] 1) a, time: according to onset after the cause is identified, or with emerging/existing respiratory symptom aggravation within a week; b, image changes: lung transmittance reduced, not completely explained by pleural effusion, atelectasis or lung nodules; c, causes of pulmonary edema: cannot be interpreted as heart failure or fluid overload; d, oxygenation: mild, 200 mmHg < oxygenation index ≤ 300 mmHg when PEEP (positive end-expiratory pressure)/CPAP (continuous positive airway pressure) ≥ 5 cmH_2O; moderate, 100 mmHg < oxygenation index ≤ 200 mmHg when PEEP/CPAP ≥ 5 cmH_2O; severe, oxygenation index ≤ 100 mmHg when PEEP/CPAP ≥ 5 cmH_2O; 2) endotracheal intubation and mechanical ventilation more than 24 h; 3) intra-abdominal pressure < 20 mmHg. Exclusion criteria: 1) patients with advanced cancer; 2) preexisting chronic diseases in the heart, lung, liver, kidney or other organs; 3) blood diseases; 4) immunosuppressed patients.

Design and treatment programs

Within 24 hours after being admitted, the treatment group received 10.0 g of cooling rhubarb leachate extracted with 30 mL of boiling water via nasogastric tube instillation at appropriate temperature, plus conventional treatment, three times a day for seven days. The control group received conventional treatment. Conventional treatments included endotracheal intubation, mechanical ventilation, fluid therapy, anti-infective therapy and nutritional support.

Clinical indicators

The selected patients underwent placement of a pulse contour cardiac output (PiCCO) catheter (PV2014L16; PULSION, Germany) through the femoral artery for continuous monitoring. Thermal dilution methods were used to determine extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI) changes in patients at baseline and on days 3, 5 and 7 after treatment. A blood gas analyzer (GEM Premier3000) was used to detect arterial oxygen changes, and the oxygenation indexes of the two groups were compared.

Statistical analysis

SPSS 18.0 software package was used for statistical analysis of the data. Measurement data were expressed as mean ± standard deviation ($\bar{\chi}\pm s$); comparisons between measurement data for the two groups were performed using a t-test. Numerical data were compared using the χ^2 test. The differences between groups were compared using analysis of variance (ANOVA), and further pairwise comparisons were performed using the least significant difference test. $p<0.05$ indicated that the difference was statistically significant.

Results

General clinical data and causes of disease

The differences in age, sex, weight, height, acute physiology and chronic health evaluation (APACHE) II score, and PEEP between the rhubarb treatment group and control group were not statistically significant ($p>0.05$; Table 1).

Changes in EVLW and vascular permeability before and after treatment

EVLWI and PVPI in the two groups showed no significant difference before treatment ($F=0.36, 0.42, p>0.05$). Three, five and seven days after treatment, EVLWI and PVPI in both groups declined to various degrees ($F=0.63, 0.56$; $p<0.05$); the differences on further pairwise comparisons were statistically significant ($p<0.05$). The EVLWI and PVPI of patients in the treatment group were significantly lower than those of the control group on the 5th ($F=0.70, 0.42, p<0.05$) and 7th days ($F=0.84, 0.35, p<0.05$) after treatment (Table 2, Figure 1, Figure 2).

Changes in oxygenation before and after treatment

The oxygenation index in both groups showed no significant difference before treatment ($F=0.35$, $p>0.05$).

Three, five and seven days after treatment, the oxygenation index of the patients in both groups increased to various degrees ($F=1.09$, $p<0.05$), the differences on further pair-wise comparison were statistically significant ($p<0.05$). The oxygenation index of patients in the treatment group on the 5th day ($F=0.39$, $p<0.05$) and 7th day ($F=1.08$, $p<0.05$) after treatment was significantly higher than that of the control group (Table 2, Figure 3).

Discussion

ARDS is a complex disorder. First proposed in 1967, the mortality rate has been as high as 75%. In the past 40 years,

TABLE 1 Comparison of patient data between the treatment and control groups.

Group	Cases (n)	Sex (male/female)	Age (years old)	Weight (kg)	Height (cm)	PEEP (cmH_2O)	APACHE II score (points)	Oxygenation index
Treatment group	40	25/15	(59±12)	65±7	168±10	9.8±2.5	19.5±2.5	115±26
Control group	40	22/18	(57±10)	68±6	170±10	10.5±2.4	19.8±2.3	110±27
χ^2 value		0.22	0.18	0.11	0.82	1.58	0.64	0.06
p-value		0.45	0.67	0.74	0.417	0.21	0.43	0.81

Note: APACHE (acute physiology and chronic health evaluation) II score.

TABLE 2 Changes in EVLW/vascular permeability and oxygenation index of patients before and after treatment between the two groups ($\bar{\chi}$±s).

Index	Group	Cases (n)	Baseline (pre-treatment)	Day 3 after treatment	Day 5 after treatment	Day 7 after treatment
EVLWI (mL/kg)	Treatment group	40	12.4±4.1	9.5±3.8	6.3±2.6[a,b]	4.7±2.2[a,b]
	Control group	40	11.7±4.8	9.3±4.1	8.4±2.7[a]	7.1±1.9[a]
PVPI	Treatment group	40	6.0±0.8	4.6±1.4	2.8±0.9[a,b]	1.7±0.8[a,b]
	Control group	40	5.0±0.9	4.7±1.2	3.8±0.8[a]	2.7±0.7[a]
Oxygenation index (mmHg)	Treatment group	40	115±24	128±31[a]	186±32[a,b]	294±51[a,b]
	Control group	40	113±25	125±32[a]	167±27[a]	212±50[a]

EVLWI: extra vascular lung water index; PVPI: pulmonary vascular permeability index.
Compared with baseline (pre-treatment), [a]$p<0.05$; compared with the control group, [b]$p<0.05$.

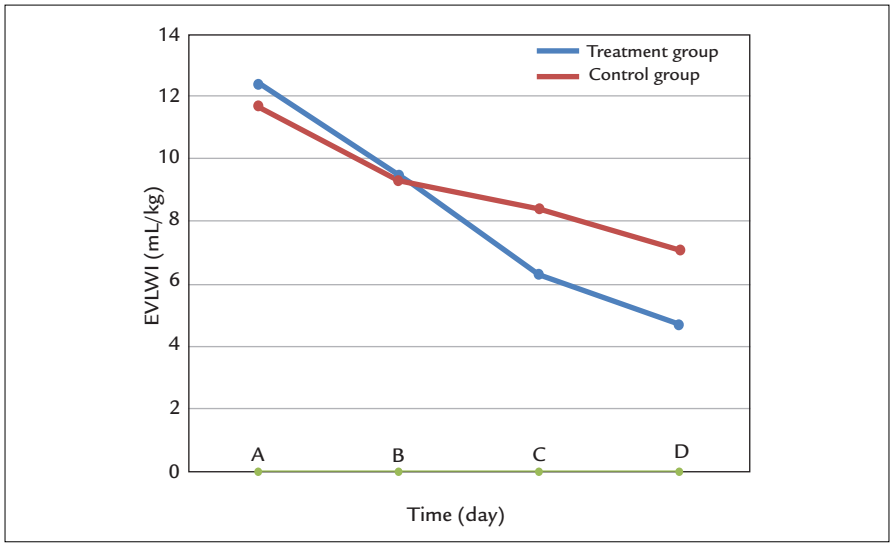

FIGURE 1 Changes in EVLWI (mL/kg) in patients before and after treatment between the two groups. A. Before treatment; B. Three days after treatment; C. Five days after treatment; D. Seven days after treatment.

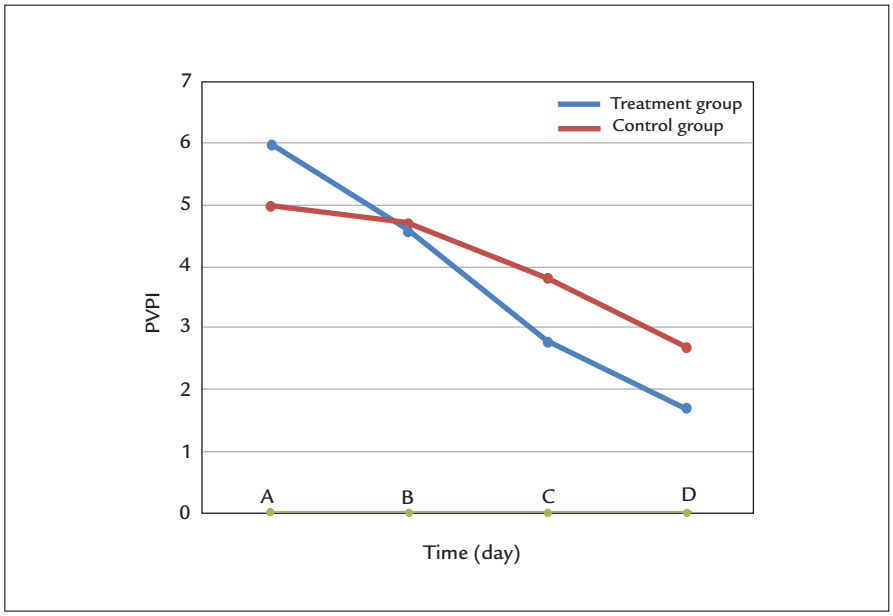

FIGURE 2 Changes in vascular permeability in patients before and after treatment between the two groups. A. Before treatment; B. Three days after treatment; C. Five days after treatment; D. Seven days after treatment.

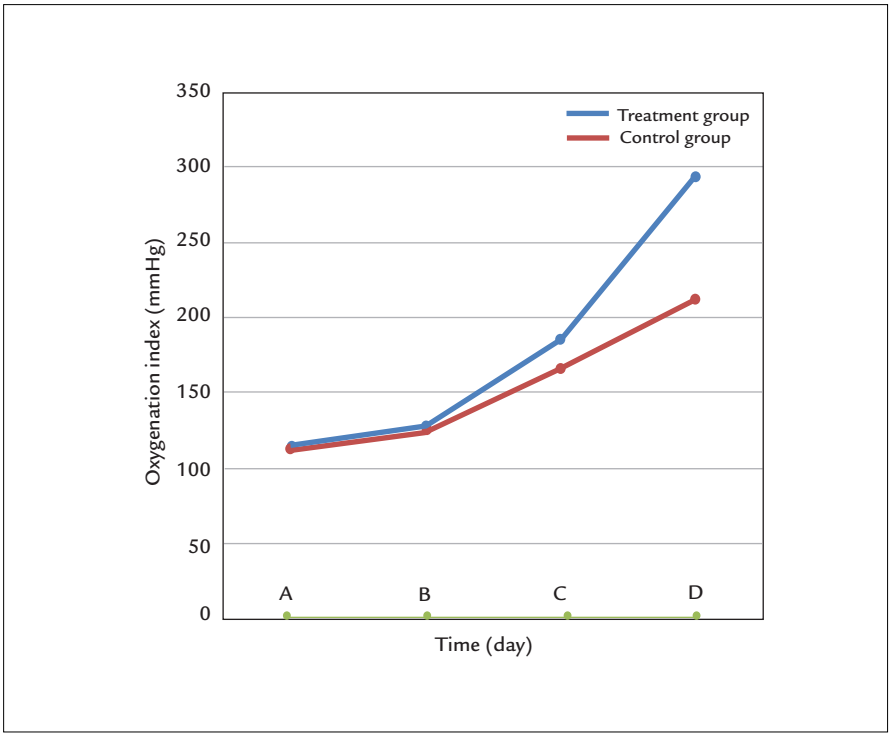

FIGURE 3 Changes in oxygenation index in patients before and after treatment between the two groups. A. Before treatment; B. Three days after treatment; C. Five days after treatment; D. Seven days after treatment.

through persistent efforts, the mortality rate of ARDS in the United States and Europe decreased to 25-40%. However, the prognosis of ARDS in China did not seem to improve to the same degree. An epidemiological survey of Beijing and Shanghai showed that the mortality rate of ARDS was as high as 50.0 and 68.7%, respectively.[1,4,5] Therefore, we must objectively evaluate treatment strategies for ARDS, and explore new methods of treatment.

High permeability pulmonary edema is induced by ACM injury and increased vascular permeability; the pathological basis is excessive systemic inflammatory response that induces pulmonary capillary permeability, interstitial pulmonary edema and alveolar ventilation/perfusion imbalance, leading to hypoxemia (mainly pulmonary diffusion dysfunction). In severe sepsis or early trauma, monocyte-macrophage system effector cells (especially macrophages) are activated. Many pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, histamine and leukotrienes are released and are involved in the inflammatory reactions of ARDS; of these, TNF-α is a key part of the cytokine network and an initiating factor of inflammation, as well as one of the main molecules causing damage to pulmonary vascular endothelial cells. Studies have shown that serum TNF-α and IL-1β in patients with ARDS are significantly increased; IL-1β and IL-6 in bronchoalveolar lavage fluid are also significantly high. The IL-1β and IL-6 concentration in bronchial lavage fluid was closely related to the severity and prognosis of ARDS.[15,16]

EVLW comprises intracellular fluid, alveolar fluid, and interstitial lung fluid. Due to less significant intracellular fluid changes, intra-alveolar and interstitial lung fluids reflect the severity of pulmonary edema. An increase in EVLW is one of the important characteristics in the pathophysiology of ARDS, and an important cause of refractory hypoxemia. Timely EVLW measurement can properly reflect ACM injury and the degree of pulmonary edema, and aids in the assessment of ARDS. Due to access limitations and potential trauma, lung biopsy is not feasible for routine clinical use. Thus, EVLW is more sensitive for the identification of ARDS pulmonary edema, and has good predictive value for treatment and prognosis.[12-15]

The main components in rhubarb include emodin, rhein, aloe vera and tannins. Rhubarb has purgative activity, and is said to "remove heat and toxic materials, cool the blood and alleviate congestion." The "Compendium of Materia Medica" indicated that rhubarb "alleviated congestion, cold and heat, breaking accumulation, flow draining abiding food, cleaning up the gastrointestinal, smoothing and helpful in water and italica digestion, neutralizing and digesting food, tuning five internal organs." Research has confirmed that rhubarb, similarly to calcium channel blockers, has a protective effect by preventing calcium overload in cells; however, calcium transmembrane flow and changes in cytosolic calcium are essential for the synthesis and release of inflammatory mediators. Rhubarb can protect cell structures, maintain close connections between cells and prevent the activation of polymorphonuclear neutrophils and macrophages, thus preventing the release of large amounts of proinflammatory mediators, thereby decreasing ACM damage, and reducing EVLW, improving pulmonary edema and pulmonary compliance, and improving oxygenation.[17-21]

Our study further showed that after treatment of ARDS with rhubarb for 5 to 7 days, the EVLW was significantly reduced, the PVPI decreased and oxygenation was also improved. In short, rhubarb can reduce EVLW in patients with ARDS to some extent, and improve oxygenation without obvious toxic side effects.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Hyperglycemia in critical patients: Determinants of insulin dose choice

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Summary

Objective: To identify factors that can determine the choice of intermittent subcutaneous regular insulin dose in critically ill patients with hyperglycemia.
Method: Cross-sectional study in a general adult ICU with 26 beds, data collected between September and October 2014. The variables analyzed were: sex, age, previous diagnosis of diabetes mellitus, use of corticosteroids, use of lactulose, sepsis, fasting, enteral nutrition, use of dextrose 5% in water, NPH insulin prescription and blood glucose level. Patients with one or more episodes of hyperglycemia (blood glucose greater than 180 mg/dL) were included as a convenience sample, not consecutively. Those with continuous insulin prescription were excluded from analysis.
Results: We included 64 records of hyperglycemia observed in 22 patients who had at least one episode of hyperglycemia. The median administered subcutaneous regular human insulin was 6 IU and among the factors evaluated only blood glucose levels were associated with the choice of insulin dose administered.
Conclusion: Clinical characteristics such as diet, medications and diagnosis of diabetes mellitus are clearly ignored in the decision-making regarding insulin dose to be administered for glucose control in critically ill patients with hyperglycemia.

Keywords: blood glucose, insulin, intensive care units, hyperglycemia, diabetes mellitus, hypoglycemia.

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Introduction

Stress-induced hyperglycemia is elevated blood glucose in the presence of acute illnesses and is frequently observed in patients admitted to an intensive care unit (ICU), with or without a diagnosis of diabetes mellitus (DM).[1] A recent study demonstrates that stress hyperglycemia during ICU stay is associated with increased risk for the development of diabetes.[2] This phenomenon primarily involves the neuro-immune-endocrine response to stress, with increased secretion of cortisol, glucagon and adrenaline, and decreased secretion and action of insulin. Other factors may also be related to high blood glucose, such as exogenous glucose administration, enteral or parenteral nutrition, prolonged bed rest and use of drugs.[3]

Glycemic control in the ICU setting began to be important as of 2001, after the publication of a study by Van den Berghe et al.,[4] which demonstrated a 42% reduction in mortality and a 46% reduction in episodes of bloodstream infection in ICU surgical patients when normoglycemia (80-110 mg/dL) was achieved.[4] After these initial data, several prospective randomized studies have demonstrated that intensive glycemic control has suggested declines in mortality, multiple organ failure, systemic infections, hospital and ICU stay, and consequent reduction in total hospital costs.[4-7] Currently, preventing high blood glucose is a recommended and desirable intervention. However, the optimal range of glycemic control is controversial.[4] References to hypoglycemia in the literature include values between 40 and 80 mg/dL,[8-12] while the range of hyperglycemia is that of 180 to 200 mg/dL.[8-12]

The Brazilian Society of Diabetes (SBD) and the guidelines of the American Diabetes Association/American Association of Clinical Endocrinologists (ADA/AACE) recommend, for patients hospitalized in ICU, target blood glucose

ranges between 140-180 mg/dL and initiation of insulin therapy when blood glucose values are persistently greater than 180 mg/dL.[8,13] A US study analyzed blood glucose tests performed at the bedside in ICU and non-ICU wards of 126 hospitals in different regions of the country and showed a prevalence of hyperglycemia (> 180 mg/dL) of 46% in ICU and 31.7% outside the ICU. The prevalence of hypoglycemia (< 70 mg/dL), in turn, was 10.1% in ICU and 3.5% in non-ICU[14] settings. Other authors, in a similar study conducted in 635 hospitals, found a prevalence of hyperglycemia of 32.3% and 28.2% in non-ICU and ICU patients, respectively, whereas the prevalence of hypoglycemia was 6.1 and 5.6% in non-ICU and ICU patients, respectively.[15]

Insulin used to control hyperglycemia is categorized by the Institute for Safe Practice in the Use of Medications as a potentially dangerous drug,[16,17] that is, with increased risk of causing significant damage to patients as a result of failure to use.[18] Therefore, considering the negative clinical outcomes associated with the lack of glycemic control in critically ill patients, the implantation of glycemic control protocols in ICUs is a routine that could contribute to the increased safety of these patients.[19]

Our objective was to identify the determinants of the choice of intermittent subcutaneous insulin dose used to control hyperglycemia in critical hyperglycemic patients.

Method

Study design and population

A cross-sectional study was performed in the adult clinical and surgical ICU of a large hospital in the southern region of Brazil. This unit has 26 beds and serves patients of the public Unified Health System (SUS, in the Portuguese acronym), as well as those covered by health insurance and private patients.

The study sample consisted of patients admitted to the ICU from September to October 2014, who were not receiving continuous intravenous insulin. Patients hospitalized for less than 24 hours or without glycemic monitoring were excluded from the study.

Variables

The following variables were analyzed: age, sex, diagnosis of previous DM, presence or absence of sepsis, results of the capillary blood glucose test, insulin administration, number of episodes of hyperglycemia (blood glucose above 180 mg/dL) and amounts of International Units (IU) of regular insulin administered.

In addition, data were collected on the type of diet the patient was receiving during this period (enteral, parenteral nutrition or fasting), administration of fast insulin (regular) or intermediate-acting insulin (NPH), corticosteroids, 5% dextrose in water (D5W) or lactulose, and also the number of days of hospitalization.

The data were collected from the electronic medical chart and the vital signs sheet of each patient and refer to the 24-hour glucose monitoring of patients on a normal routine day. Patients were included for convenience and their data collected only once during the study.

Outcome

The dose of regular subcutaneous insulin to be used in episodes of hyperglycemia was indicated by the medical team on the patient's updated patient chart and administered by the nurses as prescribed.

Statistics

Quantitative variables were described as mean and standard deviation. Qualitative variables were described in the form of absolute numbers and percentages. As multiple episodes of hyperglycemia per patient were evaluated, the independence between the episodes can not be assumed. To address this limitation, we chose negative binomial regression as a valid tool for determining the association between the clinical factors of the patient and the choice of intermittent subcutaneous regular insulin dose in a sample of clustered data.[20]

Ethical aspects

We did not need to request informed consent from the patients in our study, since the data collected were tertiary and available in their medical charts. The project was approved by the Institution's Ethics Committee under the number: 737.699 on August 4, 2014.

Results

After excluding patients who were receiving continuous insulin, according to institutional protocol, 64 episodes of hyperglycemia were found in 22 patients. Among patients with episodes of hyperglycemia, we observed a mean age of 65.7 years, a higher frequency of male patients (68.2%), previous diagnosis of DM (70.3%), absence of sepsis (71.9%), treatment with D5W (54.6%), corticosteroids (43.7%), lactulose (4.6%) and enteral diet (84.4%), hospitalization time in days of 15.7 + 8.9, mean blood glucose levels at 256 + 69 mg/dL, and regular insulin dose per episode of hyperglycemia of 4.8 + 3.0 IU.

The median dose of regular subcutaneous insulin given in cases of hyperglycemia was 6 IU, and this value did not change on account of the presence of clinical factors such as age over 65 years, sex, previous diagnosis of

DM, use of corticosteroids, use of lactulose, presence of sepsis and use of NPH insulin, as shown in Figure 1.

Figure 2 showed a linear relationship between capillary blood glucose and regular insulin dose, indicating that at each 80 mg/dL increase in capillary blood glucose, there was an increase of 2 IU in the median dose of regular insulin administered.

In the univariate and multivariate analyzes, capillary blood glucose was the only factor significantly associated with the dose of regular insulin used, as shown in Table 1.

Discussion

Our study demonstrated that the only parameter valued in the choice of insulin dose to treat hyperglycemia in critical patients is the level of blood glucose. Thus, clinical characteristics of patients such as diet, drugs being used, presence or absence of sepsis or DM seem not to affect decision-making.

In the national and international literature, blood glucose level is seen as a determinant factor to choose the dose of regular subcutaneous insulin as recommended in protocols.[21] Although glycemic levels are important in normalizing blood glucose, critical patients have other important clinical features that influence glycemic control. Administration of vasopressors, corticosteroids, enteral or parenteral nutrition – as well as the discontinuation of these therapies due to a variety of procedures performed in critical patients – leads to significant daily variability in glycemic levels.[22]

Despite the benefits of adequate glycemic control in critically ill patients,[7,23-25] retrospective studies have shown an association between increased glycemic variability and increased mortality.[22,26] There is a thin threshold between protective care and a potentially harmful approach to the patient, significantly elevating the risk of severe hypoglycemia.[27] Five episodes of hypoglycemia were observed in the study population. Glycemic control should be done, avoiding the negative outcomes of hyperglycemia (> 180 mg/dL). However, it is imperative to define the safest strategy to offer this care to patients, so as to protect their health, without adding a potential risk. A study by Robba and Bilotta[28] confirms that continuous monitoring of blood glucose can contribute to minimize the risks associated with hyperglycemia, and immediate and effective management of blood glucose is necessary from the first hours of admission to the ICU. In addition, the need for a different, more individualized, glycemic control strategy targeting specific subgroups should be investigated.[27] Thorough glycemic control according to institutional protocols of continuous insulin is a practice adopted

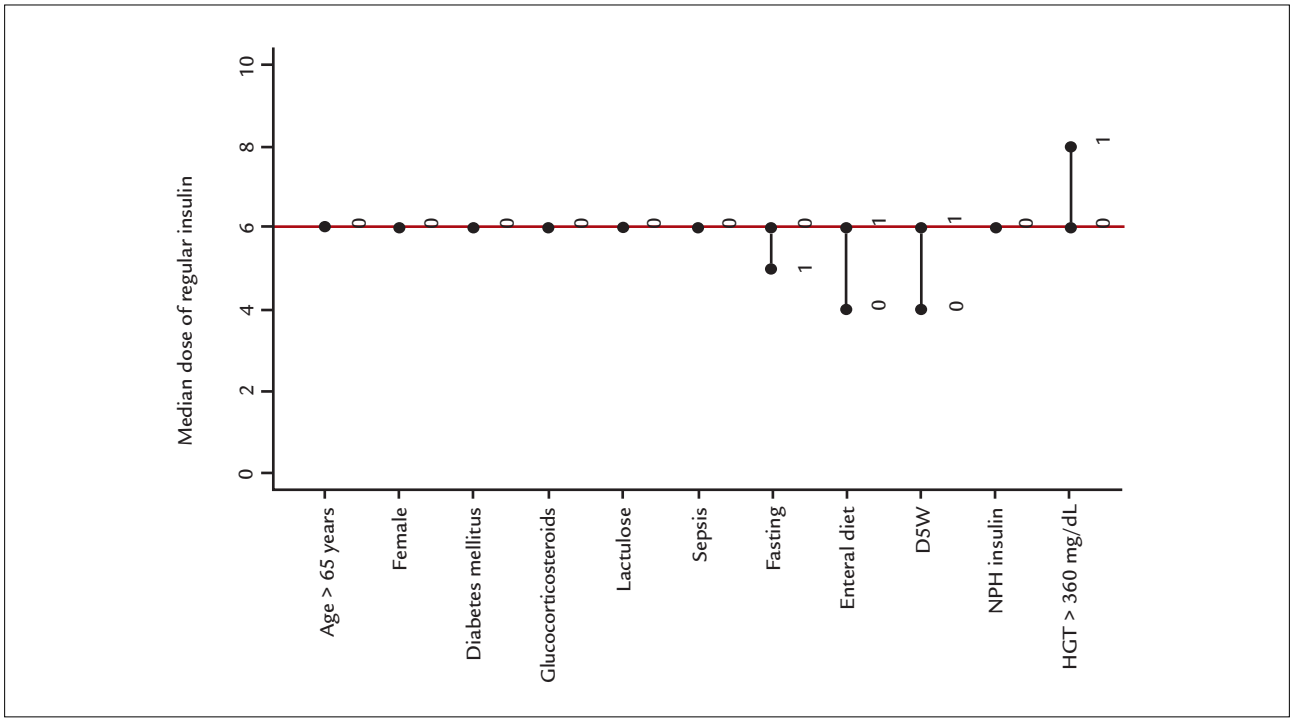

FIGURE 1 Median dose of regular insulin applied according to clinical situation.

Note: The horizontal centerline represents the median of the regular insulin dose of all episodes evaluated in the study. For each variable, 1 and 0 represent, respectively, the median of the dose of regular insulin applied in patients with and without the clinical characteristic indicated in the corresponding line.

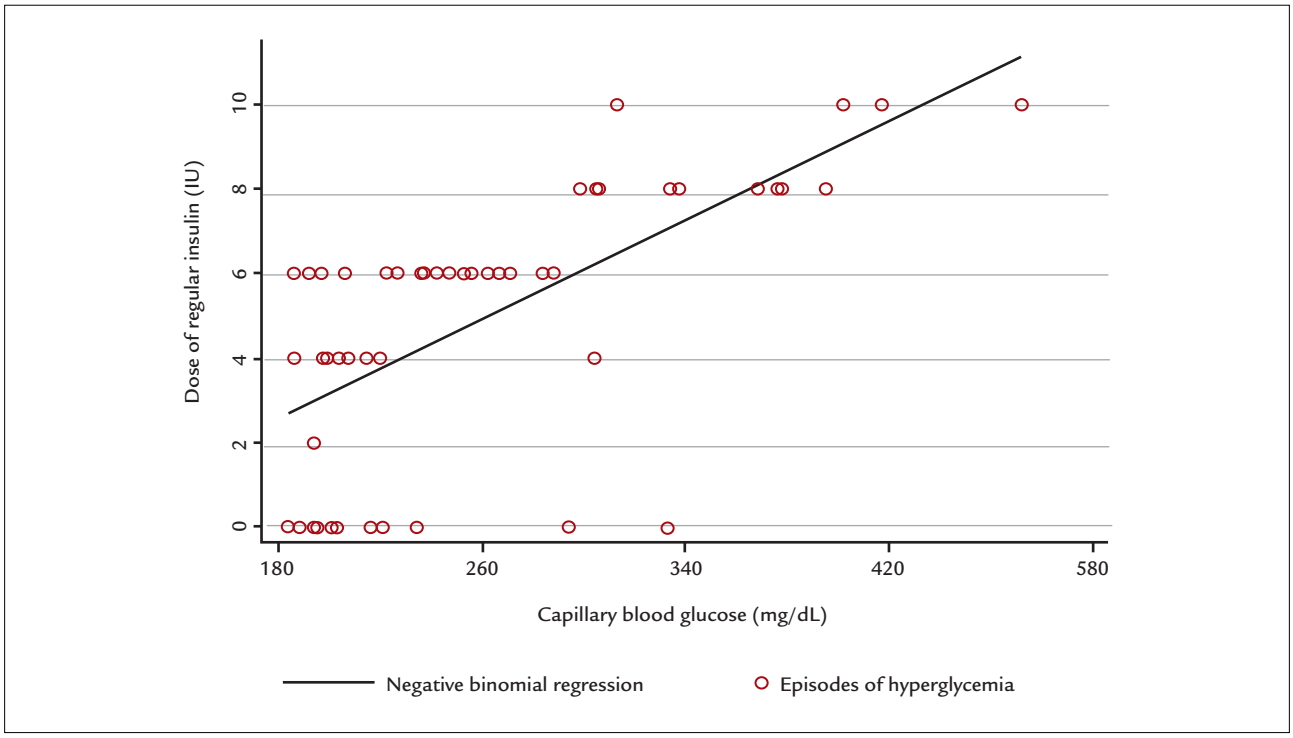

FIGURE 2 Multiple binomial regression of the dose of regular insulin given according to the capillary glycemia of the patient.

TABLE 1 Multiple binomial regression of factors associated with subcutaneously administered regular insulin dose in hyperglycemic patients who were not on continuous insulin (n=64 episodes).

Variables	Univariate Analysis		Multivariate Analysis	
	PR (95CI)	p-value	PR (95CI)	p-value
Female	1.03 (0.68-1.56)	0.9	...	...
Age per year	1.0009 (0.98-1.01)	0.87	...	...
Diabetes mellitus	1.0004 (0.65-1.53)	0.99	...	...
Corticosteroids	0.95 (0.64-1.41)	0.81	...	...
Lactulose	1.10 (0.44-2.73)	0.82	...	...
Sepsis	1.21 (0.79-1.85)	0.36	...	...
Fasting	0.84 (0.49-1.45)	0.54	...	...
Enteral diet	1.32 (0.8-2.24)	0.29	...	...
Dextrose 5% in water	1.34 (0.92-1.97)	0.12	...	...
NPH insulin	1.18 (0.76-1.84)	0.44	...	...
Capillary blood glucose	1.005 (1.003-1.007)	<0.001	1.005 (1.003-1.007)	<0.001

Note: Entry criterion for multivariate analysis: p<0.30 in the univariate analysis.
PR: prevalence ratio.

worldwide and recommended in important Guidelines.[4,29-31] However, data from more heterogeneous populations (clinical and clinical-surgical ICUs) did not show the same optimism regarding the application of this therapy for all patients.[32,33] Also, it is agreed that the need for rigorous glycemic control based on continuous insulin protocols is a marker of severity and worse prognosis in patients admitted to the ICU.[34]

The implementation of protocols for the monitoring of blood glucose in critically ill patients as well as for the establishment of intermittent administration of regular insulin to normalize blood glucose seems to be an important safety measure. The literature is filled with evidence-based guidelines and protocols designed to standardize care processes, reducing healthcare costs and improving outcomes,[35] with the expectation that patients receive better quality in care with a minimum of medical errors.[36] Theoretically, in every specialty, protocols can integrate up-to-date scientific evidence for patient management more efficiently in order to improve health outcomes and reduce inadequate care. Despite the benefits of using protocols, there is still a lack of adherence to them, which is explained by excessive hours of work among health care providers, differences in the interpretation of clinical trials and evidences, or simply hesitation in changing the practices.[35,37] Creating protocols, policies and educational programs for effective management of hyperglycemia in critically ill patients seems to be indispensable. On the other hand, considering the diverse and adverse characteristics of critical patients, these protocols need to be customized for groups with similar clinical characteristics. Since the presence of hyperglycemia in critically ill patients has a different impact on the different etiological groups, a distinct evaluation is necessary depending on the pathology and profile of the patients.[38]

Due to its cross-sectional design, our study has limitations to investigate a cause-effect relationship, and it is possible to present only associations in this outline. In addition, our study was conducted in a single center. Nevertheless, it was performed in a general ICU, covering different types of patients with multiple comorbidities, not restricted to a single specialty. In this ICU, there is no established protocol for administration of subcutaneous insulin, which was valid for the observation of different medical conducts.

Conclusion

We found that clinical characteristics of patients such as type of diet, pharmacotherapy, presence of sepsis, and previous diagnosis of DM are not taken into account to decide the dosage of insulin for glycemic control in critically ill patients.

Resumo

Pacientes críticos com hiperglicemia: determinantes da escolha da dose de insulina

Objetivo: Identificar os fatores associados à escolha da dose de insulina regular subcutânea intermitente em pacientes críticos com hiperglicemia.
Método: Estudo transversal em uma UTI geral adulta com 26 leitos. Pacientes com um ou mais episódios de hiperglicemia (glicemia capilar superior a 180 mg/dL) foram incluídos por conveniência, de forma não consecutiva. Aqueles com prescrição de insulina contínua foram excluídos da análise. As variáveis analisadas foram: sexo, idade, diagnóstico prévio de diabetes melito, uso de corticosteroide, uso de lactulose, presença de sepse, jejum, dieta enteral, uso de soro glicosado contínuo, prescrição de insulina NPH e valor da glicemia capilar.
Resultados: Foram incluídos 64 registros de hiperglicemia verificados em 22 pacientes que apresentaram pelo menos um episódio de hiperglicemia. O valor mediano administrado de insulina regular humana subcutânea foi de 6,0 UI e, entre os fatores analisados, o único associado à dose de insulina administrada visando à normalização dos níveis glicêmicos foi o valor da glicemia capilar.
Conclusão: Evidencia-se a inobservância de características clínicas dos pacientes, como dieta, uso de medicamentos e diagnóstico prévio de diabetes melito, para a tomada de decisão quanto à dose de insulina a ser administrada visando ao controle glicêmico em pacientes críticos com hiperglicemia.

Palavras-chave: glicemia, insulina, unidades de terapia intensiva, hiperglicemia, diabetes melito, hipoglicemia.

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Compulsory notification at skilled nursing facilities

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Summary

Introduction: Notifiable diseases (NDs) encompass conditions of high clinical severity and/or contagious. Being closed communities, long-term care facilities (LTCF) are places that deserve attention on their own, but one might be left wondering: what is the reality of NDs at Brazilian LTCFs?
Objective: To determine the prevalence and type of NDs at large LTCF.
Method: Active search for NDs conducted by the Hospital Infection Control Committee (HICC) in 459 beds. Due to the low turnover of patients, the monthly list kept by the HICC on NDs was analyzed. Data were grouped into males and females, and into elderly (age ≥ 60 years) and non-elderly (age ≤ 59 years).
Results: 31 diseases in 29 patients (6.9% of all inpatients – 19 males and 10 females): 23 cases of hepatitis C, five of hepatitis B, two of human immunodeficiency virus (HIV), and one case of renal tuberculosis. One patient with hepatitis B and another HIV-positive also had hepatitis C. There was no statistical significance in the comparison of the two groups with the total number of other institutionalized patients – by age and gender – for total number of NDs and cases of hepatitis C ($p>0.05$).
Conclusion: Chronic NDs and those requiring chronic treatment observed in this study suggest that Brazil needs more studies to define the dynamics of these diseases at LTCFs.

Keywords: disease notification, hepatitis, HIV, homes for the aged, tuberculosis, renal.

Introduction

Notifiable diseases (NDs) are those included in the National Notifiable Diseases Surveillance List.[1] They basically include infectious diseases with high degree of clinical severity and/or highly contagious. Aspects such as the short incubation period and the capacity for wide dissemination among the exposed population define the obligation of prompt notification. A significant number of NDs require in-hospital care at some point in their clinical course, and in these cases, the Hospital Infection Control Committee (HICC) has the power to act in places without a properly structured epidemiological surveillance service.

As people are aging fast, long-term care facilities (LTCF) for the elderly should be considered another healthcare center to be approached for NDs. LTCFs are centers with characteristics of their own, regulated by specific legislation and supervised by government agencies such as those linked to sanitary surveillance.[2]

There are, however, problems regarding the present situation of LTCFs in Brazil.

There are high rates of bed occupancy paid for by the Brazilian Unified Health System (SUS, in the Portuguese acronym) and/or belonging to philanthropic entities, resulting in long waiting lists and occasional admission criteria that exclude syndromes that are highly prevalent among the elderly, such as urinary incontinence and dementia. These circumstances, the lack of places and professionals prepared to care for this special segment of the elderly, favor the creation of high-cost institutions, a possibility not accessible to most families, or clandestine facilities, where the risk of acts that harm the elderly is greater than in authorized LTCFs. This results in basic care schemes without adequate treatment for infectious-parasitic diseases in closed communities, such as LTCFs.

What would be the status of NDs in long-term care facilities (LTCF) for the elderly? Faced with this question,

we investigated the pattern observed in a large nursing home in the city of São Paulo.

Objective

To determine the prevalence and type of ND at the Dom Pedro II Geriatric and Convalescence Hospital (HGCDPII) of Irmandade da Santa Casa de Misericórdia de São Paulo, comparing the information found with those reported in the Brazilian medical literature.

Method

The HGCDPII is a large LTCF that had 459 active beds in September 2008. It has a HICC since 01/18/2002 that, among its activities and according to the health surveillance legislation,[3,4] actively investigates NDs.

Considering that the main characteristic of the institution evaluated is that of being a long-stay facility, that is, with low patient turnover, we opted for the analysis of the HICC on NDs based on the list issued monthly – in this case, September 2008, regardless of sex and age.

As a comparative criterion, two groups were created: group A for non-elderly institutionalized (age ≤ 59 years) and group B for elderly institutionalized (age ≥ 60 years) individuals. Statistical analysis used χ^2, dividing the sample between women and men, and ages below or equal to 59 years or above or equal to 60 years, with α at 5.0%.

Our study is part of Project no. 413/08 approved by the Research Ethics Committee of Irmandade da Santa Casa de Misericórdia de São Paulo.

Results

The 421 patients (237 men and 184 women) hospitalized at the HGCDPII in September 2008 had a mean age of 66.2 ± 14.9 years (ranging from 28 to 107 years), of whom 137 were non-elderly (mean age of 49.5 ± 7.8 years) and 284 were elderly (mean age 74.3 ± 10.0 years) individuals.

Group A (non-elderly) was composed of 100 men with a mean age of 49.0 ± 8.8 years (28 to 59 years) and 37 women with a mean age of 50.9 ± 6.3 years (33 to 58 years), while group B (elderly) included 137 men with a mean age of 70.4 ± 8.8 years (60 to 101 years) and 147 women with a mean age of 77.9 ± 9.6 years (60 to 107 years).

The list of NDs for that month cited 31 diseases in 29 patients (6.9% of the total number of hospitalized patients), 19 men and 10 women ($p>0.05$ compared to the total number of institutionalized patients). These NDs, shown in Table 1, consisted of 23 hepatitis C reports in patients with a mean age of 60.7 ± 12.6 years (34 to 82 years), five cases of hepatitis B in patients aged 58.0 ± 7.3 years (50 to 66 years), two cases of serological positivity to human immunodeficiency virus (HIV) in patients aged 55 and 66 years, and one case of renal tuberculosis (65 years old). A patient with hepatitis B (66 years old) and another positive for HIV (55 years old) also had hepatitis C. There was no statistical significance when comparing the two groups with the total number of other hospitalized patients – for age and gender – by total number of NDs and cases of hepatitis C ($p>0.05$).

Discussion

Since LTCFs are closed communities, they have significant potential for spread of infectious parasitic diseases such as febrile diarrhea, scabies, influenza, tuberculosis, hepatitis B and C,[5] which in some cases are included in the National Notifiable Diseases Surveillance List.[1] Their typical population[6] – elderly with a high degree of physical and/or mental dependence – presents a set of factors that contribute to the development, exacerbation or chronification

TABLE 1 Notifiable diseases divided by gender and age among individuals admitted to long-term care facility for seniors.

Notifiable diseases (ND)*	Total of NDs	Group A Non-elderly Age (mean): 49.5 ± 7.8 years		Group B Elderly Age (mean): 74.3 ± 10.0 years	
		Men	Women	Men	Women
Hepatitis C	23	05	04	10	04
Hepatitis B	05	02	01	01**	01
HIV-positive	02	01**	–	01	–
Renal tuberculosis	01	–	–	01	–
Total of NDs	31	08	05	13	05
Total number of individuals with NDs	29*	12 (7 M and 5 F)		17 (12 M and 5 F)	
Total number of institutionalized individuals	421	137 (100 M and 37 F)		284 (137 M and 147 F)	

*31 notifiable diseases in 29 patients, out of a total of 421 institutionalized individuals. **Also with hepatitis C.
ND: notifiable disease; HIV: human immunodeficiency virus; M: male; F: female.

of these diseases[5,7,8] such as compromised host defense mechanisms, decreased physiological reserve capacity, chronic, disabling and degenerative diseases, high exposure to infectious agents, and atypical clinical manifestations that delay definitive diagnosis and subsequent treatment.

It is estimated that the incidence of NDs in the Brazilian population is approximately 0.5% (833,123 cases in 2004 for every 179,113,540 inhabitants).[9,10] However, we found few data on NDs in Brazilian LTCFs in the literature consulted. A search conducted on 11/15/2008 at the SciELO portal http://www.scielo.br/ using the keywords "elderly" and "institutions" obtained 41 references, of which only three reviews referred partially to infections[11,12] or tuberculosis in nursing homes.[13] Authors who admittedly study infections in LTCFs in Brazil also focused their publications on bacterial infections,[14] anti-pneumococcal vaccine and immunity[15] or tuberculosis.[16] Using the keywords "diseases," "notification" and "compulsory" in the same portal and date, we found nine references in which there are no citations about LTCFs. Observations on the elderly and/or age groups were observed in four of them (two on AIDS,[17,18] one on dengue fever[19] and another on tetanus[20]).

Continuing the search for ND data in Brazilian LTCFs, we searched the same portal for publications on the four diseases observed in our sample.

The search for "hepatitis C," "elderly" and "institutions" did not match any articles. We did not find publications with the combined keywords "hepatitis C" and "institutions," either. A third search with the keywords "hepatitis C" and "prevalence" found 19 published studies with observations about unawareness of its actual prevalence-incidence, although with apparent predominance in young adults,[21] and prevalence among health professionals of 1.7% with a 50% higher risk of contamination every five years of hospital service[21] – a factor that should also be considered in LTCFs, in view of daily care with tubes, catheters and pressure ulcers, and related procedures such as laboratory tests and administration of blood products. Other publications in this research reported a prevalence of 0.3% among blood donors (mostly men aged between 26 and 45 years)[22] – less than the one verified among non-elderly institutionalized patients (6.7% of the total), possibly due to the characteristics of the two samples (healthy adults in the first and hospitalized chronic patients in the second) and prevalence of 1.5% or seven cases in a representative sample – 457 inhabitants – of the adult population of a city, two of them (28.6% of the total number of cases) aged over 60 years[23] – a prevalence close to that found in our study (1.3% of the total number of institutionalized individuals) with the difference of greater percentage of cases among the elderly (60.9% of the total) justified by the higher average age of the sample analyzed. There was also a reference to the association of hepatitis C and type II diabetes mellitus[24] – a chronic degenerative disease common in the third age and that triggers complications such as strokes and lower limb amputations, thus having potential for physical disabilities and the need for hospitalization of these individuals in LTCFs.

An equal search pattern on the same portal with the keywords "hepatitis B," "elderly" and "institutions" did not find any publication, either. The combination of the "hepatitis B" and "institutions" keywords yielded only one article on seroprevalence in patients with mental illness[25] reporting results of virus prevalence in all age groups (without presenting specific details to each one) and prevalence (1.6%) close to that observed in our sample – 5 cases from 421 hospitalized patients or 1.8% of the total. Using as keywords "hepatitis B" and "prevalence," 33 articles were located, of which only one[26] would discriminate age groups with anti-HBC seroprevalence of 33.7% an age of 60 years or older.

The diagnosis of acquired immunodeficiency syndrome (AIDS) in patients over 50 years of age is not easy in clinical practice. This is due to low prevalence, although with a progressive tendency to increase in this age group, atypical symptoms, rapid progression, high mortality rate in general hospitals, and the fact that elderly patients are often not questioned about risk factors.[17,18,27-30] Nevertheless, the percentage of HIV seropositivity in our sample (approximately 0.5% of inpatients) was close to that estimated for the Brazilian population between 15 and 49 years old (0.6%).[18,31] The literature consulted, however, did not present data on hospitalizations in Brazilian LTCFs.

The search on the http://www.scielo.br/ portal using as keywords "AIDS," "elderly" and "institutions" found no articles, while the combined search for "AIDS" and "institutions" yielded 16 publications, without references to LTCFs and/or age groups in them. The keywords "AIDS" and "elders" yielded nine articles with no mention of prevalence or LTCFs. Using as keywords "AIDS" and "prevalence," we found a list with 92 citations, some presenting references, at the extremes of age in the sample, to patients aged 60 years or older,[17,18,30,32-37] with no additional information in the text. The prevalence of men with HIV was also observed in these publications,[17,18,29-37] regardless of age range, which is in accordance with the two cases found in our sample. These articles presented cases without mention of the place of residence – community or LTCF.

With similar contamination pathways, the simultaneous finding of HIV and hepatitis C in one of the institutionalized patients can be justified by the 4.5% prevalence of this combination in individuals aged from 51 to 60 years, and 1.2% prevalence between 60 and 70 years.[38]

The relation between aging and tuberculosis also involves atypical symptoms associated with a higher percentage of adverse reactions, significant complications and high mortality.[13,16,39-41] LTCFs are considered important sites for disease spread and/or recurrence, since these are closed communities with a pattern of caring for elderly patients with a high degree of physical and/or mental dependence.[13,16] But again, there are few occurrences in the literature consulted that offer details on tuberculosis and LTCFs in Brazil. The same portal of previous searches using the combination "tuberculosis," "elderly" and "institutions" yielded a single review,[13] which has already been cited. The cross-over of the keywords "tuberculosis" and "institutions" yielded 10 references, basically studies in hospitals and institutions for specific treatment of the disease, also with two reviews on scientific production related to tuberculosis[42,43] – without LTCFs being cited. Likewise, the keywords "tuberculosis" and "elderly" yielded only six articles, four linked to the elderly in the community[39-41,44] and two reviews,[13,16] already mentioned above and which cited LTCFs solely due to the risk of local spread. Most references – 70 publications – were found with the keywords "tuberculosis" and "prevalence," but mostly related to children, young adults, students and health professionals, indigenous peoples and diagnostic methodologies. The main focus of these publications was to analyze the pulmonary form of tuberculosis, with a significant number of studies on the relation between HIV and tuberculosis and on multiresistant microbacteria. Articles with data that allow comparison with our study comment that mortality due to the pulmonary form, regardless of age, is 8.5 times greater than the extrapulmonary form (possible justification of the extrapulmonary location in the only case of this series), with a risk of death 2.3 times higher in the elderly than in young adults (a possible cause of the low percentage of cases found – 0.2% of the total number of institutionalized patients) and a prevalence of 11.2% in patients aged 60 years or older, with a tendency to fall (another plausible explanation for the low prevalence in our study).[45-47] Considering the parallelism between LTCFs and psychiatric hospitals – in the common feature regarding hospitalization for long periods – there is only one publication[48] on pulmonary tuberculosis in 6.8% of hospitalized psychiatric patients, predominantly between 39 and 53 years of age, a fact not observed in our sample.

Conclusion

As most NDs present high clinical severity and/or are highly contagious, a significant number of cases are resolved at sites prior to LTCF. Finding in our study chronic NDs and/or NDs requiring chronic and sometimes expensive treatment, is therefore justified. Considering the rapid aging of the Brazilian population, which will increase the demand for beds in LTCFs, more attention and publications on NDs in LTCFs will be necessary.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Notificação compulsória em instituição asilar

Introdução: Doenças de notificação compulsória (DNC) abrangem quadros de alta gravidade clínica e/ou de contágio. Sendo comunidades fechadas, instituições de longa permanência para idosos (ILPI) são locais que merecem atenção quanto a elas. Mas qual seria a realidade das DNC em ILPI brasileiras?
Objetivo: Determinar prevalência e tipo de DNC em ILPI de grande porte.
Método: Busca ativa de DNC pela Comissão de Controle de Infecção Hospitalar (CCIH) em 459 leitos. Em razão da baixa rotatividade de pacientes, analisou-se lista mensal da CCIH sobre DNC. Dividiram-se os dados entre homens e mulheres e entre idosos (idade ≥ 60 anos) e não idosos (idade ≤ 59 anos).
Resultados: 31 doenças em 29 pacientes (6,9% do total de internados – 19 homens e 10 mulheres): 23 casos de hepatite C, cinco de hepatite B, dois de positividade sorológica ao vírus da imunodeficiência humana (HIV) e um caso de tuberculose renal. Um paciente com hepatite B e outro com HIV positivo eram também portadores de hepatite C. Não houve significância estatística quando foram comparados os dois grupos com o total dos outros internados – por idade e gênero – pelo total de DNC e nos casos de hepatite C (p>0,05).
Conclusão: Pesquisa em 15/11/2008 no portal http://www.scielo.br/não detectou casuísticas em ILPI, exceto por revisões sobre tuberculose. DNC de caráter e/ou tratamento crônico observadas neste estudo sugerem a necessidade de maior número de publicações para definir a dinâmica dessas doenças em ILPI brasileiras.

Palavras-chave: hepatite, HIV, instituição de longa permanência para idosos, notificação de doenças, tuberculose renal.

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Alcohol and tobacco use and the diseases treated in general practice

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Summary

Objective: To characterize the use of alcohol and tobacco and correlate both to the diseases of outpatients in a general practice outpatient clinic.
Method: The ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) questionnaire was answered by 300 randomly chosen subjects assigned to different groups according to the diseases being treated at the Outpatient General and Teaching Clinic of the Department of Internal Medicine, Hospital das Clínicas of the University of São Paulo's School of Medicine (HC-FMUSP, in the Portuguese acronym), São Paulo, Brazil. The consumption of tobacco and alcohol was characterized and its correlation with the groups of diseases being treated was calculated using Chi-square and Pearson test statistics.
Results: Compared to alcohol, tobacco use was more prevalent, more intense and showed more health-, social-, legal- and financial-related damage. Tobacco smoking presented a positive significant ($p<0.0001$) correlation with respiratory diseases. According to the questionnaire's criteria, few alcohol users would be referred to clinical interventions in comparison to smokers.
Conclusion: Respiratory diseases and tobacco use were well correlated based on the ASSIST questionnaire. The preventive value of the questionnaire was more evident in relation to tobacco than alcohol consumption.

Keywords: alcohol abuse, tobacco use, screening, diagnosis.

Introduction

Diagnosing and treating alcohol, tobacco and other drug addictions early is critical to the prognosis of these disorders for patients and the society. It is estimated that about 20% of patients treated in the primary care network consume alcoholic beverages at levels that may endanger their health or be associated with diseases, signs or symptoms that lead them to seek treatment.[1]

Usually, the first contact of these patients with the health system occurs through general practitioners or family and community physicians, at the primary care level. However, studies have shown that these physicians do not diagnose or treat the harmful use of dependence-causing substances with the same frequency and precision that they would treat other chronic diseases.[2] Regarding alcohol consumption and smoking, the most relevant dependence-causing substances in general clinical practice, the focus of medical professionals is on the diseases caused by such abuse, which manifest later (liver and pancreatic diseases, as well as nervous, respiratory, cardiac diseases, etc.), and not on the underlying dependence or abuse, by itself.[2]

It is well known that substance users do not become dependent overnight. The average period between the first consequence due to alcohol use and the first intervention for this problem is around five years, and any delay in initiating treatment, as well as any inadequate treatment, worsens the prognosis. As for tobacco, the latency period between the beginning of consumption and the first symptoms takes decades, as do the first initiatives to interrupt use.[2]

The World Health Organization (WHO) Expert Committee on Problems Related to Alcohol Consumption concluded that the first step to be taken to better address the problem is to screen or track abusive or problematic substance use.[3,4] For this, it is necessary to use instruments with the function of pointing out, from a population sample or selected groups, people who consume these substances more intensely, with signs of abuse or complications resulting from these habits, and indicating intervention strategies. In the case of tobacco, the WHO

Framework Convention on Tobacco Control recommends a wide range of measures of a political, economic, institutional and medical nature, in order to face the health complications related to smoking.[5]

In addition to other instruments (CAGE,[6] AUDIT,[7] the Fagerström test[8]), the ASSIST (Alcohol, Smoking and Substance Involvement Screening Test)[9] is a questionnaire advocated by the WHO to simultaneously monitor the consumption of alcohol, tobacco, other drugs (marijuana, cocaine, crack, amphetamines, inhalants, opiates) and non-prescription addictive psychoactive drugs. It is an instrument of good sensitivity and good predictive value to detect the use and some consequences of these substances, already validated in Brazil.[10]

Its application in a general practice service, which serves patients whose complexity of clinical settings mixes the need for primary and secondary care, can be useful for the improvement of the services provided in the treatment of chronic diseases and for the establishment of prevention strategies[11] aimed at the cessation, reduction or safe consumption of substances that are available to general practitioners and in accordance with national public policies.

The primary goal of our study was to screen and stratify, based on the ASSIST questionnaire, alcohol and tobacco consumption and some of their consequences among people seeking medical care in an outpatient clinic of a university hospital. Our secondary goal was to attempt to correlate such consumption with the diseases informed in the patients' electronic medical charts.

Method

The study was conducted at the facilities of the Outpatient General and Teaching Clinic (AGD), Internal Medicine Service, Department of Internal Medicine, Hospital das Clínicas of the University of São Paulo Medical School (HC-FMUSP, in the Portuguese acronym).

The AGD is sought by patients treated within the Brazilian public Unified Health System (SUS, in the Portuguese acronym) for internal medicine consultations, with diseases that fit into all clinical specialties. The internship in this service serves as training for fifth year students and resident physicians, in the first year of specialization in internal medicine at FMUSP. This is a short-term outpatient clinic (the average length of stay is six months), which, before patients are referred to other services, has the following main purposes: to diagnose and start treatment of clinical diseases at any level of complexity, to adjust the treatment of patients with multiple chronic diseases already known, and to promote screening, counseling and chemoprophylaxis for risk factors of diseases with high morbidity and mortality.

From February 1 to November 30, 2015, 300 patients, about 1% of all patients treated in the AGD during that period, were randomly approached by the researchers while waiting for their consultation in the waiting room of the outpatient clinic. Each patient was informed by then about the characteristics of the research and those who agreed to participate signed a Free and Informed Consent Form (FICF) approved by the Research Ethics Committee of HC-FMUSP, according to Resolution No. 196/96 (Opinion No. 858.978/14). Then, in the office, they answered questions from the ASSIST questionnaire, always asked by the researchers themselves.

The ASSIST questionnaire provides information on: a) use of alcohol, tobacco and other substances throughout life and in the past three months; b) signs of dependence, problems (health, social, legal or financial) and impairment of activities of daily living related to recent use (last three months); c) impact of consumption among relatives; d) old and recent cessation attempts. In addition, based on the progressive sum of scores attributed to each given response, the ASSIST questionnaire "suggests" the type of intervention required for each patient, that is: none, brief or advanced.[9,10]

The completed questionnaires were identified by the registration number of each patient in the service, so that the authorized researchers could have access to the demographic data and the diseases treated constantly in their electronic medical records. The diseases indicated in the medical records of the study participants were grouped according to their clinical nature as: cardiovascular, respiratory, liver and pancreatic, metabolic, autoimmune, psychiatric, oncological and miscellaneous. The same patient could fit into more than one group of diseases.

The collected data were stored and processed in spreadsheets using Statistical Package for the Social Sciences (SPSS) software version 11.0. All variables studied were categorized and described as absolute numbers and/or percentages and, whenever necessary, allowed the investigation of correlations based on Chi-square method, using Pearson's test to quantify differences between groups. A level of $p<0.05$ was used to define the significance of the correlations evaluated.

Results

Of the 300 participants, 118 (39.3%) were men between 16 and 92 years of age, with mean age (standard deviation) of 57.7 (15.2) years, while 182 (60.7%) were women aged 14 to 85 years, with a mean age of 54.8 (14.9) years. There was no statistically significant difference between groups.

Table 1 shows the distribution in absolute numbers of patients with the diseases reported in electronic medical charts, divided by sex and age group. This information was obtained for only 247 of the 300 participants. Statistically significant differences were observed with predominance of psychiatric (e.g., depression and anxiety) and autoimmune diseases (e.g., rheumatoid arthritis and lupus erythematosus) in women, and a higher prevalence of cardiovascular diseases (e.g., hypertension, coronary artery disease) and metabolic diseases (e.g., diabetes, dyslipidemia) in the elderly.

Alcohol and tobacco use in the study group, identified based on the answers given to the seven questions in the ASSIST questionnaire, is described in Table 2, as well as the total score range reached and the respective intervention suggestions, calculated according to the questionnaire-embedded criteria.

Overall, although less often tried compared with alcohol throughout life, there was a more prevalent and more intense consumption of tobacco and indications that it causes more craving and complications (health, social, legal or financial) for the patient, more concern for family and close friends, and more unsuccessful cessation attempts than alcohol in this AGD group.

Statistical tests to identify correlations between alcohol consumption, as reported in the ASSIST questionnaire, with demographic variables and the groups of diseases being treated in the AGD only indicated that men consume almost three times more alcoholic beverages than women (p=0.0001). No other significant correlation was found with the other variables.

Regarding tobacco consumption, no difference was detected in relation to sex, but a positive and significant correlation was observed between the sum of scores on the ASSIST questionnaire and reference to respiratory diseases in the medical charts (p=0.0001). All persons with scores in the range that would justify advanced smoking cessation intervention (sum of scores > 26) were already undergoing treatment for respiratory disease or attempted cessation in the AGD.

No significant correlation was found between the simultaneous consumption of alcohol and tobacco with any of the groups of diseases being treated.

Discussion

Consumption of alcohol and smoking are common habits in our culture. As they are associated with several diseases of high morbidity and early mortality,[12-14] drinking and smoking are of particular interest to physicians, especially those who work in primary and secondary health care. Identifying individuals who present dependence, abuse or problems arising from these substances can allow more effective actions both at therapeutic and preventive level, although there are still few well organized initiatives in this regard.[15]

For instance, the WHO Expert Committee on Problems Related to Alcohol Consumption found that in most countries the number of people seeking or needing treatment is heterogeneous in relation to the severity of alcohol dependence and the physical and mental illnesses they present.[3] The same committee concluded that evaluation and brief intervention in the context of primary health services prove effective in reducing heavy or more advanced alcohol-related problems in a variety of different sociocultural situations, but concluded that more research on the implementation of continuous strategies to address the issue in different health systems is required.[16]

As for tobacco, supported by laws that totally restrict smoking within public places[17] and national and interna-

TABLE 1 Absolute number (N) of patients with diseases included in the respective morbidity groups, as informed in the electronic medical charts of the Outpatient General and Teaching Clinic of the Internal Medicine Service at HC-FMUSP, properly discriminated and compared by gender and age group (N=247).

	CVD	RES	L&P	MET (N)	AIM	PSY	ONC	MIS
Sex					*	*		
M	62	16	9	48	2	8	3	66
F	93	19	8	78	14	35	5	112
Age range	*			*				
≤ 30 years	2	2	0	3	2	2	0	10
31 to 60 years	70	14	10	62	9	25	3	88
> 60 years	83	19	7	61	5	16	5	80

CVD: cardiovascular disease; RES: respiratory disease; L&P: liver and pancreatic disease; MET: metabolic disease; AIM: autoimmune disease; PSY: psychiatric disease; ONC: oncological disease; MIS: miscellaneous.
* Statistically significant difference of the frequency of diseases of the respective group between the sexes or between the age groups (p<0.05), detected using Chi-square method and Pearson's test.

TABLE 2 Alcohol and tobacco consumption identified in the ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) questionnaire for the patients attended at the Outpatient General and Teaching Clinic of the Internal Medicine Service at HC-FMUSP (N=300).

	Alcohol	Tobacco
	n (%)	n (%)
1. Have you ever used alcohol/tobacco?		
No	41 (13.7)	89 (24.7)
Yes	259 (86.3)	211 (70.3)
2. How often have you used it in the past 3 months?		
Never	182 (71.6)	138 (65.4)
Once or twice	23 (9.0)	2 (0.9)
Monthly	15 (5.9)	3 (1.4)
Weekly	29 (11.4)	4 (1.9)
Daily or almost daily	6 (2.4)	64 (30.3)
In the last three months (questions 3 to 5):		
3. How often you had a strong desire or urge to use?		
Never	238 (95.8%)	144 (68.2)
Once or twice	3 (1.2)	2 (0.9)
Monthly	1 (0.4)	2 (0.9)
Weekly	3 (1.2)	2 (0.9)
Daily or almost daily	4 (1.6)	61 (28.4)
4. How often has drinking/smoking led to health, social, legal, or financial problems?		
Never	247 (99.6)	189 (89.5)
Once or twice	0 (0.0)	4 (1.9)
Monthly	0 (0.0)	1 (0.5)
Weekly	0 (0.0)	2 (0.9)
Daily or almost daily	1 (0.4)	15 (7.1)
5. How often have you failed to do what was normally expected of you because of your drinking/smoking habit?		
Never	244 (98.4)	193 (91.9)
Once or twice	2 (0.8)	7 (3.3.)
Monthly	1 (0.4)	3 (1.4)
Weekly	1 (0.4)	5 (2.4)
Daily or almost daily	0 (0.0)	2 (1.0)
6. Has a friend or relative or anyone else ever expressed concern about your drinking or smoking?		
No	186 (75.6)	84 (40.8)
Yes, but not in the last 3 months	49 (19.9)	71 (34.5)
Yes, in the last 3 months	11 (4.5)	52 (24.8)
7. Have you ever tried to control, cut down or stop using alcohol/tobacco?		
No	223 (91.0)	108 (52.7)
Yes, but not in the last 3 months	17 (6.9)	62 (30.2)
Yes, in the last 3 months	5 (2.0)	35 (17.1)
Suggested intervention according to the ASSIST questionnaire score		
None	293 (97.7)	191 (63.7)
Brief	5 (1.7)	95 (31.6)
Advanced	2 (0.7)	14 (4.7)

tional policies that encourage smoking reduction through collective and individual measures, including facilitating access to treatment drugs, programs in the area of health, organized and coordinated by entities of national and regional weight, such as the Brazilian National Cancer Institute (Inca, in the Portuguese acronym) and state and municipal health departments have multiplied in recent years. The purpose of these programs is to train health professionals, especially those in primary care, to give sufficient and necessary support to smokers who express their desire to stop smoking, regardless of whether or not they have a related disease that is already manifest.[18] It is true that the interest in such actions in the health area varies according to the context and type of medical care offered.

In our study, the WHO ASSIST questionnaire was applied to a group of AGD patients, a general practice outpatient clinic that, although located in a university hospital with characteristics of tertiary care, due to its teaching nature, also treats patients whose disease complexity is variable (primary, secondary or tertiary), including those potentially associated with the consumption of substances that are harmful to health. For the purposes of our study, and based on the demographic profile of the studied population, with an average age above 50 years, only alcohol and tobacco were considered, although the research instrument allows to approach the use of other drugs and psychoactive substances without medical prescription.

The randomly chosen sample represented the public that seeks the AGD, composed preferably by women in the age group between 55 and 60 years. Table 1 indicates the number of patients with diseases belonging to the eight groups in the study, with a clear predominance of cardiovascular and metabolic diseases and a set of other less specific conditions, grouped as miscellaneous. Data analysis showed a statistically significant predominance of autoimmune and psychiatric diseases in women and of cardiovascular and metabolic diseases in older individuals, all known and plausible associations from a clinical-epidemiological point of view.

The analysis of the results obtained from the answers given to the ASSIST questionnaire shows that more individuals have tried alcoholic beverages (86.3%) than tobacco (70.3%) throughout their lives, but among those who continued to use them, in the last three months, smoking was a habit with characteristics of almost daily consumption (30.3%), whereas alcohol was consumed in a more variable way, with only a minority (2.4%) referring daily or almost daily consumption.

Unlike smoking, for which there is no known safe limit of consumption, and whose health complications occur with daily and old habits, in the case of alcoholic beverages, not only there is a risk of diseases resulting from persistent and excessive consumption, but also occasional abuse (which can be detected by the ASSIST) puts the consumer at risk of accidents, violence and infectious and sexually transmitted diseases. This reinforces the importance of detecting cases of excessive consumption, even occasionally, in order to be able to take preventive action. On the other hand, it is worth mentioning that scientific evidence indicates that the consumption of alcoholic beverages, controlled and in small amount daily, can be a protective factor for cardiovascular diseases,[19] indicating that drinking every day is not by itself an indicator of abuse or alcoholism.

In addition to the regularity of consumption, the questionnaire revealed that persistent smokers in the last three months reported more problems associated with dependence, health, social, legal and financial issues, as well as their daily activities than consumers of alcoholic beverages. The prevalence of cravings due to lack of nicotine (ASSIST question 3), if compared to lack of alcohol, can be explained by the fact that nicotine causes strong chemical dependence and also because the detected number of daily tobacco users was much higher than that of alcohol consumers in this sample. Although smoking may have a direct causal relation with the other problems identified in the ASSIST questions 4 and 5 (health, social, legal and financial complications, as well as daily activities), it is possible that this is a two-way relation, because stressful situations, such as those cited, are known triggers of the will to smoke.

The questionnaire also revealed that cigarette smoking was a major concern among relatives and friends of the research participants, who tried more often to unsuccessfully quit this habit compared to drinkers. The information obtained from the ASSIST questionnaire may indicate a fairly accurate notion of the participants, and of those close in their lives, regarding the risks of very frequent consumption of a chemical substance.

Based on the scores attributed to the answers given to questions 1 to 7 of the ASSIST questionnaire, seven patients (2.4%) were referred for some type of intervention to stop drinking and 109 patients (36.3%) were referred for brief or advanced programs aimed at quitting smoking. It should be noted that the marked disproportion between the two may be due to the age range of the participants studied, with a tendency to consume less alcohol than younger individuals, but also, and especially, due to differences in the criteria adopted in the ASSIST questionnaire to suggest interventions to patients. That is, in comparison

with alcohol, a brief intervention is indicated for a sum of scores from 11 to 26, whereas for tobacco, the same level of intervention is indicated for scores from 3 to 26, which shows much less tolerance for tobacco than alcoholic beverages, probably resulting in a referral of the most serious cases related to drinking, but less likely to act preventively, for example in cases of excessive consumption.

Last, tobacco and respiratory diseases were responsible for the only statistically significant positive correlation found between drinking or smoking habits with the diseases indicated in the patients' electronic medical charts. All individuals with respiratory diseases (N=35) were included among the 109 who received some type of intervention to quit smoking. These data indicate that the ASSIST questionnaire seems to be an instrument capable of detecting and discriminating people who require brief or advanced interventions to interrupt tobacco use, even before health complications appear, thus highlighting their preventive potential.

Conclusion

Applying the ASSIST questionnaire made it possible to adequately identify and stratify alcohol and cigarette users with more recent and more frequent consumption, as well as with more complications resulting from them, and, based on this, indicate brief or advanced interventions in a very careful manner, taking into account the peculiarities of the dependence caused by each of the evaluated habits. Regarding alcohol, the ASSIST questionnaire applied in an internal medicine outpatient clinic served to direct the intervention only to people with very high scores, suggesting that the main goal of the instrument is to promote the treatment of consumers with more general complications, whereas in the case of tobacco, the criterion was more preventive, suggesting interventions even for people with lower scores. In addition, all patients with respiratory diseases in which tobacco may be the cause or an aggravating factor were submitted to brief or advanced intervention, which did not occur with alcohol in relation to liver and pancreatic diseases.

Resumo

Uso de álcool e tabaco e as doenças tratadas em ambulatório de clínica geral

Objetivo: Caracterizar o consumo de álcool e tabaco e correlacioná-lo às doenças em tratamento de pacientes de um ambulatório de clínica geral.

Método: As perguntas do ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) foram respondidas por 300 pacientes escolhidos aleatoriamente e enquadrados em grupos conforme os diagnósticos das doenças em tratamento no Ambulatório Geral e Didático (AGD), Serviço de Clínica Geral do HC-FMUSP; o consumo das substâncias foi caracterizado e a sua correlação com as doenças em tratamento foi calculada por meio do método do Qui-quadrado e teste de Pearson.

Resultados: O consumo de tabaco mostrou-se mais prevalente, mais intenso e maior causa de complicações (de saúde, sociais, legais ou financeiras) do que o do álcool; o consumo de tabaco apresentou correlação positiva e significante (p<0,0001) com a referência de doença respiratória no prontuário médico. De acordo com o critério proposto no questionário, poucos consumidores de bebida alcoólica seriam encaminhados para intervenção preventiva, ao contrário do que ocorreria com os fumantes.

Conclusão: A aplicação do ASSIST permitiu caracterizar e correlacionar positivamente o uso de tabaco com doenças respiratórias em tratamento. A importância do questionário como instrumento preventivo das consequências do tabagismo ficou mais evidente do que em relação às associadas ao consumo de bebida alcoólica.

Palavras-chave: abuso de álcool, uso de tabaco, rastreamento, diagnóstico.

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Spinal tumors in children

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Summary

Introduction: Spinal tumors are rare in the pediatric population, presenting many specific peculiarities when compared to adults. We have performed a broad narrative review to describe the most common spinal tumors in children, discussing their main characteristics and management options.
Method: The authors have performed an extensive review of the peer-reviewed literature addressing the aforementioned objectives.
Results: Multimodality radiological studies (plain films, 3D computed tomography scan and magnetic resonance imaging) are necessary for proper evaluation and differential diagnosis of spinal tumors in children. In selected cases nuclear medicine imaging is used to improve the chances of a more accurate diagnosis. As a general rule, a fine needle biopsy is recommended after radiological evaluation to confirm the tumor's histology. Primary bone tumors can be divided into benign bone tumors, mostly represented by vertebral hemangiomas, osteoid osteomas, osteoblastomas, aneurismal bone cysts, and eosinophilic granulomas, and malign or aggressive tumors, such as Ewing's or osteogenic sarcomas. Secondary bone tumors (spinal metastases) comprise different tumor histologies, and treatment is mainly based on tumor's radiosensitivity. The characteristics and treatment options of the main spinal tumors are discussed in details.
Conclusion: Spinal tumors in children are rare lesions that demand a thorough understanding of their main characteristics for their proper management. Understanding the nuances of spinal tumors in children is of paramount importance for improving outcomes and chances of cure.

Keywords: spinal tumors, children, adolescent, management, treatment, spine.

Introduction

Spinal tumors are rare in pediatric populations. In children, spinal diseases also have many specific peculiarities compared to adults. For instance, persistent pain lasting more than two months in children is often associated with a specific diagnosable lesion in up to 85% of patients.[1] As for spinal tumors, clinical symptoms may include not only pain, but fever, weight loss, weakness, neurological deficits, bowel and bladder dysfunction, and more.[2-4] Since spinal tumors are rare in children, a high level of suspicion is necessary for early diagnosis and treatment. Recognizing red flags (such as weight loss, neurological deficits, systemic symptoms, previous history of malignancy or serious illness, persistent and progressive pain, etc.) is mandatory for adequate and timely radiological diagnosis.[2-4] The sensitivity of radiological imaging in diagnosing tumors in children depends on tumor size and histology. Radiological imaging is based on simple plain radiographies, three-dimensional (3D) reconstruction computer tomography (CT) scan and magnetic resonance imaging (MRI). Most of the time, multimodality evaluation, which includes nuclear medicine image, is necessary to improve the chances of accurate diagnosis and proper medical management. After radiological evaluation, a fine needle biopsy is recommended to confirm tumor histology and guide treatment, as well as laboratorial evaluation for screening systemic disease.[5] A flowchart including clinical history, radiological evaluation and histological

diagnosis is proposed to facilitate the initial investigation of children with potential spinal tumors (Figure 1).

Considering the nuances involved in the diagnosis and management of spinal tumors affecting the pediatric population, we have performed a broad narrative review of this topic in order to help pediatricians and surgeons in the initial evaluation of these patients.

Method

We conducted an extensive review of the peer-reviewed literature addressing articles related to spinal tumors in children including articles found in the Pubmed Database without time restriction. A combination of the following search terms has been used either combined or grouped: "spine tumors;" "metastases;" "pediatric." For didactic reasons, we have divided the main spinal tumors into two large groups: 1) Primary bone tumors and 2) Metastatic bone tumors. We have included articles that focused on the epidemiology, clinical and radiological presentation, differential diagnosis using radiological evaluation, and potential treatment modalities of the most common spinal tumors in children.

Results

Although children may also have metastases, most bone tumors in the pediatric population are solitary and primary vertebral tumors.[6] The following are the clinical and radiological features of the most common spinal bone tumors in children.

Primary bone tumors

Benign bone tumors

These tumors would not spread to other areas, but may grow and compress adjacent structures and present with severe clinical symptoms and functional impairment.[7]

Vertebral hemangiomas

These are the most common tumors discovered incidentally on radiological exams and also the most common benign vertebral neoplasms (incidence of almost 10% in autopsy).[8] The vast majority is focal and asymptomatic.[9] Histologically, they show thin walls, blood-filled vessels and sinuses lined by endothelium with trabeculated bone interspersed.[9] Radiologically, they are represented by vascular channels with multifocal lytic areas with honeycomb appearance. CT scan (axial cut) shows a speckled pattern secondary to the vertical trabeculae in cross section views (polka dot sign).[10] Asymptomatic lesions on the MRI present with hyper signal in T1 and T2 sequences (due to its fatty component), with significant gadolinium enhancement due to their high vascularity. Some hemangiomas may have an aggressive behavior, resulting in symptomatic spinal cord compression due to extraosseous extension of the tumor, vertebral fracture or even enlargement of adjacent

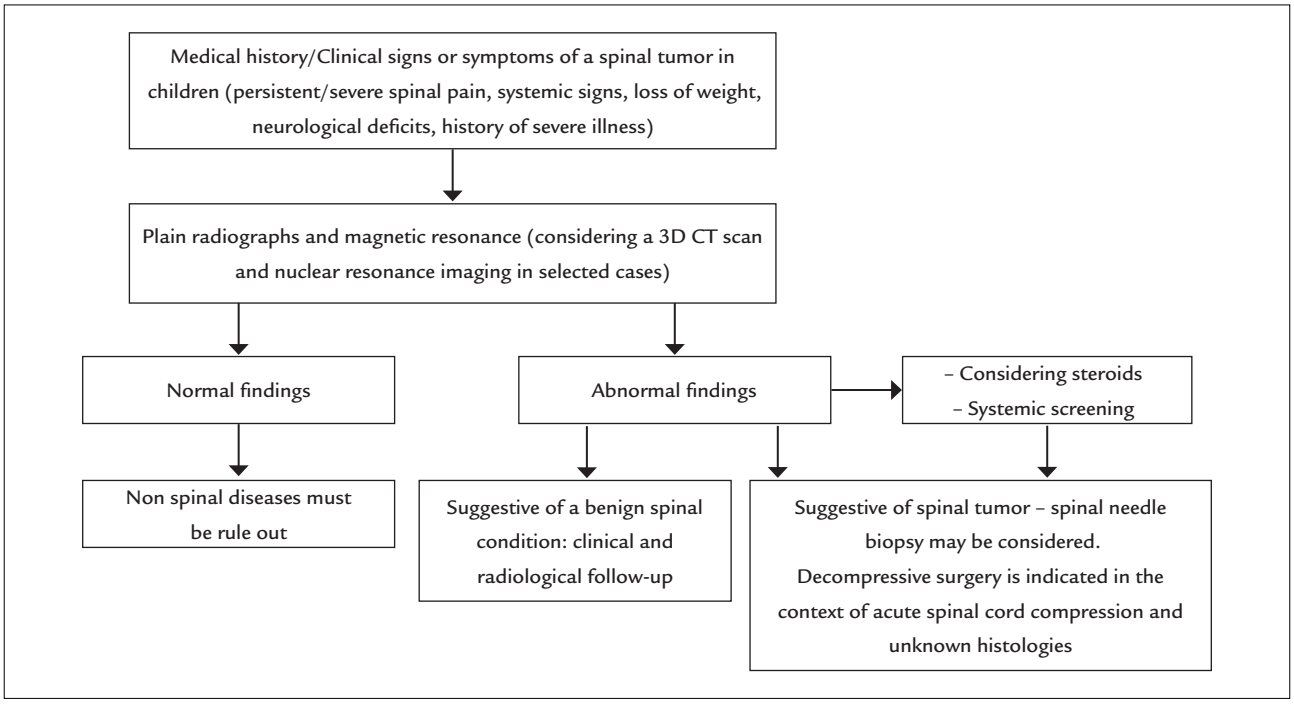

FIGURE 1 Flowchart for helping the initial management of children with a suspected spinal tumor.

blood vessels. Extraosseous involvement is associated with an inverse relation of fatty component inside the hemangioma: low signal intensity on T1-weighted images may suggest greater aggressiveness. Of note, metastases are the main differential diagnosis and generally also have a decreased T1 signal intensity. The thoracic region is the site of up to 90% of all aggressive hemangiomas, generally from T3 to T9.[10] Since they are mostly benign and usually asymptomatic, treatment is rarely necessary, and reserved for expansible and symptomatic lesions only. Treatment modalities may include vertebroplasty, balloon kyphoplasty, transarterial embolization, radiotherapy or even surgical decompression with stabilization.[10-13] Formal *en bloc* resection is not required for this tumor in most cases, since excellent rates of local control and long-term survival can be obtained with intralesional resection alone.[11,14]

Osteoid osteoma

It accounts for 11% of all benign bone tumors, with a higher incidence in males from 5 to 24 years of age.[15-18] Spinal osteomas are generally about 1 to 2 cm in size, with a radiolucent nidus and clear margins from the reactive periosteal bone.[19] It classically manifests as a well-localized night pain that may be relieved with salicylates. A compensatory scoliosis secondary to muscle spasms can be found in the concave side of the tumor.[20] Most of the lesions are found in the posterior spinal elements (lamina, transverse processes, pedicles), mainly in the lumbar spine, followed by the cervical, thoracic and sacral region, respectively. Radiologically, plain films may be normal or show a solid periosteal reaction with cortical thickening and a well-circumscribed central lucent area.[21-25] CT scan is the modality of choice for diagnosis, as it displays a focal calcified nidus within surrounding sclerotic reactive bone. Scintigraphy with technetium-99m shows typical focal uptake and a double density sign that is highly specific.[15,17,18] Finally, MRI can be sensitive, but may not identify the nidus as precisely as CT scans. Since spontaneous regression has been reported, treatment is performed only when the patient is symptomatic. When symptoms are mild or moderate long-term administration of anti-inflammatory drugs can be used as a treatment option. Surgical resection, curettage or even radiofrequency ablation are other treatment options available for different particular cases according to tumor location, intensity of symptoms, and the surgeon's experience and preference.[20]

Osteoblastoma

It is represented by tumors that are histologically identical to osteoid osteomas. This type differs from osteoid osteoma in that it can grow larger than 1 cm in diameter and has a more aggressive behavior.[21,22] It is much rarer than osteoid osteoma, but affects patients in the same age group, also with a predilection towards the male sex.[22] Similar to osteomas, they can affect all sites of the vertebral column, especially the posterior elements.[6,23] A histological variant with an aggressive behavior has been reported, with a high number of epithelioid osteoblasts and nuclear atypia – some authors reported this variation as a low grade osteosarcoma even without proper sarcomatous tissue.[4,13] Most of these tumors may be first noted as a palpable mass, and some of them may result in cord compression due to their large size.[3,4] Radiologically, plain films may show a lytic lesion with a rim of reactive sclerosis, with or without internal calcification and some surrounding sclerosis or periostitis. CT scan is better than MRI for diagnosis, showing a lytic lesion with varying degrees of matrix mineralization. On MRI, image findings can be non-specific. It usually shows a lesion with hypo- or isointense T1 and T2 central areas (calcification foci) and a hyperintense T2 sign in surrounding bone and soft tissues. It usually enhances with gadolinium.[21] Scintigraphy with technetium-99m shows typical focal uptake suggesting increased bone turnover. The treatment of choice consists of complete surgical excision, if possible, preferentially with pre-operative embolization to minimize bleeding.[3,13,22]

Aneurysmal bone cyst (ABC)

This is a benign expansible bone tumor (the neoplastic etiology is controversial), consisting of blood-filled spaces separated by connective tissue containing trabeculae of bone or osteoid or osteoclast tissues.[24,25] Most ABCs are primary, but up to one third may be associated with others tumors, such as osteosarcomas, chondroblastomas, fibrous dysplasia, and giant cell tumors.[25,26] They can affect all segments in the spine, preferentially involving posterior elements and the vertebral body.[4,25,26] Radiologically, plain films may show a sharply defined expansible osteolytic lesion, with thin sclerotic margins. CT scan evaluation is similar to plain films, but may also demonstrate a collection of clear fluid, seen more clearly on MRI.[25] If a solid component is visualized on MRI, a secondary ABC may be suspected.[4] Most of the cysts have a low T1 and T2 signal, but high-signal focal areas are commonly seen due to the variable degrees of blood decomposition inside the cysts.[4] The septations may enhance with gadolinium administration. Treatment depends on the location and extension of the ABC, but it is based on surgical resection. Pre-operative embolization is advised to reduce intraoperative blood loss. A higher recurrence rate is reported

with partial resection or curettage and bone grafting. Total surgical resection is the best treatment to reduce the rate of recurrence, but it increases morbidity.[27] Serial embolization as an isolated treatment can be indicated for patients with recurrent lesions after previous surgical treatment or in whom surgery would not be tolerated due to comorbidities or complexity.[28] An illustrative case of thoracic spine ABC is presented in Figure 2.

Eosinophilic granuloma (EG)

EG is the term used for describing single lesions composed of Langerhans cell histiocytosis.[29,30] It encompasses many different conditions characterized by the presence of granulomatous lesions with Langerhans cells.[29,30] The peak of incidence is from 1 to 3 years, affecting more males than females.[4] The spine is the second most common site affected, just after the skull, in the cervical, thoracic and lumbar vertebrae, respectively. It may cause vertebral collapse, radiologically represented as vertebra plana, which is the most common development of EG in children (in this age group the differential diagnosis of vertebra plana is non-Hodgkin lymphoma).[31,32] Clinically, EGs may cause back pain and neurological deficits. Plain films and CT scans may show a lytic lesion without sclerotic rim or

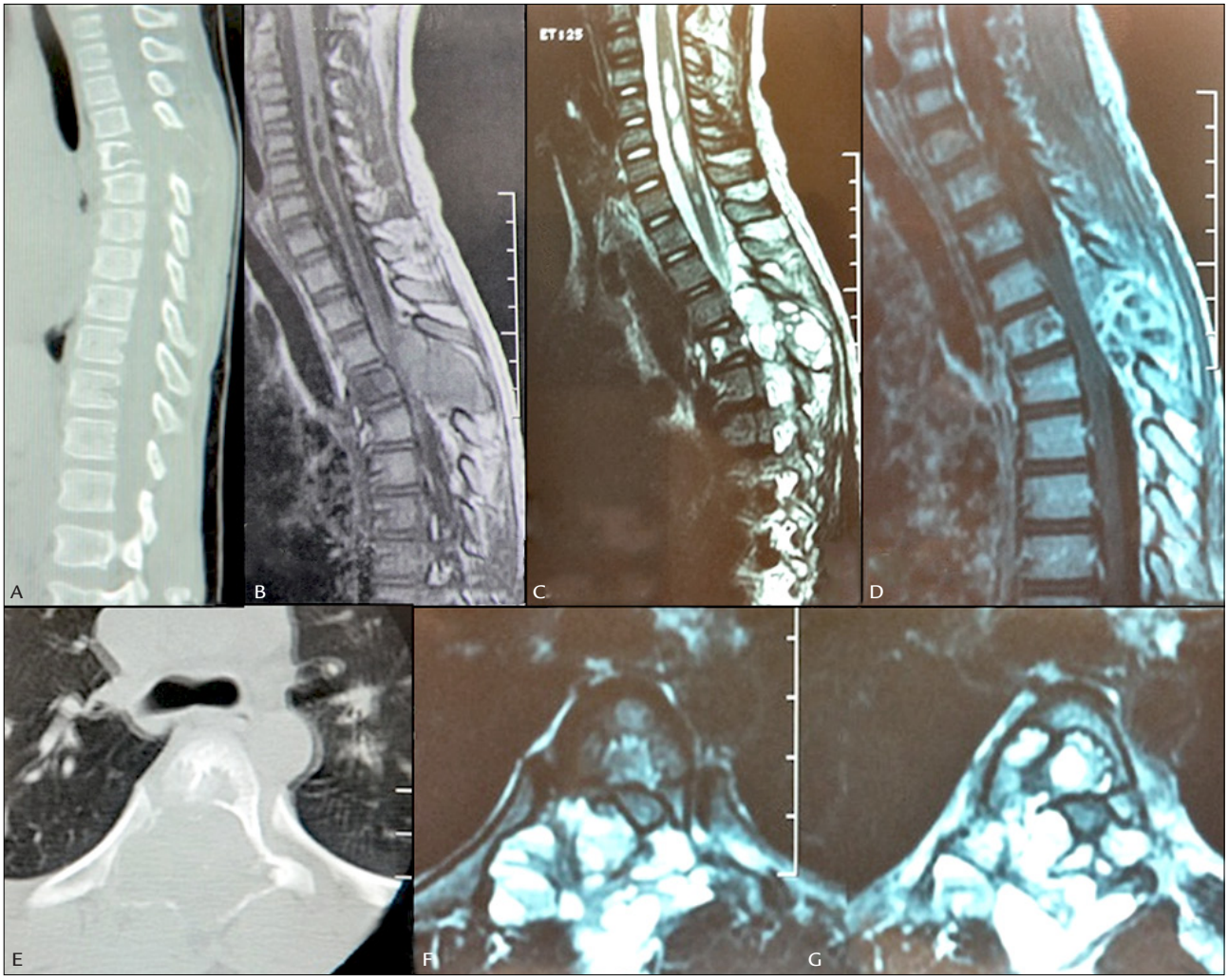

FIGURE 2 This 5 year-old patient was brought to the emergence department with 2-week progressive leg weakness and thoracic pain. A. Sagittal CT scan with a T5 osteolytic lesion involving the spinous process, pedicles and the posterior vertebral body. B. A Sagittal T1 sequence MRI showing iso signal lesion at the posterior elements of T5 and spinal cord compression. C. Sagittal T2 sequence MRI with a hypersignal heterogeneous lesions and spinal cord compression. D. Sagittal T1 sequence with gadolinium showing irregular enhancement. E. Axial CT scan showing a lytic lesion with insufflation, the same showing in axial T2 sequence, with a heterogeneous insufflation T2 hyper signal lesion with fluid content. The anatomopathological exam confirms an aneurismatic bone cyst.

vertebra plana. MRI generally presents with T1 hypointensity sign lesion, T2 hypointensity signal lesion, and gadolinium enhancement.[29] The prognosis is good in confined disease.[4,30,31] Treatment may be non-surgical in cases where symptoms are mild and there are no neurological deficits, since fibrosis occurs spontaneously in 1 to 2 years, but chemotherapy should be considered in systemic forms of the disease.[4,30,31] Surgical treatment may consist of biopsy for diagnosis, followed by curettage, steroid therapy, radiotherapy and/or decompression with or without fixation in cases of spinal cord compression.[4,30,31]

Malignant/Aggressive bone tumors

Ewing's sarcoma (ES)

About 65% of the cases of ES occur in the second decade of life, predominantly in males.[33] Only a small portion of them occurs in the spine; however, it is the most common non-lymphoproliferative primary malignant tumor of the spine in children.[33,34] Primary vertebral ES has been divided into sacral and non-sacral, based on treatment responses and survival rates (non-sacral types are rarer and have a better treatment response and survival rate).[35] Skeletal scintigraphy for staging is mandatory, since ES is generally a multifocal disease. Clinically, patients may present with persistent pain and swelling, due to its expansible nature, as well as secondary neurological deficits. Plain films may show lytic changes or vertebra plana.[35] CT scan is useful for determining the extent of involvement of both the vertebral body and the posterior elements. MRI is sensitive to detect ES in the spine, as well as to evaluate epidural compression and soft tissue involvement.[35,36] Generally, ES has a low-to-isointense signal compared with muscle on T1-weighted images and high signal on T2-weighted images, with heterogeneous enhancement with gadolinium. These findings are nonspecific. MRI is also important for monitoring the response to chemotherapy and preoperative planning.

Treatment depends on the degree of the disease: focal tumors without neurological deficits confirmed by needle biopsy may receive neoadjuvant chemotherapy to shrink the tumor and treat micrometastases, followed by surgery with wide resection and/or radiotherapy, and adjuvant chemotherapy.[35,36]

Osteogenic sarcoma

Primary spinal osteosarcoma is a rare lesion. Differential diagnosis is mainly osteoblastoma, which preferentially involves the posterior elements and extends into the vertebral body, while osteosarcomas generally occur in the vertebral body and extend to the posterior elements.[4,37] The most common location is in the lumbar spine and sacrum. Pain occurs in the vast majority of patients, with neurological deficits in about 70% of them.[4,37]

Histologically, it is characterized by cells of varying shapes, with hyperchromatic nuclei, producing osteoid or bone. It is a malignant tumor of the connective tissue.[37]

Radiologically, plain films may show a blastic lesion or osteolysis. Sometimes a purely lytic pattern may be visualized as well. CT scan may show the mineralization pattern of lytic lesions and is the modality of choice for evaluating cortical destruction.[38] MRI is nonspecific due to tumor heterogeneity: on T1-weighted images, ossified components may have low signal, soft tissue may have intermediate signal, and hemorrhage will have variable signal intensity; on T2, soft tissue and peri-tumoral edema will have high signal intensity, whereas ossified components will present with low signal. Solid components of the tumor enhance with gadolinium.[38] Ossified components/dense mineralization show as low signal changes in all sequences. Clear fluid may be present, as a differential diagnosis with ABC.[38]

The current treatment of choice is *en bloc* resection, especially for tumors confined to the vertebral body, followed by adjuvant radiotherapy and chemotherapy. The survival rates of primary spinal osteosarcomas are lower than non-spinal tumors (overall survival rates of about 30 to 40% in 5 years).[37,38]

Secondary bone tumors/Spinal metastases

Spinal metastases are the most common tumors in the spine of adults, comprising 70 to 80% of all spinal tumors in this age group.[39] Although spinal metastases are much rarer in children, with the advances in chemotherapy, surgical techniques and also the new modalities of radiation, children with malignant tumors are living more and also presenting with spinal metastases.[40] Of note, although spinal cord compression can occur in the setting of leukemia and lymphoma, they are not truly spinal metastases, since they are not solid tumors. The modality of choice for diagnosing spinal metastasis in children is MRI, which can assess the vertebrae and the spinal cord, as well as evaluate multiple sites of compression.[40,41]

In a large series of 2,259 solid malignant tumors in children, 5% (112 patients) developed spinal epidural metastases with cord compression during treatment.[40] The most common cause was ES and neuroblastoma, followed by osteogenic sarcoma, rhabdomyosarcoma, Hodgkin's disease, soft tissue sarcoma, germ-cell tumor, Wilm's tumor and hepatoma.[40] Outcome was similar for small-cell tumors (neuroblastomas, Hodgkin's disease and germ-cell tumors)

that received chemotherapy and/or radiation therapy or a decompressive laminectomy alone prior to chemotherapy and/or radiation therapy. On the other hand, children with metastatic sarcomas (soft-tissue sarcoma, osteogenic sarcoma, rhabdomyosarcoma) had a better neurological outcome with decompressive laminectomy followed by radio and/or chemotherapy than those without surgery.

A flowchart is suggested for helping the management of spinal metastases in children (Figure 3). The main consideration for treatment is tumor histology and its response to radiotherapy and/or chemotherapy. As a rule, radiation therapy is used as first treatment modality in radiosensitive tumors, and surgery is proposed to relieve spinal cord compression, especially in radioresistant tumors, such as sarcomas, or when deformity (kyphosis and/or scoliosis) or spinal instability are present.

In children, special concerns with spinal deformities must be taken into account when operating on a spinal tumor or even after radiotherapy.[42] Clinical and radiological follow-up of post-treatment deformities is mandatory, and bracing may be considered in selected cases, especially after decompressive procedures without spinal stabilization in young children.[42]

Conclusion

Spinal tumors in children are rare lesions. After clinical suspicion, initial evaluation may include 3D CT scans and MRI. Needle biopsy is recommended in most cases for diagnosis confirmation. Primary bone tumors may be benign, where treatment is individualized, or malignant, potentially requiring *en bloc* resection. Spinal metastases in children, although rare, can be treated without surgery in tumors that are responsive to chemotherapy and/or radiation therapy; surgery is reserved for specific situations (such as acute and progressive spinal cord compression or patients with instability) or tumors not responsive to adjuvant treatment. Understanding nuances of spinal tumors in children is paramount for improving outcomes and chances of cure.

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Resumo

Spinal tumors in children

Introdução: Os tumores de coluna em crianças são raros, apresentando peculiaridades únicas quando comparados com os da população adulta.
Método: Dada a escassez de trabalhos que avaliem o tema, realizou-se extensa revisão de literatura objetivando descrever os tumores de coluna que acometem a população pediátrica, discutindo características e opções de manejo.

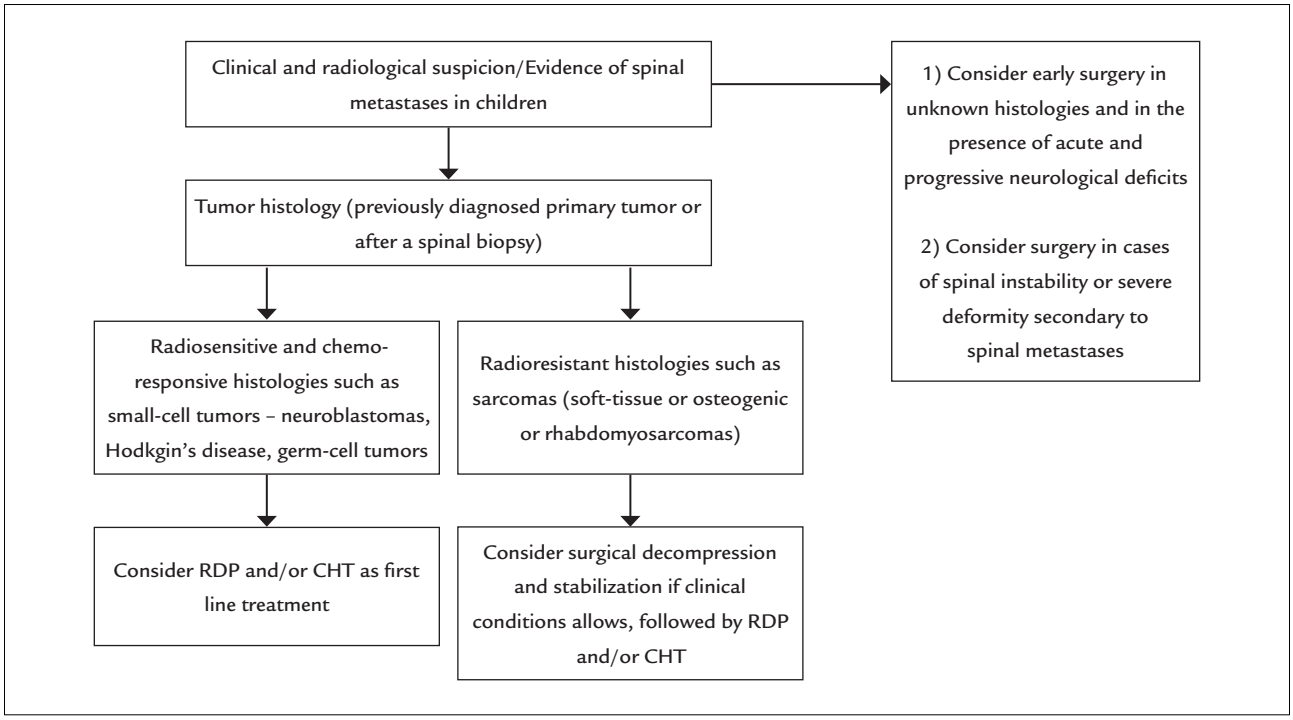

FIGURE 3 Flowchart to facilitate initial management of spinal metastases in children.

Resultados: A utilização de exames radiológicos combinados (radiografias, tomografia computadorizada com reconstrução em 3D e ressonância magnética) é necessária para avaliação adequada e diagnóstico diferencial dessas lesões. Em casos selecionados, exames de medicina nuclear aumentam as chances do diagnóstico preciso. Como regra geral, biópsia por agulha é recomendada para confirmação da histologia tumoral e tratamento subsequente. As lesões primárias de coluna podem ser benignas, representadas principalmente pelos hemangiomas, osteomas osteoides, osteoblastomas, cistos ósseos aneurismáticos e granulomas eosinofílicos, enquanto as lesões malignas são geralmente representadas por tumores agressivos, como o sarcoma de Ewing ou os sarcomas osteogênicos. Metástases de coluna podem ter diferentes etiologias, sendo o tratamento dependente principalmente da radiossensibilidade do tumor de origem. As opções de tratamento dessas lesões são descritas em detalhes.
Conclusão: Tumores de coluna em crianças são raros e o seu manejo requer um conhecimento amplo e variado das diferentes possibilidades diagnósticas. Conhecer os nuances envolvidos no tratamento dessas lesões e os sintomas iniciais é fundamental para melhorar o prognóstico e as chances de cura.

Palavras-chave: tumores da coluna, criança, adolescente, manejo, tratamento, coluna.

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Breast cancer screening in Brazil. Barriers related to the health system

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Summary

Objective: Identify factors related to the health system that lead to a late diagnosis of breast cancer in Brazil.
Method: We performed a systematic review in the PubMed and LILACS databases using as keywords "Breast cancer," "system of health" and "Brazil or Brasil." We evaluated the content of the articles using the PRISMA methodology based on PICTOS. The final date was 12/16/2015. We were able to identify 94 publications in PubMed and 43 publications in LILACS. After assessing the title and summary, and excluding 21 repeated publications, we selected 51 publications for full evaluation. At this stage, we excluded 21 articles, with 30 publications remaining for study.
Results: The population coverage is low, and there are problems related to the quality of mammography. Patients with lower income, nonwhite and less educated are more vulnerable. We observed punctual and initial experiences in breast cancer screening. Diagnosis and treatment flows must be improved. The inequality in mortality reflects the differences related to screening structure and treatment. Better results are observed in well-structured services.
Conclusion: There are several barriers in the health system leading to advanced stage at diagnosis and limiting the survival outcomes. The establishment of a rapid and effective order for diagnosis and treatment, based on hierarchical flow, are important steps to be improved in the public health context.

Keywords: breast neoplasms/prevention and control, health systems, screening programs, mammography, Unified Health System.

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Introduction

Breast cancer is a worldwide problem, with 1.7 million new cases a year. Half of the cases are in developed countries, but 62% of deaths occur in developing nations. Mortality in the United States is declining, a fact attributed to early diagnosis by mammography and to improvements in treatment. In South America, however, incidence and mortality are increasing.[1] Breast cancer is diagnosed in advanced stages in countries with limited resources due to a deficit in the ability to promote early detection, diagnosis and treatment. To assess the complexity of the health system in relation to breast cancer, the Breast Health Global Initiative (BHGI)[2] sought to categorize the organization levels of different countries in relation to breast cancer, so that the basic level encourages breast self-exam, the limited level refers to the availability of diagnostic ultrasound and mammography, the increased level includes diagnostic mammography with opportunistic breast screening, and the maximum level refers to organized population mammary screening.[2] In the United States, the rate of mammography screening is high, but in countries with budget limits there are no effective screening programs, and in some cases access to treatment is limited.[1]

Survival in developed countries is around 73%, and 57% in developing countries. In developing countries, the incidence of breast cancer is lower, while the incidence/mortality ratio is higher than in developing countries.[1] Due to the economic and logistical limitations in Brazil, mammographic screening is not a widespread reality, a fact that is reflected in the high number of patients diag-

nosed at an advanced stage, due to the absence of an organized network aimed at the early diagnosis of breast cancer. There is no organized mammographic screening, only isolated experiments.[3-5]

When assessing the barriers related to mammography screening, they can be synthetically divided into those related to the health system, those related to education or knowledge, and those related to adherence or attitude.[6] In Brazil, there are innumerous factors related to adherence/attitude, including age, socioeconomic condition and formal education. The education/knowledge category includes the factors described above, associated with the fact that mammography is not often indicated by physicians, and patients do not seek tests when they do not present symptoms or if they fear pain or cancer.[5] Barriers related to the health system are difficult to assess as there is no specific indicator. Thus, a critical evaluation of the barriers related to the health system, which impact on the screening of breast cancer, is justified.

Method

We conducted a literature review using a systematic search methodology to evaluate the barriers related to mammography screening in Brazil. We did not evaluate the methodology or quality of the study, but publications that expressed this matter. We searched the PubMed database using as keywords "Breast Cancer" and "system of health" and "Brazil or Brasil". In the LILACS database, we used as keywords "Breast neoplasms" and "Health Systems." PRISMA[7] methodology (Figure 1) based on PICTOS (Population- Intervention- Comparator- Outcome- Timing- Setting; Table 1) was adopted for article selection. The articles were grouped according to the subject addressed, trying to identify possible factors that express the limitation of the health system.

On 12/16/2015, using this methodology, we were able to identify 94 articles in the PubMed database and 43 publications in the Lilacs. We evaluated title and summary and, after excluding 21 repetitive publications, we selected 51

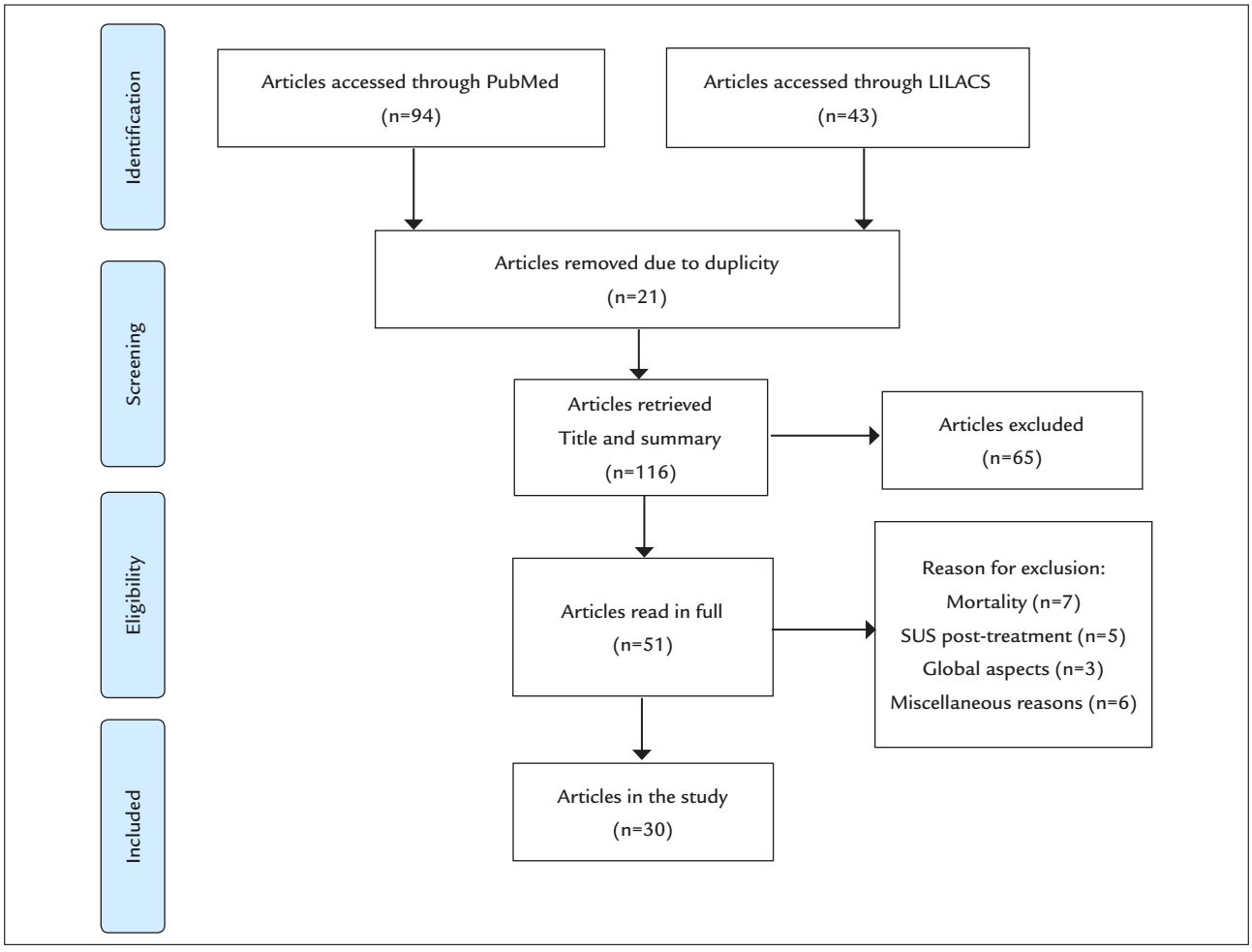

FIGURE 1 PRISMA records flow diagram.

publications for full evaluation. At this stage, we excluded 21 articles, seven related to mortality, five presenting post-treatment Brazilian Unified Health System (SUS, in the Portuguese acronym) data, three presenting global aspects related to different types of cancer, and six for different reasons (breast changes, social support to cancer, costs in the private system, ethics, cervical cancer and stage of diagnosis). Aiming at a better understanding of the barriers related to the health system in Brazil, 30 publications remained in the study, and these were the basis of our bibliographic review. The data are summarized in Figure 1. The data are mostly qualitative. We chose to present grouped results according to the subject presented (Table 2).

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Results

With 30 articles selected according to PICTOS,[4-6,8-34] we attempted to create groups according to contexts, namely:

TABLE 1 Summary of the findings observed according to PICOTS.

	Proposal	Inclusion
P/ Population	Breast cancer in Brazil	Breast cancer in Brazil; dependence to the SUS
I/ Intervention	Mammography Health management	Mammography; screening Health management
C/ Comparison	Factors related to the Health System	Mammography machine: population-based coverage, availability, quality; management; type of screening
O/ Outcome	Results found	Experience in screening, vulnerable populations, diagnostic flow, clinical stage at diagnosis, treatment and mortality
T/ Time	Any	Any
S/ Study type	Any	Any

TABLE 2 Main results summarized.

PICO	Summary of findings
Goal	Mammography 50-69 years, bi-annually
P/ Population	**SUS system population dependent on governmental actions**
	Subgroup without MMG: absence of health plan, non-white, low income
	Patients over the age of 40 who never underwent MMG
	Distance from place of residence to treatment greater than 150 km
I/ Intervention	**SUS Screening type**
	Mammography control done by the SISMAMA
	MMG usually diagnostic
	Opportunistic screening through collective action to meet demand
	Organized screening does not exist
	Organized screening being implemented at a single center in the country
C/ Comparison	**Comparison**
	Inadequate mammography coverage
	Inadequate biannual recall
	Unsatisfactory quality of mammography in the SUS
O/ Outcome	**Result**
	Difficulty in patient flow, from diagnosis to treatment
	Diagnosis in symptomatic phase
	Advanced clinical stage of cancer at diagnosis negatively influencing survival
	Mortality: Private < well-structured public < regular public services
	Gradual improvement in the supply of MMG and outcomes related to cancer staging, with no defined indicators
	Increased incidence and increased mortality: Midwest, North and Northeast regions
	Increased incidence and decrease in mortality: South and Southeast

MMG: mammography.

problem overview (3), management-related articles (4), mammogram and population coverage (3), assessment of factors related to non-adherence to mammography (4), the experience of oportunistic (4) and organized screening (2), difficulties in establishing a diagnostic flow (2), and mortality (8). Table 1 summarizes the findings.

Three articles were selected based on an overall assessment of the problem.[8-10] The Ministry of Health held a workshop where mammographic screening was discussed. Observing positive experiences, but considering the European position and recommendations of the BHGI, the Ministry restricted the orientation of mammographic screening to the age group of 50-69 years, a guideline that should be followed by health managers.[9] A 2012 thesis discussed mammography screening and public health conditions in Brazil, and is a good roadmap for health managers.[10] Evaluating the problem in a global way, there is a difference in terms of the distribution of mammography machines, with a higher proportion of unused devices in the North/Northeast of Brazil. 30-35% of women undergo proper mammography, mainly in the private sector, and 80% do not have referral from a doctor. The mean time between presentation of symptoms and diagnosis is 72-185 days, which leads to high rates of advanced stage diagnosis, with 37.0% in stage III and IV, different from that observed in the private sector, where this rate is 16.2%.[8]

Regarding health management[11,12] and information systems for the support of health management,[13,14] four articles were selected. Assessing the origin-destination flow of outpatient visits and hospitalizations related to breast cancer, we observed that the treatment is generally performed in large cities and in reference centers, and patients travel distances greater than 150 km from their city source.[11] Despite the existance of different information systems on breast cancer, they are little explored.[12] The SISMAMA system showed promising results with 50% of the examinations performed in the age group 50-69 years and about 66% of mammography reports were performed in a period inferior to 30 days.[13] National coverage is low, including 32% of women in the 50-59 age group and 25% in the 60-69 age group, though this actually depends on the age group of the macro-region. In general, the coverage of women in the 50-59 age group is higher in the Southern and Southeastern states, and lower in the North and Northeast.[14]

Evaluating the mammograms, we must observe the population-based coverage, the differences in quality of the exam, the differences related to form of the diagnosis (symptomatic or asymptomatic), and factors related to the failure to undergo mammography. Despite regional differences in population coverage in Brazil,[14] a study carried out in the state of Goiás[15] evaluated coverage based on the number of mammography machines, the number of devices in operation for the SUS, where the state coverage was 61%, divided into 13% coverage by the SUS and 48% by non-SUS.[15] Also in the state of Goiás, the study assessed the quality of the machines[16] using performance tests. The authors found initial conformity of 64.1%, and 77.1% of unacceptable rates (< 70%), which is a percentage considered high, since low quality mammography predisposes to incorrect diagnoses.[16]

There are studies that attempt to evaluate the factors related to non-mammography.[17-20] Considering biannual mammograms, the authors evaluated a population sample of women over the age of 40 (n=290) from the state of São Paulo and found that non-white elderly women (> 70 years) with low income (≤ 5 minimum salaries) were more likely to fail to undergo mammography. However, in this study, the SUS was responsible only for 28.8% of the population undergoing mammography.[17] A study carried out in the capital of the state of Piauí (n=433), evaluating women aged 40-69 years, revealed that 24.7% of the sample had never undergone mammography, and among those who had undergone the examination, 17.5% had mammograms more than two years earlier, and 66.6% in the previous year. In this population, 56.3% of the exams were funded by the SUS system. Factors related to failure to undergo mammography included non-white ethnicity, low educational index, low income and absence of health plan, highlighting the importance of the social and racial context for not undergoing mammography.[18] This fact is more serious when the regular repetition of the exams is assessed. A study conducted in the city of Taubaté (state of São Paulo) showed that correct adherence to biannual repetition occurred in only 30% of the population, and differential access to public or private health services contributed to such a reduced rate.[19] Another factor that must be carefully evaluated is the result of mammography, both diagnostic and screening. The detection rate was 8.8 cases/1,000 mammograms in asymptomatic patients (screening) and 61.7/1,000 mammograms in symptomatic patients, reflecting a large number of advanced stage at diagnosis in symptomatic women.[20]

There is no organized screening in Brazil, but collective mobilization/actions to provide mammography and organized screening models are described.[4,21-23] A collective action to provide mammography performed in the city of Marília (state of São Paulo) yielded 0.84 diagnosed cases/1,000 mammograms. The cost of the mobilization per case diagnosed was considered high, suggesting the superiority of implementing screening services.[22] Investigating a population of 4,037 women in the city of Porto Alegre

(state of Rio Grande do Sul), with patients being divided into symptomatic or asymptomatic, the authors found nine cases in 7,656 women-years,[4] with 60% adherence in one year, suggesting that opportunistic screening in sites with a high incidence of breast cancer is positive. Regarding lost years of life, an increased risk of death from breast cancer was observed in the range of 50-59 years, and a significant increase in the range 40-49 years.[23]

Regarding organized screening, we must consider the regional experience in the interior of the state of São Paulo[3,5,24] with a biannual screening proposal in the age range of 40-69 years. In the first two years of the project, 17,964 women were investigated and 76 cases were diagnosed, with an increase in the early stage rate from 14.5% to 43.2%. Similar to other studies, the authors describe that 42.1% of this sample had never undergone a previous mammogram in their lives, especially among women of low socioeconomic class and low education. The strategy of mobile units and the family health program were important in identifying these women.[5] After years of initiating the project, the authors noted that the rate of early stage in asymptomatic women was 70.8%, with only 5.6% reporting difficulty in obtaining a mammography examination, and the success of the program was due to intense community involvement associated with free mammography, tests performed according to the norms of the health system, and mammography performed near the patients' home.[24] The authors report the importance of the nurse in the management and operationalization of the screening action.[6]

As for the issue of health system,[25,26] difficulty in establishing a diagnosis and treatment flow is observed, which contributes to increase the time between diagnosis and beginning of treatment. Thus, in Brazil, 36.9% of the patients take more than 60 days between the diagnosis and the start of treatment. The women most susceptible to delay are not white, do not have a partner, have little formal education, are at an early stage of the disease and covered only by the SUS system.[25] It is true that there are multiple steps since the initial evaluation, with false-negative results, follow-up, diagnosis and treatment, which requires a structured and agile system to optimize time. Failure to give access for asymptomatic women, fear, low education, age and false-negative results contribute to the delay.[26]

In terms of the relationship between mortality and the health system,[27-30] a study carried out in the city of Juiz de Fora, state of Minas Gerais (n=282), revealed, in the univariate analysis, that patients treated in public hospitals presented worse survival. However, in this population, the advanced stage of the disease at the time of diagnosis was more frequent in public hospitals, possibly explaining the absence of this relationship in the multivariate model.[27] Another study carried out in Juiz de Fora (n=437) showed in the multivariate model that public services and non-white race/color had higher mortality risk due to breast cancer.[28] In the state of Rio de Janeiro, there was an inverse association between the presence of mammography and mortality.[29] Another study conducted in Rio de Janeiro evaluating 15 hospital units (n=310) showed better survival[30] in patients treated in services with private health plans and Oncology Centers (p=0.02), hospitals with a large number of procedures (p=0.007), and the time between diagnosis and treatment lower than 6 months (p<0.0001), which emphasizes the importance of well-structured public services.

For the analysis of trend and mortality curves,[31-34] in the period between 1980 and 2002, there was increase mortality by breast cancer in the southern region of the country.[31] In the period from 1991 to 2010, there was an increase in mortality rates in Brazil, in the North, Northeast and Midwest regions, although they remained stable in the South region and decreased in the Southeast region. This is similar to that observed in developed countries and reinforces the need for appropriate screening and treatment programs.[32] This disparity was also observed in the Brazilian macro-regions in the period from 1980 to 2009, probably due to regional inequalities. There was decline and stabilization in regions with a higher socioeconomic level and the opposite in regions with low socioeconomic status.[33] A study comparing mortality in the USA and in the Brazilian Oncology Hospital showed that, for the same staging, overall survival was similar. However, when comparing clinical stages, there was a higher percentage of patients in advanced clinical stage in Brazil, which negatively affected the survival of the group. The conclusion was that, by undergoing the appropriate treatment, the main factor associated with high mortality is the advanced cancer stage at diagnosis.[34]

Discussion

Screening for breast cancer through mammography is the best methodology for secondary prevention in the general population, promoting early detection in the asymptomatic phase, leading to a substantial reductions in morbidity and mortality caused by late diagnosis. A meta-analysis with articles from the Cochrane database on mammographic screening did not show a reduction in mortality risk when evaluating studies with adequate randomization. However, the evaluation of studies with suboptimal randomization yielded a reduction in mortality

risk of approximately 25%, and about 19% after all these studies were grouped.[35] The reduction in breast cancer mortality in several developed countries was probably due to the association of screening programs and improvements in adjuvant therapy.[1] We draw attention to an American study that compared historical data from the Surveillance, Epidemiology, and End Results (SEER), assessing clinical stage, and found a reduction in advanced stages of cancer close to 8%.[36] However, this study was much questioned for evaluating global data, with part of the population not being screened and population coverage below the satisfactory value.[37]

Changes in mortality occur mainly after the age of 50 years, with the age limit being 69 to 74 years. Therefore, to achieve a reduction in breast cancer mortality, mammography should be performed on a large scale at the general population level. The Brazilian Society of Mastology suggests that the initial age should be 40 years,[38] which was the guideline established by the American Cancer Society until 2015, updated in 2016 to 45 years.[39] Eusoma,[40] the US Task Force and the Brazilian Ministry of Health,[10] suggest that this exam should be performed from the age of 50 years.[5]

In developing countries, the majority of the population has low incomes, being dependent on government actions and public health infrastructure, with multiple diseases competing for limited resources. Public health practices are linked to national guidelines, available methodologies and capacity to absorb demand in the public network. In this context, the BHGI argues that organized population-based mammography screening should be conducted only in developed countries.[2]

There is now a lot of literature against and in favor of mammographic screening. Pro-mammography factors include: decreasing the size of diagnostic lesions, with implications for diagnosis and treatment; studies demonstrating a decrease in mortality due to breast cancer; years of life saved; an acceptable rate of hyperdiagnosis (1 to 10%); the frequency of subtypes; and the progression of carcinoma in situ. It is worth mentioning that, in order to achieve this goal, it is necessary to have population coverage, good quality exams, associated with a fast and efficient diagnostic flowchart.[35,37,40] Cons include partial evaluation of systematic reviews;[35] discussions about the actual decline of advanced tumors in the US;[36] hyperdiagnosis (31%);[36] and studies that show that there are lives saved by mammography screening, but their numbers are limited.[41] Usually, those who deal with the patient are in favor of screening,[37,39] while epidemiologists are more cautious,[41] presenting a somewhat more negative view.[36] Thus, many studies suggest that the patient should know all the points involved in mammographic screening, and should be aware of the pros and cons associated with the potential gain related to screening,[41] which is possible from a theoretical point of view, but very difficult in medical practice.

The truth is that organizing a mammographic screening requires technology, money, training, education, proper staffing and patient adherence. Every program must have a beginning, a middle and an end,[38] that is, measures from planning to the appropriate destination of suspected and positive cases, and community intervention.[5,24] Associated with this, the team should be trained to evaluate mammographic screening, and not only mammographic diagnoses, respecting quality and logistics standards, as is the case in Europe.[40] Barriers related to the health system are the main limiting factors for not performing mammography in developing countries. This fact is influenced by accessibility to the services of health, unsatisfactory medical adhesions, cost of the exams and difficulties related to complementary exams and follow-up. The evaluation of factors related to the health system and adherence to mammography is complex, since there is no specific indicator. We noted in our review, problems related to information management, distribution of mammography machines in the public network, quality of mammography, and other issues associated with the operationalization of organized screening and effective treatment.

In developing countries, these issues are more evident, as health resources are limited. And while there are controversies in the literature, the negative points of breast screening are considered, as health resources are used preferentially in more effective programs such as cervical cancer. In these countries, BHGI suggests self-examination in conjunction with diagnostic mammography and ultrasonography.[2] The IARC encourages self-examination education and clinical breast examination as a screening methodology in low-income countries, with sufficient evidence for mammographic screening in the 50-69 age group in developed countries.[42] In Brazil, there is economic and structural diversity. The Brazilian census (PNAD survey) revealed that mammography examinations are less frequent in the North region, compared to the higher examination rate in the Southeast,[43] which proves the uneven mammographic coverage in the country.[14] Another reflex of the association of screening and treatment are the trend curves related to mortality, with a rise in the North, Northeast and Midwest, stabilization in the South, and a decrease in the Southeast region.[32] It should be noted that the decrease in mortality is only observed

in places where the association between screening and treatment is effective.[1] Similarly, as examples of Southern[4] and Southeastern[5] Brazil, there are programs in the structuring phase that have presented promising results.

In Sweden, the benefits of mammography screening are well known.[35] In Europe, the rules for mammographic screening are clear and the indicators are acceptable and desirable,[40] but understanding the multiple steps involved in the process is only achieved once the program is properly structured.[38] Evaluating screening quality control, for example, we observed the quality of mammography, the recall rates for complementary exams, diagnostic rates in incidence and prevalence screening, rates of invasive tumors, proportion of tumors measuring less than 1.0-1.5 cm, sensitivity of the needle biopsy, benign/malignant open biopsy ratios, and time between examinations and surgery.[38] In Brazil, since organized screening is not done, there is much to be implemented in terms of quality. In the experience in the interior of the state of São Paulo, symptomatic patients are observed in the initial phase of network structuring,[5] which is not ideal in screening programs. However, structuring the service, acquiring technology, training staff[38] and participating in quality programs, coupled with adherence strategies,[24] represent important steps to achieve improvement. Access to mammography refers to: presence of this technology and ease of access by the general population, including the quality of the exams and the possibility of performing complementary tests for biopsy and differential diagnosis.[38] Other regional centers need to be set up, as proposed in Europe.[40] Lack of knowledge of processes makes management-related analyses difficult, and these are often partially evaluated, based on mammography, test results, and cancer mortality. Organized screening targets asymptomatic patients and should be associated with a hierarchical and effective network of examinations until diagnosis, which should be rapid, comprehensive, and effective. This overrides the allocation of technological, financial and human resources.

It is estimated that the SUS system is responsible for 75% of health at the national level, with the supplementary healthcare system being responsible for the rest of the population. Breast cancer is a population-based disease and, therefore, the limitations of the SUS affect disease diagnosis, leading to advanced stages and respective increased mortality curves.[32] Logistical and technological limitation leads to delayed examinations and diagnosis,[8] with low population coverage,[32,43] seen in our study population, and is one of the main barriers related to the health system, as presented in the results section. The SISMAMA system is an important auxiliary tool for health management,[13] but there is much to be done. There is a need for evaluation of populations vulnerable to mammography,[3,5,17,18] as well as strategies to improve their access.[5,24]

Law No. 11.664 authorized on 04/29/2008 access to mammography for women over 40, but it was superseded by Directive No. 1253 on 12/11/2013, which limited mammography to the age group of 50-69 years, according to the public policies related to the age range that should undergo mammography. Currently, the Ministry of Health suggests that the examination should target the age range of 50-69 years,[5] in keeping with the installed technological base and availability to the population. A Brazilian publication questions the possibility of screening in the age group of 45-69 years,[44] as recommended in 2016 by the American Cancer Society.[39] The difficulties and results observed in Brazilian literature[3,5,24,38] limit the proper analysis of the subject, due to the lack of results related to the second round screening, where we evaluate breast cancer detection rate in subsequent-screening examinations and indicators related to the control of quality.[40]

The health system must be structured, allowing access to mammography, complementary examinations, diagnosis and effective treatment. There is a migration of patients within the SUS that reflects its hierarchical system, but logistical and structural limitations increase the time between diagnosis and treatment.[25] Mammographic screening is the responsibility of primary health care, and is associated with procedures of small and medium complexity. Oncological treatment is the responsibility of Oncology Centers (CACONs), which perform procedures of medium and high complexity. Directive No. 3535 issue on 09/02/1988, and Health Ministry Directive No. 741 issue on 12/19/2005 regulate the hierarchy of the oncology system, but because they are treatment services, the stage at the beginning of treatment is a reflection of the diagnostic conditions and the structuring of the health system. Hospital cancer registries show us advanced stages of diagnosis, which reveals the logistic limitations prior to treatment, associated with longer periods until diagnosis,[8] with many symptomatic patients presenting advanced disease.[8] It is interesting that breast cancer patients in high-demand centers and referral hospitals have better survival rates,[30] possibly due to logistical facilities and use of treatment protocols.

The absence of prospective and randomized studies on the subject in the literature evaluated is a limitation of our study, but this has already been reported in other developing countries.[45] We report the main results found in Brazil comparing them with the main results reported

in the literature. We attempted to present the subject in a global manner, not judging its merit, in order to evaluate the results of the absence of organized screening, presenting possible reasons that could influence the facts and be used to further structure the health system. Our study does not aim to judge the health system, but to contribute to the reflection on the subject, since a structure is being constructed and progress has occurred, as shown in the trend curves of different macro-regions.

In view of the scenario presented above, we observed that breast cancer patients in Brazil are mostly dependent on the public health system, the SUS, which is responsible for the diagnosis and treatment of the vast majority of the population. Limitations of the health system are clear given the advanced stage of disease at diagnosis, and limit survival outcomes. Measures related to increased quantity, quality and regularity of mammography will allow adequate coverage of asymptomatic patients. Establishing a rapid and effective diagnostic flow, coupled with appropriate treatment, within a hierarchical context are important steps to be taken to promote women's health.

Conclusion

In Brazil, the number of mammography machines in operation is limited, time to diagnosis is high, and disease stage at diagnosis is advanced. Population coverage is low, with problems related to the quality of mammography. Lower income, less educated and non-white patients are the most vulnerable. There are reports of collective actions to provide mammographic examination, and early experiences of opportunistic screening. The flow of diagnosis and treatment should be improved. Inequality in mortality is a reflection of screening and treatment limitations, so that well-structured public services perform better.

Resumo

Rastreamento do câncer de mama no Brasil. Barreiras relacionadas ao sistema de saúde

Objetivo: Identificar fatores relacionados ao sistema de saúde que determinam atraso no diagnóstico do câncer de mama no Brasil.
Método: Utilizou-se metodologia de revisão sistemática nas bases de dados PubMed e LILACS, pesquisando os termos "Breast cancer", "system of health" e "Brazil or Brasil". Não se avaliou a qualidade da publicação, mas seu conteúdo, sendo ele categorizado em função da metodologia PRISMA baseada no PICTOS. Na data limite de 16/12/2015, foi possível identificar 94 publicações na PubMed e 43 publicações na LILACS. Avaliando o título e resumo, e excluindo-se 21 publicações repetidas, foi possível identificar 51 publicações para avaliação completa, na qual foram excluídos 21 artigos, restando 30 publicações.
Resultados: Observou-se que a base de mamógrafos é limitada, o tempo até o diagnóstico é elevado, e o estadio ao diagnóstico é avançado. A cobertura populacional é baixa, havendo problemas na qualidade da mamografia. As pacientes de menor renda, menor escolaridade e etnia não branca são as mais vulneráveis. Observam-se exemplos de mutirões e experiências iniciais de rastreamento. Necessita-se de aprimoramento do fluxo de diagnóstico e tratamento. A desigualdade na mortalidade é reflexo da estrutura para rastreamento e tratamento, observando-se melhores resultados em serviços públicos bem estruturados.
Conclusão: Há diversas barreiras relacionadas ao sistema de saúde que refletem no estádio avançado ao diagnóstico e limitam os resultados na sobrevida. O estabelecimento de um fluxo de diagnóstico e tratamento rápidos e efetivos, dentro de um contexto hierarquizado, são importantes etapas a serem aprimoradas dentro do contexto da saúde pública.

Palavras-chave: neoplasias da mama/prevenção e controle, sistemas de saúde, programas de rastreamento, mamografia, Sistema Único de Saúde (SUS).

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