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SUMMARY

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REVIEW ARTICLES

Many reasons to talk about suicide

Muitas razões para falarmos sobre suicídio

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Approximately 1 million people die each year from suicide worldwide.[1] This is the second leading cause of death among adolescents and young adults.[1] Although recognized by the World Health Organization as a public health priority, mental disorders and suicide are beset by ignorance and stigma, which hinders proper treatment and prevention.

Recently, teenage suicide has been the subject of news because of a supposed online challenge called "Blue Whale," probably originating in Russia, which would encourage risky behavior among participants and ultimately suicide. It has also been widely discussed after being portrayed in an American drama series, *13 Reasons Why*, which has been watched by many young people in Brazil and the world. Both the online challenge and the television drama pose risks, but the community's interest in the subject is an important opportunity to educate people about suicide.

The online challenge, in line with many websites, blogs and messaging lists that encourage other risky behaviors (such as self-mutilation and restrictive eating behavior) found its way in the lives of fragile adolescents who often already suffer from mental illnesses. Associated with psychopathology, these adolescents frequently face social isolation and are part of families that are unable to identify and deal with their difficulties. While using digital tools, adolescents somehow feel understood and belonging to a social group. Dysfunctional symptoms and behaviors are thus justified and encouraged, and ultimately intensified.

The drama series, on the other hand, has a less explicit potential to stimulate suicidal behavior, even though its producers advocate a positive effect on young people. The plot portrays suicide as a glamorized act that is the consequence of specific events and cannot be prevented, achieving specific functions successfully, which is mainly revenge. Also, suicide is shown explicitly, emotionally impacting any viewer, especially the most fragile ones. In view of these characteristics,[2] the experience of a fiction narrative such as these for those who already have risk factors for suicide, including depression, family history of suicide, previous suicide attempts or previous self-injury, suicidal ideation and lack of social support, can actually represent encouragement for suicidal behavior, especially in the presence of other triggers, such as access to lethal methods, impulsivity, substance abuse and acute stress events.[3]

Suicide is still marked by ignorance and stigma not only in society as a whole, but also within the medical community, both in relation to the suicide of patients and the physicians themselves. It is estimated that 45% of people who commit suicide consulted a physician in the month prior to their death, and there is rarely any documentation of suicide risk assessment.[4] Many doctors mistakenly think that those who talk about suicide do not really want to kill themselves, that asking about suicidal intent and plan for those who feel depressed may encourage suicide, or that people do not want to talk about their thoughts about death. These are all myths that interfere with proper evaluation and management of the cases.

As for physician suicide, male doctors have a 1.41 times higher rate than the general male population, while female doctors have a 2.27 times higher rate than that observed in the general female population.[5] Surprisingly, despite substantially higher rates of depression[6] compared to the general population, and also suicide,[5] depressed students and physicians[6] and suicide victims[7] have lower treatment rates. Among the reasons for not seeking treatment, stigma and self-stigma, denial of the presence of depression and fear of the negative impact that psychiatric treatment may have on performance and professional image in an extremely competitive environment have a strong effect. In addition to depression, suicide risk factors among medical students

and physicians include temperament characteristics such as perfectionism, being too demanding of themselves, and rigid cognitive models such as not allowing error and not placing oneself in the position of those who need care. In addition, pressure at work, conflict between family and patient dedication and career, burnout, and sleep restriction are important risk factors.[8,9]

In order to reduce suicide rates globally, it is necessary to reduce ignorance and stigma about mental disorders. Recently, the World Health Organization has taken an important step in this direction. For the first time, the WHO chose, as a theme for World Health Day (04/07/2017), a mental health condition: depression. The campaign slogan, "Let's Talk," emphasizes the importance of reducing stigma and depression. Medical doctors, regardless of specialty, should be aware of the mental health of their patients – as well as their own – and suicide risk should be evaluated whenever indicated. Anti-suicide strategies need to be part of public health policies, as well as school and university policies. A change in medical culture – regarding the requirements of training, the balance between professional and personal life, and the ways that the profession can affect a doctor's mental health – is in order.[10] Doctors seeking and offering help for mental suffering should be culturally accepted and encouraged. Silence, shame and fear are great obstacles to psychiatric care that need to be removed.

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Guidelines for the treatment of central nervous system metastases using radiosurgery

Diretrizes para tratamento de tumores metastáticos de sistema nervoso central com radiocirurgia

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

Grades of recommendation and levels of evidence

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

Objective

The purpose of this guideline is to evaluate the radiosurgery technique for the treatment of patients with central nervous system (CNS) metastatic tumors.

Description of evidence collection method

Through the elaboration of six relevant clinical questions related to the proposed theme, we sought to present the main evidence regarding safety, toxicity and effectiveness of radiosurgery in the treatment of CNS metastases. The study population consisted of male and female patients of all ages, with metastatic CNS cancer independent of histological type and presence or absence of comorbidities. For this, a systematic review of the literature was carried out in primary scientific databases (Medline – PubMed; Embase – Elsevier; Lilacs – Bireme; Cochrane Library – Record of Controlled Trials). All articles available through Thursday, April 2, 2015 were considered. The search strategy used in Medline searches is described in Appendix 1. The articles were selected based on critical evaluation, seeking the best evidence available. The recommendations were elaborated after discussion with the elaboration group composed by three members of the Brazilian Society of Radiotherapy. The guideline was reviewed by an independent group, which specializes in evidence-based clinical guidelines. After completion, the guideline was released for public consultation for 15 days, the suggestions obtained being forwarded to the authors for evaluation and possible insertion in the final text.

Introduction

Brain metastases are the most frequent intracranial tumors in the adult population. It is estimated that 6 to 30% of patients diagnosed with malignant systemic disease will have cerebral metastases at some point in their natural progression.[1-3]

In recent years, the incidence of brain metastasis has been increasing mainly due to the implementation in clinical practice of cranial magnetic resonance imaging (MRI), which has good accuracy in detecting early neoplastic lesions in the CNS. In addition, there was a significant improvement in the control of extracranial disease, something associated with the use of new systemic therapies available for the treatment of several cancers.[4-6]

In the adult population, the primary tumors most frequently related to the development of CNS metastases are lung, melanoma, kidney, breast and colorectal cancer.[7]

Regarding pathogenesis, CNS metastases are most commonly due to hematogenous spread. Metastases are usually located directly at the junction of the gray matter and white matter where the diameter of the blood vessels

is reduced favoring the clusters of tumor cells; 80% of metastases appear in the cerebral hemispheres.[8]

Clinical manifestations vary according to the number, volume, and location of CNS metastases. The main symptoms described are headache, nausea, vomiting, focal neurological dysfunction and cognitive dysfunction.[9]

Local treatment for CNS metastases depends primarily on the prognosis of the clinical condition and age of the patient. There are several tools available to aid in the classification of patients with brain metastasis regarding prognostic factors and their possible impact on median survival. These tools may therefore facilitate the decision of the most appropriate local treatment for cancer.[10,11]

For patients considered to have poor prognosis, treatment should be focused on the control of symptoms caused by cerebral metastasis aimed at maintaining neurological functioning and quality of life. For those with good prognosis, local treatment should aim to eradicate and control metastatic CNS disease. In this scenario, the options available are surgical resection and radiotherapy (whole brain radiotherapy or radiosurgery), either alone or combined.

Radiosurgery is a radiotherapy technique that is capable of delivering high doses of radiation at pre-defined small target volumes. It is a complex technique that utilizes multiple treatment fields (coplanar and non-coplanar beam plans) that converge to the desired target(s), allowing adjacent healthy tissues to be significantly spared and treatment to be performed quickly, non-invasively and safely.[12]

1. What is the toxicity of radiosurgery for brain metastases?

Toxicity after the use of radiosurgery is generally low. Patients are unlikely to have side effects that negatively impact their quality of life.

Fokas et al. showed levels of acute toxicity grade 3 (headache, nausea and vomiting) as low as 3% in patients undergoing radiosurgery. Similarly, rates of chronic toxicity grade 3 (alopecia, headache, motor and neurocognitive deficits, visual and auditory deficits) of only 6% were observed.[13] (**B**)

Kim et al. used the Common Terminology Criteria for Adverse Events, version 3.0 to measure the toxicity of 58 patients who underwent radiosurgery for the treatment of CNS metastases. Ten patients had some degree of toxicity identified (five patients with grade 1 toxicity, one patient with grade 2 toxicity, and four patients with grade 3 toxicity). The events observed included headache, vertigo, hemiparesis, visual acuity deficit or cerebral necrosis.[14] (**B**)

Flickinger et al. demonstrated that only four patients out of 116 evaluated developed perilesional edema with worsening of neurological symptoms requiring the introduction of supportive therapy with steroids. Of the entire cohort of patients, intracranial tumor hemorrhage occurred in only three (2.5%) patients.[15] (**B**)

Lim et al. conducted a randomized phase 3 clinical trial with patients diagnosed with non-small cell lung cancer with 1 to 4 brain metastases who underwent radiosurgery followed by chemotherapy, or chemotherapy alone. Treatment with radiosurgery was well tolerated and there was no difference in neurocognitive function between the two study groups.[16] (**A**)

Even when the tumor is located in critical areas, radiosurgery is feasible. Luther et al. observed that motor function improves by 31% or remains stable in 50% of patients with brain metastases located in the motor cortex treated with radiosurgery.[17] (**B**) Other authors have evaluated the role of radiosurgery in patients with brainstem metastases. Asymptomatic perilesional edema occurred in 4%, while 2.4% of the patients developed tumor hemorrhage at the treatment site.[18,19] (**B**)

Recommendation

Radiosurgery has low morbidity and is associated with low rates of side effects.

2. What is the maximum number and size of metastatic lesions in the brain for radiosurgery treatment to be performed?

Empirical doses and volume thresholds were established for single dose radiosurgery in order to minimize the risks of side effects. Existing recommendations define up to four lesions and a maximum diameter of 4 cm as the ideal group for the indication of primary radiosurgery, or dose boost after whole brain irradiation[20-23] (**A**) (Table 1). Nevertheless, there are retrospective series of patients with up to 15 metastatic lesions treated with radiosurgery who had clinical progression, complications and responses similar to those treated with up to four lesions.[24,25] Some authors suggest that total tumor volume is more important than the absolute number of lesions,[26-28] but this statement requires further investigation. (**B**)

TABLE 1 Main studies recommending adequate number and size of lesions to indicate radiosurgery.

Study	Grade of recommendation	Number of lesions	Size (diameter)
RTOG 90-05[23]	A	1	< 4 cm
RTOG 95-08[20]	A	1-3	3 cm
Kondziolka[21]	A	2-4	≤ 25 mm
Mehta[22]	A	3-4	4 cm

Recommendation

Radiosurgery should preferably be performed in patients with up to four lesions and a maximum diameter of 4 cm.

3. What are the advantages of radiosurgery compared to whole brain radiotherapy?

Radiosurgery has the advantage of offering a more conformed and localized treatment, with larger ablative doses than whole brain radiotherapy.[29-32]

Thus, it minimizes the deleterious effects of whole brain radiotherapy with regard mainly to neurocognitive deficit and declining quality of life.[22,30,32-34] (**A**)

Another important point is that radiosurgery offers higher rates of local control, even in patients with histologically radioresistant tumors (requiring higher doses of ionizing radiation, e.g., melanoma, renal tumors, and sarcoma) compared with whole brain radiotherapy.[35,36] (**B**)

Recommendation

Radiosurgery decreases the risk of neurocognitive decline and can positively impact the patients' quality of life.

4. What is the effectiveness of radiosurgery in the approach of patients with brain metastases?

Radiosurgery alone for the treatment of brain metastases produces local control rates ranging from 65 to 94%.[15,37,38] (**B**)

The main factors related to local control after radiosurgery are: characteristics of tumor lesion and treatment dose. Doses lower than 14 Gy and cystic and necrotic lesions are associated with a greater likelihood of recurrence.[39,40] (**B**)

The efficacy of radiosurgery does not depend on the histological type of the primary tumor since local control rates are similar in both radiosensitive and radioresistant tumors.[41-43] (**B**)

Recommendation

Radiosurgery is effective for the treatment of patients with brain metastases, even in those with histologically radioresistant primary tumors.

5. What are the benefits and disadvantages of performing two treatment modalities involving radiosurgery and whole brain radiotherapy in patients with brain metastases?

There have been some randomized phase 3 trials evaluating the use of radiosurgery (RS) associated with whole brain radiotherapy (WBRT) or WBRT alone in patients with brain metastases and limited disease (1 to 4 intraparenchymal lesions).[20,21]

Aoyama et al. reported a 12-month CNS recurrence rate of 46.8% for the WBRT+RS group and 76.4% for RS alone ($p<0.001$), and 73 and 89% ($p=0.002$) of local control for the RS and WBRT+RS groups, respectively. However, there was no difference in overall survival between groups.[29] (**A**)

Chang et al. reported that patients treated with WBRT+RS have a rate of learning decline and mean functional memory of 52 versus 24% in the RS group. Although brain metastasis-free survival rates at one year were higher in the WBRT+RS (73%) than in the RS (23%) group, there was no difference in overall survival and RS patients were easily rescued with new therapy.[30] (**A**)

Brown et al. presented data according to which the addition of WBRT to RS, despite improving local control (50.5 x 84.9% at one year with RS alone and WBRT+RS, respectively), did not lead to an increase in overall survival and was negatively correlated with some cognitive decline, especially for memory, verbal fluency and immediate memory in the WBRT+RS group ($p<0.05$).[44] (**A**)

In a systematic review that included the meta-analysis of individual data from randomized clinical trials, the authors noted that in patients aged less than 50 years, with 1 to 4 lesions and good performance, the use of RS alone led to longer overall survival, whereas the initial omission of WBRT did not produce any more failures in CNS.[45] (**A**)

In addition, despite worse local control rates and higher rates of salvage treatment, RS proved in the economic analysis to be more cost effective than WBRT+RS.[46] (**B**)

Recommendation

The addition of whole brain radiotherapy in patients treated with radiosurgery allows greater intracranial local control, despite no positive impact on overall survival. The use of whole brain radiotherapy may be related to worsening of cognition, verbal function and memory.

6. After surgical resection of brain metastases, is there a role for adjuvant radiosurgery in the surgical bed?

In the postsurgical adjuvant scenario, one of the standard treatment regimens is to perform whole brain radiotherapy.[47-48]

However, in order to avoid the detrimental effects of whole brain radiotherapy, some authors advocate the use of adjuvant radiosurgery in the surgical bed.

A phase 2 clinical study evaluated the use of radiosurgery with a median dose of 18 Gy in patients with performance status ≥ 70 and ≤ 2 resected brain metastases. Local and regional failure rates of 22 and 44%,

respectively, were demonstrated at 12 months. There was more benefit for lesions < 3 cm and deep.[49] (**B**) Several other studies with patients treated similarly showed local control rates of approximately 75 to 90% and 60 to 80% after one and two years of follow-up, respectively. These results are comparable with the local control achieved in patients who received postoperative whole brain radiotherapy.[50-54] (**B**)

Moreover, postoperative radiosurgery improves local control compared with observation alone for completely resected brain metastases. Data from a randomized phase 3 trial demonstrated that local control rates are statistically significant higher in patients who received radiosurgery (local control rates in 6 months and 12 months were 83%, 57% and 72%, 45%, for radiosurgery and observation groups, respectively).[55] (**A**)

Recently, two important studies were presented in ASCO and ASTRO. Kayama et al. conduced a non-inferiority phase 3 trial (JCOG0504) to assess the effectiveness of radiosurgery for residual and recurrent brain metastases after surgical resection. Patients were randomized to receive radiosurgery or whole brain radiotherapy. The overall survival rates were similar in both groups.[56] (**A**) Similarly, Brown et al. randomized patients with 1 to 4 brain metastases to either whole brain radiotherapy or radiosurgery after surgical resection. More cognitive deterioration was observed in whole brain radiotherapy group. No differences in overall survival were demonstrated between the groups and better quality of life was reported in the radiosurgery arm.[57] (**A**)

Recommendation

After surgery, adjuvant radiosurgery may be employed to replace whole brain radiotherapy.

Appendix 1

Search strategy – MEDLINE

(Central Nervous System [Mesh] OR Central Nervous Systems OR Nervous System, Central OR Nervous Systems, Central OR System, Central Nervous OR Systems, Central Nervous) AND (Neoplasm Metastasis [Mesh] OR Metastases, Neoplasm OR Neoplasm Metastases OR Metastasis OR Metastases OR Metastasis, Neoplasm) AND (Radiosurgery [Mesh] OR Radiosurgeries OR Radiosurgery, Stereotactic OR Radiosurgeries, Stereotactic OR Stereotactic Radiosurgeries OR Stereotactic Radiosurgery OR Gamma Knife Radiosurgery OR Gamma Knife Radiosurgeries OR Radiosurgeries, Gamma Knife OR Radiosurgery, Gamma Knife OR Stereotactic Body Radiotherapy OR Body Radiotherapies, Stereotactic OR Body Radiotherapy, Stereotactic OR Radiotherapies, Stereotactic Body OR Radiotherapy, Stereotactic Body OR Stereotactic Body Radiotherapies OR CyberKnife Radiosurgery OR CyberKnife Radiosurgeries OR Radiosurgeries, CyberKnife OR Radiosurgery, CyberKnife OR Radiosurgery, Linear Accelerator OR Linear Accelerator Radiosurgeries OR Radiosurgeries, Linear Accelerator OR Linear Accelerator Radiosurgery OR Radiosurgery, Linac OR Radiosurgeries, Linac OR LINAC Radiosurgery OR Radiosurgeries, LINAC)

Conflict of interest

The authors declare no conflict of interest.

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Foix-Alajouanine syndrome mimicking a spinal cord tumor

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Summary

Subacute necrotizing myelopathy (SNM) or Foix-Alajouanine syndrome is a rare disease characterized by progressive neurological dysfunction caused by a spinal dural arteriovenous fistula (AVF). Radiological diagnosis is usually suspected when there is intramedullary nonspecific enhancement and perimedullary flow voids. Ring-enhancement is rarely reported in the scope of AVF, which poses a diagnostic challenge and raises the suspicion of a spinal cord tumor. In such situations, biopsy can be required and delay proper diagnosis. We report the case of a patient with SNM, who underwent biopsy on the assumption of it being a spinal cord tumor.

Keywords: dural arteriovenous fistula, Foix-Alajouanine syndrome, spinal cord glioma, subacute necrotizing myelopathy.

Subacute necrotizing myelopathy (SNM) is an uncommon disease characterized clinically by progressive neurological dysfunction.[1,2] In most of the patients, it is caused by a spinal dural arteriovenous fistula (dAVF), also known as Foix-Alajouanine syndrome.[1,3] dAVF leads to spinal venous hypertension and infarction, as the pathological end-stage of the disease.[1] Such acute/subacute deterioration occurs in 14.8% of the patients.[4]

This 71-year-old lady was admitted to our department after suffering from a progressive neurological deterioration of the lower limbs, as well as sphincter dysfunction over the last two years. Five days before admission, the patient was affected by severe lumbar pain, which was followed by rapid severe paraparesis. Imaging revealed an expansive lesion at D12-L1 with ring-enhancement and subtle perimedullary flow voids (Figure 1). The patient underwent biopsy of the lesion, on the assumption of it being a spinal cord tumor. Initially, it was misinterpreted as a high-grade glioma on frozen specimens, but final histological analysis revealed the typical findings of SNM. Superselective spinal angiography confirmed dAVF diagnosis (Figure 1), and the patient was taken to surgery for definitive treatment.

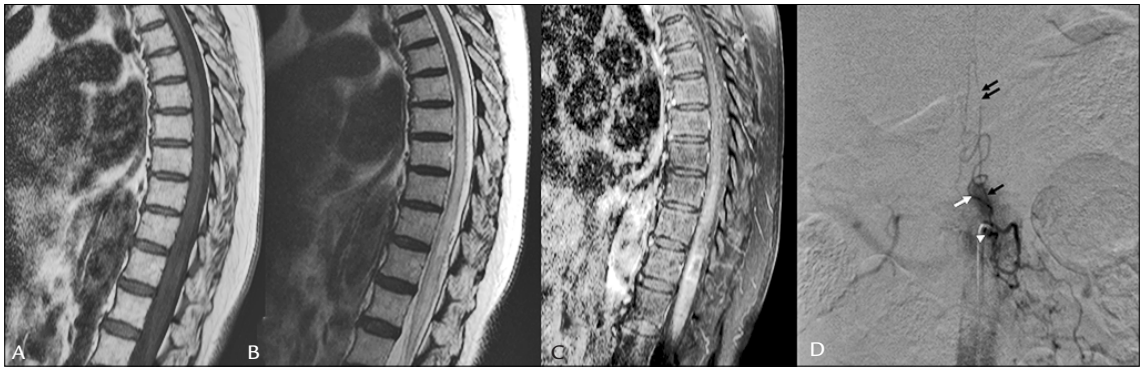

FIGURE 1 Sagittal T1- (A), T2- (B), and T1-weighted with gadolinium enhancement and fat suppression (C) showed diffuse fusiform enlargement of the spinal cord up to the level of the conus medullaris together with ring-like enhancement at D12-L1. A subtle serpentine pattern of flow voids was observed on T2-weighted images (B). In D, superselective angiogram in frontal view revealed enlarged vessels on the left side of the spinal canal at the level of D12 (white arrow head), as well as the Adamkiewicz artery (black arrows) and the draining vein (white arrow).

SNM imaging in the scope of dAVFs typically shows focal enlargement of the spinal cord, isointense signal on T1-weighted images, intramedullary increased signal and perimedullary flow voids on T2-weighted images, as well as nonspecific enhancement.[5] Ring-enhancement is rarely reported,[1] which poses a diagnostic challenge and raises the suspicion of a spinal cord tumor. In such situations, biopsy may be required and delay proper diagnosis.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Síndrome de Foix-Alajouanine simulando um tumor intramedular espinal

Mielopatia necrotizante subaguda (MNS) ou síndrome de Foix-Alajouanine é uma doença rara que se caracteriza por disfunção neurológica progressiva causada por uma fístula arteriovenosa espinal dural. O diagnóstico radiológico é comumente suspeitado quando aparece captação não específica de contraste e de artefatos de fluxo (*flow voids*) perimedulares. Raramente, a captação de contraste exibe o aspecto em anel, constituindo um grande desafio diagnóstico. Nesses casos, o principal diagnóstico diferencial é um tumor intramedular, e os pacientes são encaminhados para biópsia da lesão, atrasando o diagnóstico definitivo. Relatamos o caso de uma paciente com MNS, a qual foi submetida à biópsia da lesão em virtude de suspeita de tumor intramedular.

Palavras-chave: fístula arteriovenosa espinal dural, síndrome de Foix-Alajouanine, tumor de medula espinal, mielopatia necrotizante subaguda.

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Assessment of HER-2 status in invasive breast cancer in Brazil

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Summary

Objective: To characterize the frequency of HER-2-positive breast cancer in Brazil.
Method: In this prospective observational study, we first ascertained the HER-2 status of invasive breast cancer specimens by automated immunohistochemistry (IHC). For specimens classified as 2+ by IHC, we performed in situ hybridization (ISH).
Results: From February, 2011 to December, 2012, 1,495 breast specimens were registered, and 1,310 samples collected at 24 centers were analyzed. Median patient age was 54 years, and the majority of samples were obtained from segmental (46.9%) or radical mastectomy (34.4%). The predominant histological type was invasive breast carcinoma of no special type (85%), 64.3% had tubule formation (grade 3), and estrogen/progesterone receptors (ER/PR) were positive in 77.4/67.8% of the specimens analyzed, respectively. Using IHC, we found a negative HER-2 status (0 or 1+) in 72.2% of specimens, and 3+ in 18.5%; the 9.3% scored as 2+ were further analyzed by ISH, of which 15.7% were positive (thus, 20.0% of samples were HER-2--positive by either method). We found no association between HER-2 scores and menopausal status or histological type. Tumors classified as 3+ came from younger patients, and had higher histological grade and less frequent expression of ER/PR. In the North region of Brazil, 34.7% of samples were 3+, with lower frequencies in the other four regions of the country.
Conclusion: Our findings provide estimates for the frequency of HER-2 positivity in Brazil and raise the hypothesis that biological differences may underlie the different distribution of breast-cancer phenotypes among different Brazilian regions.

Keywords: breast neoplasms, immunohistochemistry, in situ hybridization, erbB2, trastuzumab, HER-2.

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Introduction

Breast cancer, which affects one out of eight US women during their lifetime,[1] is the second most common tumor worldwide, with an estimated 1.67 million new cases and 522 thousand deaths in 2012.[2] In Brazil, breast cancer is the most common tumor among women, affecting almost 60,000 patients in 2014.[3] Currently, breast cancer is considered a group of different diseases on the basis of molecular subtypes, with this classification bearing relevant prognostic and predictive implications.[4] Between 15 and 20% of breast tumors display *HER-2* gene amplification or overexpression of the HER-2 protein,[5-7] a transmembrane tyrosine kinase receptor involved in cell proliferation and migration that confers worse prognosis, with faster disease progression and decreased survival, compared with HER-2-negative tumors.[8] One of the most important advances in breast cancer therapy has been the introduction of trastuzumab and other HER-2-targeting antibodies, which increase the survival of patients with metastatic disease,[9-11] and reduce the risk of relapse in early

stages of the disease.[12-14] As a result of these potential benefits, HER-2 testing is currently recommended for primary, recurrent and metastatic breast cancer lesions.[7]

In order to establish tumor HER-2 status in the clinic, a prerequisite for anti-HER-2 therapy, a paraffin-embedded tissue block of invasive breast carcinoma is required. When the primary tumor is assessed, specimens may be obtained through a core-needle biopsy, as well as from an incisional or excisional surgical procedure.[7] More often, one of two methods is routinely used for the assessment of HER-2 status: immunohistochemistry (IHC) and one of the variants of in situ hybridization (ISH), namely fluorescent ISH (FISH), chromogenic ISH, and silver ISH. IHC is more widely available; however, it is more prone to interpretation error. Conversely, ISH methods have the disadvantages of requiring better tissue quality, being more expensive and technically demanding than IHC and of being limited to only a few centers.[15] Because each assay type has diagnostic pitfalls, an algorithm has been proposed by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP).[7] As a result, samples classified as negative or positive by validated IHC analysis of their invasive tumor component require no further testing, whereas equivocal tests (i.e., samples classified as 2+ by IHC) should be followed by ISH testing.[7]

There is a wealth of information in the literature regarding the frequency and determinants of HER-2 positivity in many countries and settings. On the other hand, only a few studies have been conducted in Brazil, most of which relatively small in size or retrospective in nature.[16-18] In the current study, we prospectively attempted to investigate the frequency of HER-2-positive breast cancer in a large sample of Brazilian women, along with the standardization of preanalytic procedures used in the assessment of HER-2 and the association between HER-2 status and various tumor and patient features, including geographic location.

Method

Role of the sponsor and ethical aspects

This study was sponsored by Roche Brazil, which participated in the design, analysis and publication of results. The sponsor appointed a Scientific Committee, composed by pathologists and a medical oncologist, which was responsible for study oversight and which vouches for the accuracy of the data and the current manuscript. All participating patients provided written informed consent, and the study was approved by the Ethics Committees of all participating institutions. The initial version of the manuscript and subsequent changes based on input from all authors was under the responsibility of a medical-writing company (Dendrix, São Paulo).

Study oversight

In order to standardize the technique, the sponsor provided initial training with regard to study procedures, including the performance of IHC and ISH for HER-2, to all participating institutions. Positive and negative controls were provided by the Scientific Committee to participating laboratories. During the conduction of the study, the Scientific Committee regularly assessed the quality of the local readings, providing further training, if necessary.

Selection of patients and samples

In this prospective, observational study, an attempt was made to sequentially collect all samples of primary invasive breast cancer identified at participating pathology laboratories in the five geographic regions of Brazil during a defined period of time (from February, 2011, to December, 2012). Eligible patients were women with no neoadjuvant therapy regimen, and surgical specimens had to be obtained by radical mastectomy or segmentectomy, or histological material obtained by core-needle biopsy, or conventional surgical biopsy. Samples for which there was insufficient residual material for IHC and ISH were excluded from analysis. For each sample, locally collected data were centrally registered regarding preanalytic procedures, tumor size and location, margin status, histological type, architectural, nuclear and histological grade,[19] mitotic activity, presence of necrosis, lymphatic invasion and lymphoplasmacytic response, the number and nature (sentinel or not) of dissected and involved lymph nodes, and the presence and features of ductal carcinoma in situ (DCIS). IHC for estrogen receptor (ER), progesterone receptor (PR) and Ki-67 was performed at each participating laboratory using local standards, with expression of ER/PR in more than 1% of cells being considered positive. Data were centrally collected regarding antibody used, dilution, incubation time and temperature, antigen retrieval, amplification system, and result (negative or positive, according to the percentage of reactivity in the invasive neoplasm).

IHC analysis for HER-2

For HER-2, the IHC procedure was performed locally at each participating laboratory in an automated fashion, using Ventana equipment (Ventana Medical Systems, Tucson, AZ). Fixation was performed using 10% neutral buffered formalin at 15 to 20 times the volume of tissue

and with the goal of penetrating no more than 2 to 3 mm of solid tissue or 5 mm of porous tissue in a 24-hour period. Tissue fixation was performed in sections ≤ 3 mm for 4 to 8 hours at room temperature (15-25°C). Sections of 5 µm were placed on electrically charged glass slides, samples were incubated with primary rabbit anti-HER-2 antibody PATHWAY® (4B5), and the UltraView DAB detection kit was used. All subsequent automated steps were undertaken using the BENCHMARK platform. A pathologist with IHC experience evaluated the controls and qualified the stained product before interpreting the results. Semi-quantitative grading of the reaction was used to classify each sample into one of four scores:[20] 0, cell membrane staining was absent or observed in less than 10% of the tumor cells; 1+, weak or incomplete staining of the membrane in more than 10% of the tumor cells; 2+, moderate to complete staining of the membrane in more than 10% of the tumor cells; 3+, complete intense staining of the membrane observed in more than 30% of the tumor cells. Samples classified as 0 and 1+ were defined as HER2-negative; 2+, as equivocal; and 3+, as HER2--positive. Samples classified as 2+ were further evaluated by ISH for confirmation of the gene amplification. Figure 1A depicts a representative case classified as score 3+.

ISH analysis for *HER-2*

A pathologist previously trained by Roche Research Department in microscopic interpretation of breast carcinoma samples, ISH procedures and recognition of single and amplified copies of HER-2 (analyzed in a common optical microscope, using objective lenses of the order of 40X to 60X) assessed the controls before interpreting the outcomes. *HER-2* gene was visible as a black signal (silver) and the chromosome 17 centromere (Chr17) was visible as a red signal (alkaline phosphatase). Figure 1B depicts a representative case. Signals were enumerated using 20X, 40X, 60X or 100X. Background silver and red markings were taken into account during enumeration. Only cells with representative diameters of the mean population of invasive carcinoma cells in the target area were evaluated. In genetically heterogeneous target areas for the number of *HER-2* copies, only representative cells of the population of invasive carcinoma with the largest mean number of signals were counted. Heterogeneity, polysomy and monoallelic deletion were noted, if present. Once the adequate target area was identified, the number of copies of *HER-2* and Chr17 present in 20 representative cells were evaluated. The status of the *HER-2* gene was given by the ratio of the mean number of *HER-2* copies to the mean number of copies of Chr17, per cell, in the invasive tumor component. *HER-2* gene status was classified as negative, when the *HER-2*/Chr17 ratio was below 2.0, and positive, when the *HER-2*/Chr17 ratio was above 2.2. Cases with *HER-2*/Chr17 ratio between 1.8 and 2.2 were more closely investigated by the enumeration of 20 additional cells, with the final ratio being calculated taking into account the 40 cells counted.

Statistical analysis

Given the descriptive nature of this study, no formal sample-size calculation was performed. Patient and tumor characteristics were summarized in aggregate and according to groups of interest. With the aim of investigating features associated with HER-2 status, comparisons among groups were made using the Chi-square test for categorical variables and analysis of variance for continuous variables, with data transformation or use of the non-parametric Mann-Whitney (two groups) or Kruskal-Wallis (three or more groups) tests for non-normally distributed variables. All statistical analyses were performed using SAS® software, version 9.3 (SAS Institute, Cary, NC), and two-tailed p-values < 0.05 were considered significant.

Results

Overall characteristics of the laboratories and patients

Twenty-four Brazilian laboratories from 22 of 27 Brazilian Sates/Federal District participated in the study. From February 2011 to December 2012, 1,495 specimens of breast tissue were registered in the study database, 185 of which were excluded from analysis: 124 were not assessed due to major protocol violations (often because samples were obtained before center activation [N=84] or signed informed consent was missing [N=21]). Therefore, a total of 1,310 samples were included in the analysis. The number of analyzed specimens per laboratory ranged from 3 to 188, with 22 of them contributing at least ten specimens and four contributing more than 100 specimens each. At sample collection, mean patient age was 55.4 years (range 22 to 93), and the state of origin was São Paulo (the most populous state in Brazil) and Rio Grande do Sul in 37.3 and 22.4% of cases, respectively. Among the patients with known menopausal status, 67.2% were postmenopausal.

Preanalytic procedures

Specimens were obtained from segmental mastectomy in 46.9% of cases, 34.4% came from radical mastectomy, 14.5% from large-core-needle biopsy, and 4.2% from conventional biopsy. The median time from surgery initiation to specimen collection was 1.2 hour; the median time

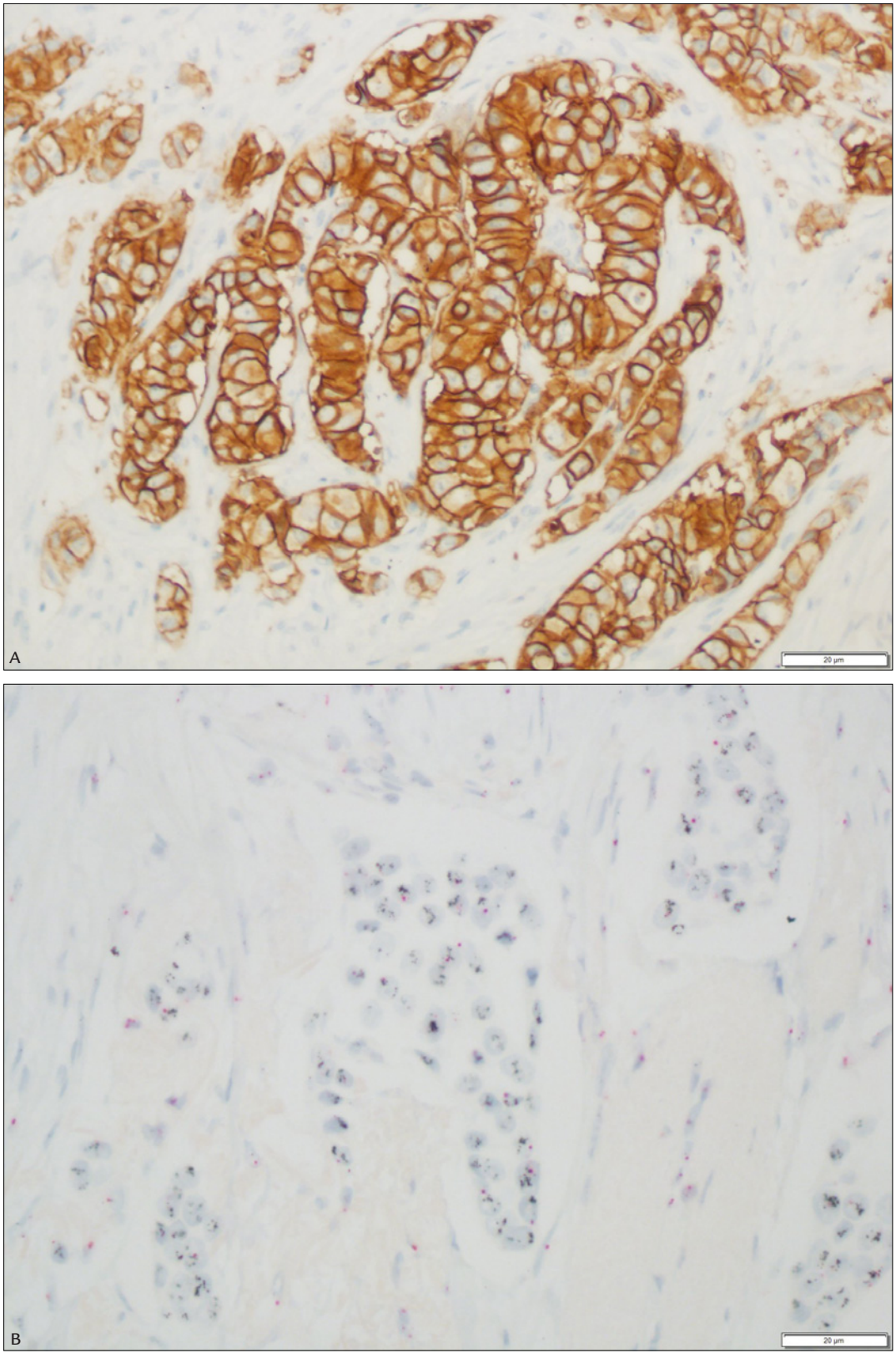

FIGURE 1 A. Representative microphotograph of a breast cancer specimen classified with a score of 3+ by immunohistochemistry (400x). B. Representative microphotograph of a breast cancer specimen classified as positive by in situ hybridization (400x).

from surgery to sample registration in the laboratory was 6.3 hours; the median time from sample registration in the laboratory to gross examination was 19.0 hours; and the median time from specimen collection to gross examination was 24.0 hours (for 29.3% of the specimens, this time exceeded 48 hours). Specimens were processed fresh in 12.4% of the cases, and buffered formalin was the most commonly used fixative solution (62.1%), followed by non-buffered saline formalin (36.0%).

Characteristics of tumor specimens

Considering the 1,310 patients, 58% had undergone a prior core biopsy, 7.7% had a prior surgical biopsy, and 5.6% had the primary tumor already resected. Considering the 1,310 tumor samples included in the analysis, 85% were invasive breast carcinoma of no special type (IBC), and 5.4% were invasive lobular carcinoma (ILC). Other histological types, including mixed IBC and ILC (1.8%), were less frequent. Tumors had a mean size of the long axis of 26.8 mm (range 0.7 to 170 mm), were in the left and right breast in 49.6 and 49.2% of the cases, respectively. In 24.8% of the samples, the quadrant was unknown, while 42.2% of the tumors were in the upper outer quadrant, and 18.8% were in the upper medial quadrant. Nipple involvement was reported in 8.7% of the 652 cases with the information available. The resection margin was involved in 11.2% of cases, and the mean distance to the nearest margin of the tumor was 8.7 mm. The most frequent features were poor tubule formation (grade 3; 64.3%), nuclear grade 2 (47.0%) and low mitotic index (54.7%). Necrosis in the infiltrative component was reported in 24.4% of the specimens, with a median estimated percentage of necrosis of 10.0%. Lymphovascular invasion was present in 37.9% of the specimens, and lymphoplasmacytic response was mild in 53.3%. The sentinel lymph node was assessed in 56.2% of patients, identified in 77.6% of those cases, and involved in 67.8% of the latter. The mean numbers of positive and resected lymph nodes were 2.6 and 7.3, respectively. DCIS coexisted with invasive carcinoma in 46.7% of specimens; among these, 44.9% had nuclear grade 3, and 55.9% had comedonecrosis. ER was tested in 80.9% of specimens, and was positive in 77.4% of these; PR was tested in 80.8% of specimens, and was positive in 67.8%. Ki-67 was assessed in 57.3% of the specimens, with a mean estimated percentage of reactivity in the invasive neoplasm of 29.2%.

HER-2 status

A mean of 101.9±120 days had elapsed between the date of surgery and the date of the IHC analysis, and 230±172.2 days until the ISH assessment. HER-2 analysis by IHC was possible in 99.4% of the samples, and results are displayed in Table 1. Using the ASCO/CAP criteria of 2007,[20] 72.2% of the specimens were negative, and 18.5% were positive. Among the 9.3% of samples with an IHC score of 2+, all of which undergoing assessment by ISH, HER-2 status was considered positive in 15.7% of the samples, negative in 73.6%, and inconclusive in 10.7% (Table 1). Thus, considering both methods, a total of 260 out of 1,302 specimens was HER-2-positive (20.0%; 95CI 17.9-22.3).

TABLE 1 HER-2 status of 1,302 analyzed specimens.

Method and result	Number (%)
Immunohistochemistry (N=1,302)	
0	627 (48.2%)
1+	313 (24.0%)
2+	121 (9.3%)
3+	241 (18.5%)
In situ hybridization (N=121)	
Negative	89 (73.6%)
Positive	19 (15.7%)
Inconclusive	13 (10.7%)
Either method (N=1,302)	
Negative or inconclusive	1,042 (80.0%)
Positive	260 (20.0%)

Features associated with HER-2 status

The association between selected patient/tumor features and HER-2 status was investigated using IHC scores (Table 2). There was no association between HER-2 scores and menopausal status when all IHC scores were considered. Likewise, there was no statistically significant association with histological type when a global test was used for the cross-tabulation of all IHC scores and histological types. However, HER-2 scores varied nominally according to individual histological types; for example, an IHC score of 3+ was found in only six of 69 (8.7%) invasive lobular carcinomas. Samples with a score of 3+ came from significantly younger patients, had a higher histological grade, and less frequent association with ER or PR expression (Table 2).

When HER-2 scores were compared across the five geographic regions of Brazil, samples from the North region of the country were more likely to present a score of 3+ than samples from other regions (Table 2). The distribution across the country regions was also investigated considering the following phenotypes defined based on the expression status of HER-2 and hormone receptors: phenotype I, tumors positive for ER or PR, but negative

TABLE 2 Association between patient/tumor features and HER-2 status by immunohistochemistry.

Features	HER-2 status				p-value
	0	1+	2+	3+	
Age, years					
Mean (±SD)	56.3±12.2	55.5±12.7	57.7±12.8	51.8±11.9	<0.001
Menopausal status					
Postmenopausal	69.7%	66.3%	72.9%	57.7%	0.065
Premenopausal	30.1%	33.2%	27.1%	41.1%	
Menarche	0.2%	0.5%	0	1.1%	
Histological grade*					
Mean (±SD)	6.4±1.5	6.4±1.5	6.8±1.4	7.1±1.4	<0.001
Estrogen receptor					
Positive	77.2%	87.4%	87.5%	58.2%	<0.001
Negative	22.8%	12.6%	12.5%	41.8%	
Progesterone receptor					
Positive	68.4%	78.1%	76.9%	47.0%	<0.001
Negative	31.6%	21.9%	23.1%	53.0%	
Geographic region					
Midwest	54.2%	16.7%	4.2%	25.0%	<0.001
North	40.8%	20.4%	4.1%	34.7%	
Northeast	55.2%	19.0%	4.9%	20.9%	
Southeast	47.1%	23.5%	12.0%	17.4%	
South	44.8%	30.1%	9.6%	15.5%	

SD: standard deviation.
*Histological grade was assessed using the system of Elston and Ellis.[19] For each patient, the grade is the sum of individual grades for architecture, nuclear grade and mitotic activity (each individual grade ranging from 1 to 3, and the total grade ranging from 3 to 9).

for HER-2 (0 or 1+ by IHC, or 2+ by IHC, but negative by ISH); II, tumors positive for HER-2 (3+ by IHC or positive by ISH), irrespective of the status of the hormone receptors; and III, triple-negative tumors (negative for HER-2, ER and PR). Since not all patients from all regions underwent ER/PR assessment, and given the exploratory nature of this analysis, no statistical tests were conducted; Figure 2 displays the distribution of the three phenotypes across geographic regions.

Discussion

The primary objective of the present study was to characterize the distribution of HER-2 status across Brazil, a large country with substantial ethnic and social heterogeneity. The estimated percentage of HER-2-positive breast tumors (20.0%) is in line with estimates from other countries.[20,21] With regard to previous studies from Brazil, Carvalho et al. have found a frequency of 19.4% of HER-2-positive tumors in a retrospective study using only IHC and involving 5,687 consecutive cases of invasive breast cancer assessed from July 2009 to March 2011.[16] Of note, these authors used the same ASCO/CAP definition used herein. We believe the patient sample investigated in the present study to be fairly representative of the general population of patients with breast cancer seen at public institutions from the Southeast and South regions of Brazil, which contributed nearly two-thirds of specimens, and which comprise 56.5% of the Brazilian population.[22] With a mean age of approximately 55 years, IBC in the vast majority of cases, and ER/PR expression in nearly two-thirds of cases, such patients may be considered a convenience sample from this country.

Breast cancer is a major health problem worldwide. Determination of the expression status of HER-2 and hormone receptors is currently required for all breast tumors in order to establish the best therapeutic approach in individual patients. The ASCO/CAP guidelines recommend that a Food and Drug Administration-approved IHC, bright-field ISH or FISH assay should be preferentially used for HER-2 testing.[7,20] Silver ISH is a rapid automated assay that has been shown to have a high concordance with FISH in determining the status of *HER-2* gene amplification in invasive breast carcinoma. In a study conducted by Papouchado et al., in which 298 samples

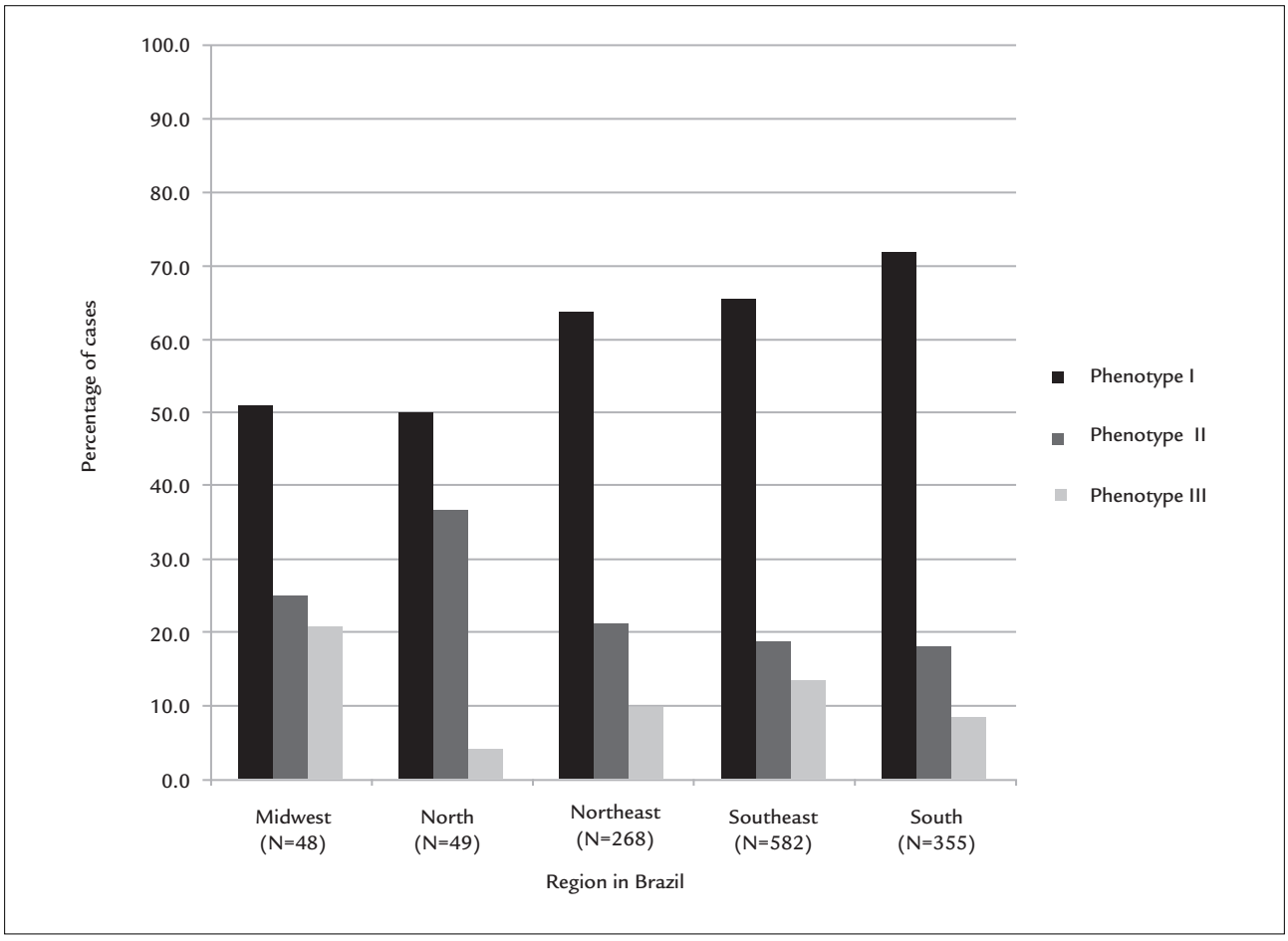

FIGURE 2 Distribution of tumor phenotypes per geographic region of Brazil, with number of samples analyzed in each region. Phenotype I denotes tumors positive for estrogen receptor (ER) or progesterone receptor (PR), but negative for HER-2 (0 or 1+ by immunohistochemistry [IHC], or 2+ by IHC, but negative by in situ hybridization [ISH]); II, tumors positive for HER-2 (3+ by IHC or positive by ISH), irrespective of the status of ER/PR; and III, triple-negative tumors (negative for HER-2, ER and PR). The sum of percentages in each region does not equal 100% due to missing data on ER/PR assessment.

were evaluated by ten pathologists, an overall agreement of 98.9% between silver ISH and FISH was observed.[23] Studies have shown a higher accuracy of HER-2 testing when it is performed at high-volume central reference laboratories rather than at local laboratories, with the discordance rate between local and central testing being as high as 26%.[24,25] A low concordance between local and reference laboratories has also been reported in Brazil, and the authors have argued that it may be related to inexperience with HER-2 scoring, a low-volume load of HER-2 assays, and technical issues related to IHC in local laboratories.[26] Given the impact of preanalytic variables IHC and FISH results,[27] and aiming at improving the accuracy of HER-2 testing, the ASCO/CAP guidelines include recommendations regarding type of fixative, time between sample collection and placement into fixative, and fixation duration. According to the 2007 guideline, time from tissue acquisition to fixation should be as short as possible, with samples for HER-2 testing being fixed in 10% neutral buffered formalin for a minimum of 6 and a maximum of 48 hours.[20] In the updated guideline, the maximum duration of fixation was altered to 72 hours.[7] In the present study, the median time from specimen removal to macroscopic examination was 24 hours, and for nearly one-third of specimens this interval exceeded 48 hours. For 162 specimens, processing was performed in fresh tissue.

Exploratory analyses were performed to investigate possible associations between HER-2 scores by IHC and tumor and patient characteristics. Of note, a lower frequency of positivity for the expression of ER and PR was observed for specimens with scores 0 and 3+. This finding

is probably explained by the fact that tumors scored as 0 are enriched for the triple-negative phenotype, whereas those scored as 3+ are known to have less frequent expression of ER and PR than breast tumors in general.[6] When the distribution of HER-2 status and breast-cancer phenotypes was analyzed considering the five regions of Brazil, the North region had a higher percentage of HER-2-positive tumors, whereas the Midwest region had a higher percentage of triple-negative tumors than the other regions (Figure 2). Interestingly, Carvalho et al. have reported higher percentages for the North region both for HER-2-positive and for triple-negative tumors.[16] Likewise, a group from the Northeast region of Brazil reported that nearly 50% of 633 patients with invasive breast cancer had HER-2-positive tumors by IHC.[17] The relevance of these findings is still unclear, and whether they represent underlying biological phenomena or simply the play of chance remains to be investigated. The lower number of samples from the North and Midwest regions as compared with the other three regions is one limitation of the current study.

Conclusion

In summary, one out of five invasive breast tumors diagnosed in Brazil is positive for HER-2. Identifying these cases has obvious therapeutic implications, and adequate use of testing algorithms should be widely implemented in order to ensure patients have the chance to derive the expected benefit. To our knowledge, this is the largest prospective study evaluating HER-2 status in Brazilian patients with invasive breast carcinoma. In addition to data regarding patient and tumor molecular characteristics, the current study provides important data on the procedures and materials used for the assessment of the expression status of HER-2 and hormone receptors in this country.

Resumo

Avaliação de HER-2 no câncer de mama invasivo no Brasil

Objetivo: Estimar a frequência de câncer de mama positivo para HER-2 no Brasil.
Método: Neste estudo observacional e prospectivo, verificamos o escore de HER-2 de espécimes de câncer de mama invasivo por imuno-histoquímica automatizada (IHQ). Para amostras classificadas como 2+ por IHQ, fizemos hibridização *in situ* (HIS).
Resultados: De fevereiro de 2011 a dezembro de 2012, 1.495 espécimes de mama foram registrados, e 1.310 amostras coletadas por 24 centros foram analisadas. A idade mediana das pacientes foi 54 anos, e a maioria das amostras foram obtidas a partir de mastectomia segmentar (46,9%) ou radical (34,4%). O tipo histológico predominante foi o carcinoma invasivo da mama, sem tipo especial (85%); 64,3% tinham formação de túbulos (grau 3); e os receptores de estrógeno (RE)/progesterona (RP) foram positivos em 77,4%/67,8% das amostras analisadas. Por IHQ, encontramos HER-2 negativo (0 ou 1+) em 72,2% das amostras, e 3+ em 18,5%; os 9,3% de casos classificados como 2+ foram analisados por HIS, e 15,7% deles foram positivos (assim, 20,0% das amostras foram positivas para HER-2 por qualquer método). Não encontramos associação entre escores de HER-2 e estado menopausal ou tipo histológico. Tumores classificados como 3+ vieram de pacientes mais jovens, tinham maior grau histológico e foi menos frequente a expressão de RE/RP. Na região Norte do Brasil, 34,7% das amostras foram 3+, com frequências mais baixas nas outras quatro regiões do país.
Conclusão: Nossos resultados permitem estimar a frequência de positividade do HER-2 no Brasil, gerando a hipótese de que pode haver diferenças biológicas subjacentes à distribuição dos fenótipos de câncer de mama entre as diferentes regiões brasileiras.

Palavras-chave: neoplasias da mama, imuno-histoquímica, hibridização *in situ*, erbB2, trastuzumabe, HER-2.

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Chronic joint symptoms in adults: A population-based study

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Summary

Objective: To analyze factors associated with chronic joint symptoms (CJS) in adults.
Method: A population-based, cross-sectional study was performed with a sample of 1,217 adults aged between 20 and 59 years, in the city of Viçosa, in 2014. The sampling process was performed by conglomerates and sample was selected using a two-stage cluster-sampling scheme. First, 30 of the 99 census tracts of Viçosa were randomly selected using a random sampling scheme, without replacement. Household questionnaires were applied to obtain CJS data, sociodemographic conditions, behavioral factors and health status. Multivariable analysis was conducted using Poisson regression, adjusted for the sampling design effect, using the svy commands in Stata software.
Results: Prevalence of CJS totaled 31.27%, significantly higher in women (18.45). Age ranges 40-49 (PR 1.50; 95CI 1.16-1.92) and 50-59 years (PR 1.55; 95CI 1.07-2.25); overweight (PR 1.60; 95CI 1.28-2.00); obesity (PR 1.60; 95CI 1.11-2.29); and those who self-reported performing heavy work (PR 1.27; 95CI 1.09-1.48) showed higher prevalences of CJS.
Conclusion: Women and individuals who were older, overweight and performing heavy work had a higher risk of CJS in this adult population residing in Viçosa, MG, Brazil.

Keywords: health surveys, rheumatic diseases, joints, adults.

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Introduction

Chronic joint symptoms (CJS) are defined as the presence of pain, edema, morning stiffness and mobility limitation on most days for a minimum period of six weeks.[1] These symptoms are usually associated with arthritis and can affect individuals at different ages, leading to functional limitations in daily and professional activities.[2]

The health impact of CJS prevalence estimates is difficult to establish because these symptoms are self-reported rather than medically diagnosed. However, there is evidence that both self-reported symptoms and medical diagnosis have good validity.[3] In addition, for population screening, evaluating CJS is more feasible and may be an alternative for prevention, early diagnosis and insertion of interventions that may reduce the impact of probable chronic arthropathy, as well as the financial cost with expensive drug treatment.

There are reports of CJS prevalence in some countries, such as those found in the telephone health survey of individuals aged 18 years and older in the United States.[4] In this survey, 10% of respondents reported having CJS, reaching 33% when reporting medical diagnosis of arthritis is included. Prevalence in 2005 was 14% in that country.[5] In a survey conducted in Italy, 27% of respondents reported having joint pain/swelling, and 14.7% had morning stiffness.[6] More recently a population-based survey conducted in Australia with individuals between 16 and 96 years of age has obtained a prevalence of 11%[7] for symptoms. These differences in prevalence among studies may be related to the way the data are obtained or differences arising from the population, requiring further investigation.

In Brazil, studies aimed at investigating the prevalence of CJS are scarce, with only three investigations, of which two were developed with elderly populations. In

these studies, prevalence rates were respectively 44.2% among elderly individuals from Minas Gerais[8] and 45.6% in an elderly population from São Paulo.[9] With adult populations, to date, the only study found was conducted by Silva et al.,[10] who identified a prevalence of 36.5% in the south of Brazil.

Considering the scarcity of studies, particularly in the adult population, taking into account the impact on productive capacity and quality of life of this population and on the possibility of early identification of diseases such as arthritis, our study aimed to verify the prevalence of CJS and its associations with socioeconomic, demographic, behavioral and biological factors, in adults of Viçosa, Minas Gerais, Brazil.

Method

This is a cross-sectional, population-based study conducted between September 2012 and April 2014 in Viçosa, Minas Gerais. The reference population consisted of adults between 20 and 59 years of age, complete at the time of the research, of both sexes and living in the urban area of the municipality. This age group comprised approximately 52% of the total population, or 43,431 individuals.[11]

We used Epi-Info software, version 3.5.2®,[12] to calculate the sample size, with the following parameters: reference population (43,431 individuals); confidence level of 95%; expected prevalence of CJS was 36.5%,[10] sample error of 4.0 percentage points; and study design effect of 1.7. Ten percent (10%) was added to compensate for declines and losses and 20% to adjust for confounding variables. The calculated sample was 1,217 individuals. It should be emphasized that the sample of our study is probabilistic, composed of conglomerates and in two stages (census and domicile).

Procedures for data collection included the selection of census tracts, according to recommendations described in the literature. Thirty (30) sectors were selected, without replacement. After sorting the sectors, we identified four blocks for each sector, numbered their corners, and then established the starting point for data collection in each block clockwise, also by drawing lots.

All individuals residing in the household were contacted and invited to participate in the study. We considered it a loss when households were visited for at least four times, including a visit at night and at weekends, but the interviewer did not locate the individual to be interviewed. Those who declined to participate in the study were contacted again by the study supervisor and, in case the disagreement remained, were counted as refusals. Exclusion criteria were as follows: pregnant women, individuals who were bedridden or unable to obtain the measures, and those who had a mental disability that prevented them from answering the questions in the questionnaire. Data collection was always conducted by a team of professionals trained to apply the questionnaires and the anthropometric measurements were performed by a single evaluator with the purpose of minimizing variations and maintaining the internal validity of the study. Details on the procedures for planning and carrying out the study can be obtained from the study by Segheto et al.[13]

The dependent variable included CJS, defined as the affirmative response to the presence of pain or tenderness, swelling or hardening of the joints that lasted most days, for at least one month and a half, considering the last 12 months. The questions were adapted from the arthritis module of the Behavioral Risk Factor Surveillance System.[4]

As independent variables, the following sociodemographic characteristics were evaluated: sex (male and female); age in years categorized as age group every 10 years; skin color according to Vigitel[14] and also categorized as white or non-white; formal education in years categorized as 0-4 years, 5-8 years, 9-12 years and > 13 years; and social class based on the tool of the Brazilian Association of Research Companies[15] and grouped as upper (A + B), middle (C) or lower (D + E).

Behavior-related variables included smoking habit and physical activity level (PAL). Smoking was categorized as smokers, former smokers and non-smokers regardless of frequency and amount of cigarettes.[16] The level of physical activity in leisure was assessed according to the International Physical Activity Questionnaire (IPAQ), validated for the Brazilian population,[17] including the fourth domain relating to recreation, sports, exercise or leisure activities. PAL was calculated by adding the time spent with moderate physical activities plus twice the time with vigorous activities, and categorized as irregularly active (< 150 minutes of activities in the week) or physically active (≥ 150 minutes of activities in the week).[18]

Body mass index (BMI) was calculated based on the ratio of body mass to stature squared, both self-reported. We used the criteria proposed by the World Health Organization (WHO)[19] to categorize the BMI (≤ 25 kg/m^2 = adequate; 25 kg/m^2 to 29,99 kg/m^2 = overweight, and ≥ 30 kg/m^2 = obese), with low-weight individuals grouped into the normal weight category.

The self-reported diagnosis of diseases (hypertension, diabetes and arthritis) was evaluated through objective questions.[14,20,21] In addition, family history of arthritis or rheumatism, and heavy and repetitive work over the last 12 months have been evaluated asking the following questions: "Do you have any relatives with arthritis or rheu-

matism?" "Do you have the need to lift heavy weights or need a lot of muscular strength during work activities, and do you repeat the same task many times?"[10]

Control was performed in 10% of the sample, by telephone, with ten random questions being reproduced.[13] After these procedures, the data were entered twice in Epi-Data, by previously trained typists, and checked using "data compare." Consistency checks and analyzes were performed using statistical package Stata version 13.0.[22]

The analysis was weighted by gender, age and formal education, with weights determined by the ratio of the proportions of individuals, according to the Brazilian Census Bureau – IBGE,[11] and in the sample, using svy commands. Initially, a descriptive analysis of the prevalence of CJS with its respective confidence intervals (95CI) was performed. Proportions, prevalence ratios and their respective 95% confidence intervals were presented to verify the associations between the dependent and each independent variables. Multiple analysis was performed using Poisson regression. Variables with $p<0.20$ were included in the bivariate analysis, and the criterion for their permanence in the final model was $p<0.05$.

This project was approved by the Human Research Ethics Committee of Universidade Federal de Viçosa (protocol no. 008/2012). All participants signed an informed consent form in two counterparts prior to the start of data collection.

Results

Most of the evaluated individuals were young (20-29 years old), non-white, had higher education, belonged to the middle class, did not smoke, were physically inactive, self-reported adequate nutritional status, no diagnosis of hypertension or diabetes mellitus, no family history of arthritis, did not perform heavy work, and always performed repetitive tasks (Table 1).

The estimated prevalence of CJS was 31.27%, statistically higher among women and individuals in the age group of 40-49 years. Regarding skin color, there was no difference for the presence of CJS. Chronic joint symptoms

TABLE 1 Sociodemographic, behavioral and health characteristics of the population. Viçosa, MG, 2012-2014.

Variable	Proportion (%)	Confidence interval (95CI)
Sex		
Male	49.20	(45.73-52.67)
Female	50.80	(47.32-54.26)
Age range (years)		
20-29	32.78	(24.34-42.50)
30-39	25.24	(21.07-29.91)
40-49	22.93	(18.30-28.31)
50-59	19.05	(15.10-23.74)
Skin color		
White	39.60	(33.45-46.09)
Non-white	60.39	(53.90-66.54)
Education (years)		
0-4	19.04	(12.32-28.23)
5-8	15.19	(11.30-20.11)
9-12	21.47	(18.09-25.29)
≥13	44.29	(32.57-56.67)
Social class (ABEP)		
Upper (A and B)	24.53	(19.00-31.06)
Middle (C)	64.68	(59.92-69.16)
Lower (D and E)	10.77	(7.30-15.61)
Smoking		
Non-smoker	65.47	(59.88-70.65)
Current smoker	16.17	(13.16-19.71)
Former smoker	18.35	(13.78-24.01)

(*continues*)

TABLE 1 (cont.) Sociodemographic, behavioral and health characteristics of the population. Viçosa, MG, 2012-2014.

Variable	Proportion (%)	Confidence interval (95CI)
Level of physical activity in leisure		
Physically inactive	78.03	(71.37-83.49)
Physically active	21.96	(16.50-28.62)
Self-reported nutritional status*		
Adequate	50.98	(45.41-56.52)
Overweight	32.64	(28.61-36.95)
Obesity	16.37	(12.55-21.06)
High blood pressure		
No	82.77	(78.69-86.20)
Yes	17.22	(13.79-21.30)
Diabetes mellitus		
No	94.50	(90.39-96.91)
Yes	5.49	(3.08-9.60)
Family history of arthritis		
No	94.65	(93.20-95.81)
Yes	5.34	(4.18-6.79)
Heavy work		
No	66.66	(57.34-74.83)
Yes	33.34	(25.17-42.65)
Repetitive tasks		
Never	28.30	(22.11-35.42)
Always	71.70	(64.57-77.88)

*The nutritional status was obtained based on the ratio between body mass and squared stature, both self-reported. The cut-off points adopted were ≤ 25 kg/m^2 = adequate; 25 kg/m^2 to 29.99 kg/m^2 = overweight; and ≥ 30 kg/m^2 = obese.[19]

were more frequent in individuals with more years of formal education (p<0.01) and belonging to the middle class, with similar distribution in the upper and lower classes (p=0.22). Regarding behavioral characteristics, CJS were more frequent in non-smokers and in physically inactive individuals (p<0.05). Regarding nutritional status, overweight individuals presented a higher prevalence of CJS compared to individuals who self-reported adequate nutritional status or obesity (p<0.01). CJS were more frequent in subjects who reported normal blood pressure and absence of family history of arthritis (p<0.01). Regarding the diagnosis of diabetes mellitus, there was no difference between individuals who reported having or not having this diagnosis (p=0.14). As for the performance of heavy work, CJS was more frequent in individuals reporting that they did not perform such activities; however, 24.57% of the participants reported repetitive work (p<0.01) (Table 2).

Female subjects, those aged 40 to 49 years and 50 to 59 years, those overweight and obese, and those who needed strength for work activities (Table 3) were all associated with CJS.

Discussion

Studies of this nature, which estimate the presence of CJS in adults, are still scarce. Our study found a prevalence of CJS of 31.27%, higher than that found in the US population,[4] as well as in the Italian[6] and Australian[7] populations, which presented respectively a prevalence of 10, 27 and 11%. In Brazil, a population-based study conducted in the city of Pelotas, Rio Grande do Sul, estimated prevalence data for CJS at 36.50%.[10] The factors associated with the higher prevalence of CJS are sex, age, overweight and heavy work.

The differences observed in our study regarding the prevalence of CJS compared with those described in other countries[4,6,7] may be related to the different characteristics of each of the populations analyzed, including social class, culture and quality of life, and more. Another important aspect that may have influenced the different prevalences observed when comparing our study with those performed with the North American and European population is the methodology used to investigate CJS. Studies conducted by the Centers for Disease Control and Prevention[4] and by Busija et al.[7] were performed by telephone and may have

TABLE 2 Prevalence of chronic articular symptoms, according to sociodemographic, behavioral and health variables. Viçosa, MG, 2012-2014.

Variables	Frequency (%)	p-value*
Sex		<0.01
Male	12.82	
Female	18.45	
Age range (years)		<0.01
20-29	6.47	
30-39	8.26	
40-49	8.41	
50-59	8.13	
Skin color		0.05
White	20.33	
Non-white	10.94	
Education (years)		<0.01
0-4	7.93	
5-8	5.33	
9-12	7.70	
≥13	10.32	
Social class (ABEP)		0.22
Upper (A and B)	6.42	
Middle (C)	21.13	
Lower (D and E)	3.75	
Smoking habit		0.03
Non-smoker	19.29	
Current smoker	4.18	
Former smoker	7.80	
Level of physical activity in leisure		0.01
Physically inactive	27.03	
Physically active	5.66	
Self-reported nutritional status**		<0.01
Adequate	11.49	
Overweight	11.55	
Obesity	8.25	
High blood pressure		<0.01
No	23.68	
Yes	7.59	
Diabetes mellitus		0.14
No	29.39	
Yes	1.50	
Family history of arthritis		<0.01
No	28.34	
Yes	2.73	
Heavy work		<0.01
No	18.06	
Yes	12.94	
Repetitive tasks		<0.01
No	6.33	
Yes	24.57	

*Chi-square test ($p<0.05$).
**The nutritional status was obtained based on the ratio between body mass and squared stature, both self-reported. The cut-off points adopted were ≤ 25 kg/m² = adequate; 25 kg/m² to 29.99 kg/m² = overweight, and ≥ 30 kg/m² = obese.[19]

TABLE 3 Descriptive characteristics and prevalence of CJS according to sociodemographic, behavioral and health factors among adults in Viçosa, MG, 2012-2014.

Variables	Gross prevalence ratio (95CI)	p-value	Adjusted prevalence ratio*	p-value
Sex		<0.01		<0.01
Male	1.00		1.00	
Female	1.39 (1.13-1.72)		1.49 (1.23-1.81)	
Age range (years)		<0.01		0.02
20-29	1.00		1.00	
30-39	1.66 (1.31-2.10)		1.30 (0.99-1.72)	
40-49	1.86 (1.47-2.34)		1.50 (1.16-1.92)	
50-59	2.16 (1.65-2.83)		1.55 (1.07-2.25)	
Skin color		0.06		0.61
White	1.00		1.00	
Non-white	1.22 (0.99-1.50)		1.07 (0.82-1.39)	
Education (years)		<0.01		0.64
≥13	1.00		1.00	
9-12	1.54 (1.25-188)		1.15 (0.76-1.74)	
5-8	1.50 (1.19-1.89)		1.29 (0.74-2.24)	
0-4	1.79 (1.30-2.45)		0.86 (0.55-1.35)	
Social class (ABEP)		0.11		0.55
Upper (A and B)	1.00		1.00	
Middle (C)	1.25 (0.99-1.58)		1.21 (0.94-1.56)	
Lower (D and E)	1.33 (0.85-2.08)		1.06 (0.75-1.52)	
Smoking habit		0.07		0.42
Non-smoker	1.00		1.00	
Current smoker	0.88 (0.59-1.30)		0.90 (0.60-1.36)	
Former smoker	1.44 (1.05-1.98)		1.11 (0.80-1.56)	
Level of physical activity in leisure		0.15		0.42
Irregularly active	1.00		1.00	
Physically active	0.84 (0.66-1.07)		1.12 (0.83-1.51)	
Self-reported nutritional status**		<0.01		<0.01
Adequate	1.00		1.00	
Overweight	1.59 (1.26-2.02)		1.60 (1.28-2.00)	
Obesity	2.00 (1.37-2.92)		1.60 (1.11-2.29)	
High blood pressure		<0.01		0.83
No	1.00		1.00	
Yes	1.54 (1.25-1.90)		0.66 (0.30-1.44)	
Diabetes mellitus		0.60		0.33
No	1.00		1.00	
Yes	0.88 (0.53-1.44)		1.01 (0.71-1.56)	
Family history of arthritis		0.01		0.09
No			1.00	
Yes	1.37 (1.07-1.76)		1.23 (0.96-1.56)	
Heavy work		<0.01		<0.01
No	1.0		1.00	
Yes	1.43 (1.19-1.72)		1.27 (1.09-1.48)	
Repetitive tasks		0.02		0.38
No	1.00		1.00	
Yes	1.53 (1.08-2.17)		1.06 (0.92-1.22)	

CJS: chronic joint symptoms.
*All variables were adjusted.
**The nutritional status was obtained based on the ratio between body mass and squared stature, both self-reported. The cut-off points adopted were ≤ 25 kg/m² = adequate; 25 kg/m² to 29.99 kg/m² = overweight, and ≥ 30 kg/m² = obese.[19]

underestimated the prevalence of CJS by excluding individuals who do not own a telephone.

Regarding the difference in prevalence between the sexes, we found that the prevalence was higher in women (RP 1.38; 95CI 1.13-1.69) compared to men, corroborating the study by Silva et al.,[10] which showed a prevalence 1.5 times higher (95CI 1.3-1.6) than in men. The literature states that the highest estimate of CJS prevalence in women may be related to differences and variations in the profile of female sex hormones.[23,24] In addition, hormonal variations in association with overweight may trigger an endocrine imbalance of systemic repercussion that will act to destroy joint cartilage.[25]

We observed an increase in the prevalence of CJS with age, so that in the age group from 40 to 49 and 50 to 59 years the prevalence of CJS was 1.50 times (95CI 1.16-1.92) and 1.55 times (95CI 1.07-2.25) higher compared to the age group 20-29 years. These results are similar to those observed in other studies.[7,9,10] Aging promotes a physiological wear of the joints that, combined with insufficiency in the repair of articular cartilage, mainly in the presence of comorbidities,[25,26] can render the prevalence higher in older individuals.

Similar to other studies,[10,27] overweight and obesity were associated with increased prevalence of CJS. One explanation for this association is the mechanical stress caused by excess weight[28,29] and the proinflammatory properties of some adipocytokines,[10] such as visfatin.[30] Reducing body weight could be a strategy aimed at decreasing the prevalence of CJS in adults.

Performing heavy work was associated with the presence of CJS. Importantly, organic tissues need to have a sufficient amount of function and tension to maintain their integrity.[31] If this tension does not have adequate stress, there may be atrophy and, in case of excessive stress to the organic capacity, degenerative changes.[31] This may be related to the response to cumulative mechanical stress on the joints, which can cause symptoms from an early stage of osteoarthritis.[10]

CJS can cause functional limitation, decrease in quality of life and emotional disturbance in the study population. The clinical significance of symptom complaint is uncertain, but the identification of its prevalence and associated factors, especially those modifiable, may contribute to early diagnosis and establishment of interventions that reduce the impact of future arthropathy.

In order to reduce the prevalence of CJS and limit its impact on the individual, society and public health agencies, the following strategies are recommended: broadening access to primary health care; promoting education among patients, the general population and health professionals; encouraging weight control and appropriate practice of physical activity; and raising awareness of ergonomics at work. The results of our study may serve as a basis for the implementation of public policies, through educational programs aimed at the self-care of adults with chronic joint symptoms to prevent future disabilities.

Despite all the methodological procedures followed for the development of our study, such as sample selection, interview training, and quality control, our study has limitations, one of which is to obtain estimates for CJS based on self-report not medically confirmed. However, it is not feasible for population studies to perform clinical exams because they are more expensive than self-report. Another important limitation is the occurrence of memory bias related to the pain, swelling and hardening of the joints in the last 30 days prior to the home interview, which may underestimate the prevalence of these factors. Finally, it is impossible to establish a causal line according to the temporality of the study design. Nevertheless, estimates of the prevalence of self-reported chronic diseases have been considered a simple and objective way to obtain health information, with good levels of agreement with data on the actual prevalence of the disease in the population.[32]

We thus conclude that the prevalence of CJS is high. There was a positive and independent association between CJS and female gender, age, overweight, obesity and heavy work. By identifying potentially modifiable factors associated with CJS, such as nutritional status and work overload, it is possible to establish early intervention strategies that result in the minimization of future risks of osteoarticular disease. In addition, studies using this approach and performing this type of screening may prevent future disability.

Resumo

Sintomas articulares crônicos em adultos: um estudo de base populacional

Objetivo: Analisar os fatores associados aos sintomas articulares crônicos (SAC) em adultos.
Método: Trata-se de um estudo transversal, de base populacional, com 1.217 adultos, na faixa etária de 20 a 59 anos, na cidade de Viçosa, MG, 2014. A amostragem foi realizada por conglomerados em duplo estágio, sendo as unidades de primeiro estágio os setores censitários, e, em seguida, os domicílios. Foram sorteados 30 setores dentre os 99 de Viçosa, por meio de amostragem casual simples, sem reposição. A coleta de dados foi composta por apli-

cação de questionário contendo questões relativas a variáveis de SAC, sociodemográficas, comportamentais e de saúde. Para verificar as associações, apresentaram-se proporções, razões de prevalência e seus respectivos intervalos de confiança de 95%. A análise múltipla foi realizada por meio da regressão de Poisson, utilizando o conjunto de comandos svy do software Stata, o qual considera o efeito da expansão da amostra na análise dos dados.

Resultados: A prevalência estimada de SAC foi de 31,27%, maior nas mulheres (18,45%). Estiveram associadas ao SAC as mulheres (RP 1,49; IC95% 1,23-1,81); as idades de 40 e 49 (RP 1,50; IC95% 1,16-1,92) e 50 e 59 anos (RP 1,55; IC95% 1,07-2,25); o sobrepeso (RP 1,60; IC95% 1,28-2,00); a obesidade (RP 1,60; IC95% 1,11-2,29); e aqueles que autorreferiram realização de trabalho pesado (RP 1,27; IC95% 1,09-1,48).

Conclusão: O sexo feminino, a faixa etária de 40 a 59 anos, o sobrepeso, a obesidade e a realização de trabalho pesado foram fatores de risco para SAC em adultos de Viçosa, MG.

Palavras-chave: inquéritos epidemiológicos, doenças reumáticas, articulações, adultos.

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Quality of life in breast cancer survivors

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Summary

Objective: To evaluate the influence of functional capacity (FC) and how it affects quality of life (QoL) in breast cancer survivors.
Method: A total of 400 breast cancer survivors were studied – 118 without metastasis, 160 with locoregional metastasis and 122 with distant metastasis. The European Organization for Research and Treatment for Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Breast Cancer-Specific (EORTC QLQ-BR23), and the Karnofsky Performance Scale (KPS) were used to evaluate FC and QoL.
Results: Women with distant metastases presented lower KPS 75.3 (SD=12.5) ($p<0.001$). For QLQ-C30, the mean of the Functional Scale for patients with distant metastasis was 57 (SD=19) ($p<0.001$), and the mean of the Symptom Scale for patients with distant metastasis was 37 (SD=20) ($p<0.001$). Both the scales for pain and fatigue showed the highest mean in the groups. For the Global Health Scale, patients without metastasis scored a mean of 62 (SD=24) points, while those with locoregional metastases scored a mean of 63 (SD=21.4), and distant metastasis scored 51.3 (SD=24) points. In the group with distant metastases, 105 (87%) had pain, and the average KPS was 74 (SD=12.0) ($p=0.001$).
Conclusion: Breast cancer was associated with decreased FC, compromised QoL in women with locoregional and distant metastases compared to those without metastasis.

Keywords: survivors, breast neoplasms, quality of life, functional capacity.

Introduction

Breast cancer is the most prevalent type of cancer among women throughout the world and is considered the most commonly diagnosed type of cancer. However, due to new technologies and treatments, the number of women living with the disease increases every year, which explains the growing interest in quality of life (QoL) of breast cancer patients.[1-5]

The number of breast cancer survivors is increasing around the world; thus, it is important to improve the health-related QoL of this population. Ability to perform daily activities, patient satisfaction and levels of functionality are all essential to determining QoL in breast cancer survivors. Persistent symptoms associated with the adverse effects of treatment, such as pain and fatigue, can interfere with functional capacity (FC) and directly affect QoL, and consequently should not be left untreated.[5-10]

Decreased FC may affect the QoL of patients, especially those with advanced cancer. This is important because 38% of the women diagnosed annually already have advanced cancer.[6]

FC and autonomy are some of the most important indicators of health in cancer patients. The current understanding of FC is quite holistic in that it includes not only areas of physical performance, such as muscular strength, cardiopulmonary endurance and range of motion, but also the emotional and psychological state as well as environmental and social circumstances.[11-16]

According to the World Health Organization's International Classification of Functioning, Disability and Health (ICF), function is defined as the interactions between an individual, their health condition and the social and personal context in which they live.[16-18] It is the complex interaction between these factors that determines function and impairment. In the context of breast cancer, morbidity associated with the disease and its treatments can lead to impairments in physiological, psychological or behavioral attributes (body functions and structures),

eventually leading to limitations in the ability to execute daily activities and participate in social events.[16]

Considering the aspects above, FC is not only a marker of health-related QoL in breast cancer survivors but also a key aspect in the development of rehabilitation techniques. These techniques are used to improve function in breast cancer survivors and identify functional limitations that help to make decisions concerning treatment and rehabilitation.[16]

Functional limitations may have a significant impact on QoL, but less is known about the impact of other variables such as age, presence of metastasis and pain on functional limitation in breast cancer survivors. This study aimed to assess the influence of pain, metastasis and sociodemographic variables on functional performance and QoL of breast cancer survivors.

Method

The sample was comprised of a total of 400 breast cancer survivors in different disease stages at the time of diagnosis: S0=5 (1.25%), SI=113 (28.25%), SIIA=4 (1%), SIIB=20 (5%), SIIIA=66 (16.5%), SIIIB=63 (15.75%), SIIIC=7 (1.75%) and IV=122 (30.5%), undergoing chemotherapy, radiotherapy, surgery or hormone therapy, or exclusively palliative care. Three study groups were identified in the sample: 118 patients without metastasized breast cancer, 160 with locoregional metastases and 122 with distant metastases. The research took place in the oncology centre at a referral hospital in a medium-sized city in the northeast of Brazil from July 2014 to April 2015.

Patients were selected by means of non-probability sampling, and patient interviews were conducted during medical consultations.

Patients eligible for the study had been diagnosed with breast cancer, were undergoing treatment and/or palliative care, and were over 18 years of age. Women without cognitive ability or speech, as well as patients without previous treatment, and those previously diagnosed with depression were excluded.

Ethical issues were considered, and the local Research Ethics Committee approved the present study (no. CAAE 17956113.9.0000.5293) in compliance with the Declaration of Helsinki and Resolution 466/12 of the Brazilian National Health Council, which addresses research on human beings. Before starting the interview, the researcher explained the study objectives and requested a free and informed consent ensuring that participation was voluntary and that answers would be anonymous and confidential.

Sociodemographic data including age, place of origin, education, marital status, occupation, religion, clinical data, metastasis, type of treatment, and pain symptoms were obtained from the patients and patient records.

The functionality of the breast cancer survivors was assessed using the Karnofsky Performance Scale (KPS). KPS measures functionality, with scores ranging from 0 (which indicates the death of the patient) to 100 (patient performs their daily activities normally).[19,20]

To assess QoL, the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire--Core 30 (EORTC QLQ-C30) was used. The questionnaire is valid and reliable for assessing QoL of cancer survivors, and thus it is considered useful in many clinical trials and research. The EORTC QLQ-C30 (version 3.0) is composed of three scales, corresponding to the patient's condition in the prior week. The first is the Global Health Scale. The second is the Functional Scale, consisting of five domains: physical, emotional, social, cognitive and role-playing. The third, the Symptom Scale, consists of three domains (pain, fatigue, nausea and vomiting) and six single items (dyspnea, sleep disorders, loss of appetite, constipation, diarrhea, and financial difficulties).[13,21] Questions 01-28 contained in the instrument are arranged in a four-point Likert scale, where the respondents classified each item with responses ranging from strongly disagree (1 point) to strongly agree (4 points). Questions 29 and 30, in turn, also used the Likert scale, but with answers ranging from 1 to 7 points, classified as unsatisfactory to satisfactory, respectively. All items are linearly transformed into scales ranging from 0 to 100. In the case of the Functional Scale and Global Health Scale, higher scores indicate a higher level of functioning or overall QoL. On the other hand, for the Symptom Scale and single items, higher scores imply a higher level of symptoms or problems.[21]

The QLQ-BR23 module, created specifically for breast cancer survivors, has been translated and validated in Portuguese. It consists of 23 questions, using a Likert scale with the mismatch response to the lower value of 1, and the highest value of 4. This module is divided into two scales, one of which is a Functional Scale that includes four items on body image, two on sexual function, one on sexual pleasure, and one on future prospects. The other scale is the Symptom Scale, which includes seven items on systemic therapy, four on symptoms of breast cancer, three on symptoms of the arm, and one on hair loss.[21]

Authorization for the use of these instruments was requested via e-mail with the EORTC group, and a copy of the questionnaire and manual were presented for data analysis.

Statistical treatment

Initially, a descriptive analysis of qualitative variables was performed through the distribution of absolute and

relative frequencies. For the quantitative variables (sociodemographics such as age, clinical such as KPS, and the instrument variables EORTC QLQ-C30 and QLQ-BR23), measures of central tendency and dispersion (mean and standard deviation) were used. Then, analysis of variance (ANOVA) was performed to verify any relation among KPS, Symptom Scale, Functional Scale, and Global Health Scale of the EORTC QLQ-C30, as well as scales of symptoms and functional QLQ-BR23 with patients without metastases and with the presence of locoregional or distant metastases. It was concluded by ANOVA that there was a significant difference between women with and without metastases. Tukey test, a multiple comparison test, was used to evaluate the magnitude of these differences. Student's t-test was used to determine any correlation between KPS (FC) and pain. To investigate the relations among the EORTC instrument variables according to KPS, we used the Pearson correlation, which is a parametric correlation. The study used a significance level of 5%, and all the calculations were performed with SPSS.V.13.

Results

As shown in Table 1, lower FC (KPS) was observed in women with metastasis ($p<0.001$). The mean score of patients without metastasis was 90.5 points (SD=9.7), with locoregional metastasis scoring 87.5 (SD=8.8) and distant metastasis scoring 75.3 (SD=12.5). Differences in FC were detected in the comparison between groups regarding metastases: without and locoregional ($p=0.045$), without and distant ($p<0.001$), locoregional and distant metastases ($p<0.001$). As for Functional Scale and Global Health EORTC QLQ-C30, there were also differences among the groups ($p<0.001$). Concerning the Symptom Scale (EORTC QLQ-C30), variations were observed between the following groups: without and with distant metastases ($p=0.001$); with locoregional and distant metastases ($p<0.001$). Regarding the Symptom and Functional Scales (EORTC QLQ-BR23), differences were also detected between women with locoregional and women with distant metastasis ($p<0.001$).

In Table 2, correlating pain and FC with the presence of metastases, it was identified that the total sample, 287 (71.75%) patients, had pain and an average KPS of 82.2% (SD=12.3), $p<0.001$. For women with distant metastases, 105 (87%) complained of pain and the average KPS was 74% (SD=12.0), $p=0.001$ (Table 2).

In Table 3, FC (KPS) was closely related to QoL by EORTC QLQ-C30, mainly in the following scales: Functional Scale, Symptom Scale and Global Health Scale in women without, with locoregional and distant metastases ($p<0.001$).

Discussion

It is usual for breast cancer survivors to suffer from persistent arm morbidity (i.e., pain, limited range of motion, reduced strength) with decreased upper limb function after surgery and/or adjuvant treatment.[16] This study found a significant relation between metastases (locoregional and distant) and decrease of FC, which in turn affects QoL. This result is generally observed when women with distant metastases are compared to women without metastasis. The presence of distant metastases seems to decrease FC in patients, limiting daily activities and consequently reducing QoL of breast cancer survivors. Such reduced functionality can lead to physical inactivity, and contribute to worsening of the health status in breast cancer survivors.[16,22]

Additionally, pain and FC affect the performance status, a factor decisive in the decision to undergo therapy or palliative care alone. Thus, patients with good FC (KPS ranging from 60 to 90%) are presumed strong enough to receive any treatment, which is considered the standard to participate in clinical trial studies.[23,24] This study found that even patients with a KPS of 40% received some type of treatment despite the patient's lower FC and increased propensity to poorer QoL.[2,7]

Therefore, quantification of physical function is becoming an important element in the verification of health-related QoL, considering that cancer is often associated with decreased physical capacity, which interferes with daily activities, especially for those with metastases.[23-25] Most patients in our study had metastases, mainly locoregional, which is similar to findings by Montazeri et al.[25] that patients with advanced cancer may have poorer QoL.[7,8,13] Zimmerman et al.[26] also confirmed performance status to be an important determinant of QoL in advanced cancer.

Pain is very frequent in cancer patients. In our study, breast cancer survivors with metastases suffered from more pain than those without metastasis. Pain was correlated to decreased FC, compromising the QoL of these women.[16]

QoL also has been considered an important predictor of prognosis for cancer patients.[27,28] The assessment of QoL can determine the impact of disease and treatment in patients.[29] We used EORTC QLQ-C30 and EORTC QLQ-BR23 to assess QoL, and observed a positive correlation between FC and QoL. Evaluating all domains, women without metastasis showed better QoL (EORTC) and FC (KPS) than those with locoregional and distant metastases.

In this study, we found that breast cancer was associated with decreased FC, compromising QoL in women

TABLE 1 Quality of life and functional capacity relating to metastases.

Variable	Presence of metastases	N	%	Mean	Standard deviation	p-value*	Comparison between groups with metastases	p-value**
		KPS						
Women with breast cancer	Without	118	29.5	90.5	9.7	<0.001	Without and locoregional	0.045
	Locoregional	160	40.0	87.5	8.8		Without and distant	<0.001
	Distant	122	30.5	75.3	12.5		Locoregional and distant	<0.001
		Functional Scale EORTC QLQ-C30						
	Without	118	29.5	67.2	20.0	<0.001	Without and locoregional	0.996
	Locoregional	160	40.0	67.0	18.0		Without and distant	<0.001
	Distant	122	30.5	57.0	19.0		Locoregional and distant	<0.001
		Scale Global Health EORTC QLQ-C30						
	Without	118	29.5	62.0	24.0	<0.001	Without and locoregional	0.896
	Locoregional	160	40.0	63.0	21.4		Without and distant	0.001
	Distant	122	30.5	51.3	24.0		Locoregional and distant	<0.001
		Symptom Scale EORTC QLQ-C30						
	Without	118	29.5	22.1	16.3	<0.001	Without and locoregional	0.466
	Locoregional	160	40.0	25.0	16.0		Without and distant	<0.001
	Distant	122	30.5	37.0	20.0		Locoregional and distant	<0.001
		Symptom Scale EORTC QLQ-BR23						
	Without	118	29.5	61.4	19.1	<0.001	Without and locoregional	<0.001
	Locoregional	160	40.0	26.0	15.2		Without and distant	<0.001
	Distant	122	30.5	26.0	14.3		Locoregional and distant	0.992
		Functional Scale EORTC QLQ-BR23						
	Without	118	29.5	23.5	18.1	<0.001	Without and locoregional	<0.001
	Locoregional	160	40.0	64.0	17.0		Without and distant	<0.001
	Distant	122	30.5	58.1	19.2		Locoregional and distant	0.018

*Analysis of variance (ANOVA).
**Multiple Comparison Test (Turkey).
Significance level of 5%.

TABLE 2 Correlation between pain and functional capacity and the presence of metastases.

Variable	N	%	Mean	Standard deviation	Minimum	Maximum	p-value*
Pain			**KPS**				
Without metastasis							
No	51	43.0	93.9	7.5	70.0	100.0	0.001
Yes	67	57.0	87.9	10.7	50.0	100.0	
Locoregional metastases							
No	45	28.0	90.0	8.8	60.0	100.0	0.065
Yes	115	72.0	87.0	8.7	60.0	100.0	
Distant metastases							
No	17	14.0	85.0	11.2	50.0	100.0	0.001
Yes	105	87.0	74.0	12.0	40.0	90.0	
Total							
No	113	28.3	90.8	9.2	50.0	100.0	0.001
Yes	287	71.7	82.2	12.3	40.0	100.0	

*Analysis of variance (ANOVA).
Significance level 5%.

TABLE 3 Correlation between functional capacity and quality of life according to the EORTC QLQ-C30 and BR23 in women with breast cancer metastases.

Breast cancer survivors	EORTC	KPS		
		Correlation	Type	p-value***
Without metastasis	Functional Scale*	0.57	Accented	<0.001
	Symptom Scale*	-0.54	Accented	<0.001
	Global Health Scale*	0.52	Accented	<0.001
	Functional Scale**	-0.43	Appreciable	<0.001
	Symptom Scale**	-0.28	Low	0.002
Locoregional metastases	Functional Scale*	0.57	Accented	<0.001
	Symptom Scale*	0.53	Accented	<0.001
	Global Health Scale*	0.51	Accented	<0.001
	Functional Scale**	-0.22	Low	0.005
	Symptom Scale**	-0.30	Appreciable	<0.001
Distant metastases	Functional Scale*	0.70	Accented	<0.001
	Symptom Scale*	-0.63	Accented	<0.001
	Global Health Scale*	0.70	Accented	<0.001
	Functional Scale**	0.17	Low	0.070
	Symptom Scale**	0.41	Appreciable	<0.001

*EORTC QLQ-C30.
**EORTC QLQ-BR23.
***Spearman test.

with locoregional and distant metastases compared to those without metastasis. Probably, functional limitations and physical inactivity are linked to worse QoL.

Recently, high FC has been associated with survival in breast cancer survivors. In a large, prospective population-based cohort of early-stage breast cancer survivors, the Life After Cancer Epidemiology (LACE) cohort, participants were asked if they could accomplish a list of daily activities.[30] At least one functional impairment existed in 39% of breast cancer survivors at the median follow-up time of nine years post-diagnosis, irrespective of clinical, lifestyle and sociodemographic factors.[30] Survivors who were older, less educated and obese had a higher risk of having greater functional limitation. Women with functional limitations were less physically active compared with those without impairment.[30] Functional limitations were linked to a significantly increased mortality from all causes. This is not a new finding, since it is known that, for women in the general population, physical inactivity is a strong predictor of mortality.[31,32]

Functional limitations impact the QoL of breast cancer survivors. Breast cancer care needs to integrate important information on patient FC by means of self-report, consequently adjusting the treatment accordingly. This is essential in order to fully understand the multiple functional limitations associated with breast cancer and to improve rehabilitation care for breast cancer survivors.

Breast cancer affects different aspects of QoL for thousands of women around the world.[33] From the time of diagnosis, the initial stages of treatment and the months following treatment completion are difficult times for patients and relatives. During these times, breast cancer patients can easily suffer from poor adjustment and decreased QoL. As a result, it is critical for health care professionals to become familiar with the impact of a breast cancer diagnosis and its treatment on patient QoL.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Qualidade de vida em sobreviventes do câncer de mama

Objetivo: Avaliar a influência da capacidade funcional (CF) sobre a qualidade de vida (QV) de mulheres sobreviventes de câncer de mama.
Método: 400 mulheres sobreviventes de câncer de mama foram avaliadas –118 sem metástases, 160 com metástases locorregionais e 122 com metástases a distância. Para avaliar a capacidade funcional e a qualidade de vida, os

seguintes instrumentos foram utilizados: European Organization for Research and Treatment for Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Breast Cancer-Specific (EORTC QLQ-BR23) e Karnofsky Performance Scale (KPS).

Resultados: Mulheres com metástases a distância apresentaram menor KPS 75,3 (DP=12,5) (p<0,001). Quanto ao QLQ-C30, a média da escala funcional para pacientes com metástases a distância foi de 57 (DP=19) (p<0,001). A média da escala de sintomas das pacientes com metástase a distância foi de 37 (DP=20) (p<0,001). A escala de dor e fadiga apresentou a maior média nos grupos. Em relação à Escala Global de Saúde, as pacientes sem metástase tinham uma média de 62 (DP=24); com metástase locorregional, 63 (DP=21,4); e com metástase a distância, 51,3 (DP=24). Para o grupo com metástase a distância, 105 (87%) tiveram dor, e a média do KPS foi de 74 (DP=2,0) (p=0,001).

Conclusão: O câncer de mama foi associado com diminuição da capacidade funcional, comprometendo a qualidade de vida das mulheres sobreviventes do câncer de mama com metástases locorregional ou a distância, quando comparadas àquelas sem metástases.

Palavras-chave: sobreviventes, neoplasias da mama, qualidade de vida, capacidade funcional.

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Functional decline in the elderly with MCI: Cultural adaptation of the ADCS-ADL scale

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Summary

Objective: Translate, transcultural adaptation and application to Brazilian Portuguese of the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale as a cognitive screening instrument.
Method: We applied the back translation added with pretest and bilingual methods. The sample was composed by 95 elderly individuals and their caregivers. Thirty-two (32) participants were diagnosed as mild cognitive impairment (MCI) patients, 33 as Alzheimer's disease (AD) patients and 30 were considered as cognitively normal individuals.
Results: There were only little changes on the scale. The Cronbach alpha coefficient was 0.89. The scores were 72.9 for control group, followed by MCI (65.1) and by AD (55.9), with a p-value < 0.001. The ROC curve value was 0.89. We considered a cut point of 72 and we observed a sensibility of 86.2%, specificity of 70%, positive predictive value of 86.2%, negative predictive value of 70%, positive likelihood ratio of 2.9 and negative likelihood ratio of 0.2.
Conclusion: ADCS-ADL scale presents satisfactory psychometric properties to discriminate between MCI, AD and normal cognition.

Keywords: mild cognitive impairment, Alzheimer's disease, activities of daily living.

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Introduction

An accelerated aging process in the population can be observed in both developed and developing countries. In Brazil, from 1940 onwards, the aging process has increased morbidity and mortality due to external causes and chronic-degenerative diseases, such as dementia.[1] The evolution of these diseases is often marked by the progressive decline in functional capacity, with consequent impairment of quality of life.[1-3]

According to the World Alzheimer Report (2011), more than 65 million people worldwide have dementia, 58% of which live in underdeveloped countries. This research also reveals that studies conducted over the last 10 years have shown that only one fifth of dementia cases are routinely recognized and documented in developed countries. In underdeveloped countries, such as Brazil, the situation is even more serious, as up to 90% of the relatives of patients with this clinical condition had not even received guidelines regarding the disease and available treatments.[2,4]

In recent years, mild cognitive impairment (MCI) has been recognized as an intermediate stage between normal

cognition and dementia.[5] MCI indicates that the affected individual presents greater chances of conversion to dementia caused by Alzheimer's disease (AD) and other degenerative processes than individuals with normal cognition for their educational level.[5]

MCI usually affects one or more domains of cognition, and is classified into the amnestic and non-amnestic subtypes, according to the presence or absence of memory impairment. The amnestic type is mainly characterized by memory complaints and may reflect AD in the pre-dementia symptomatic phase. The non-amnestic type is characterized by deficits in any other domain of cognition, for example, executive function, reasoning, attention, and more.[5] The latter, most often progresses to other forms of dementia (not AD).[6-8]

According to Bagen et al., elderly people with MCI present difficulties in the performance of activities of daily living (ADL).[9] However, there are problems related to the identification and classification of the activities involved. Subtle deficits were identified in advanced and instrumental ADL, which would generally go unnoticed, compromising quality of life and determining the risk of conversion to AD.

Functionality may represent an important marker in the differential diagnosis between individuals with normal cognition and amnestic MCI. However, the existing instruments for functional assessment are heterogeneous, making comparisons difficult. Most tests used are not validated and culturally adapted for use in the Brazilian population with MCI. In addition, doubts remain as to which ADL are compromised and how best to assess them.[9-13]

In this context, the purpose of this article is to report the results of the process of translation, cross-cultural adaptation and application of the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale as an instrument for evaluating the functionality of the Brazilian population for the diagnosis of dementia and its non-dementia clinical phase, also known as MCI.

Method

This is a cross-sectional study in which individuals were recruited from June 2012 to May 2013 by convenience sampling obtained at the Mild Cognitive Impairment outpatient clinic of the Jenny de Andrade Faria Institute for Elderly Care at the Federal University of Minas Gerais (UFMG) Clinics Hospital. All of the participants and/or their companions/caregivers signed the informed consent form (ICF). This study was approved by the UFMG Research Ethics Committee under no. 0318.0.203.000-11.

The ADCS-ADL scale was created in 1997 by Galasko et al.[14] It is a questionnaire with 23 Likert-type questions for functional assessment, in which the subject must express their degree of agreement or disagreement with the questions in the questionnaire (independent, partially independent and totally dependent). It is adapted for elderly people with MCI and it is completed based on the data provided by an informant. The questionnaire describes the performance of patients in the prior month in various activities: Basic (BADL), instrumental (IADL) and advanced (AADL) ADL.[15,16]

The procedure for translation and cultural adaptation followed an internationally accepted protocol proposed by Beaton et al.[17] The technique used was back-translation associated with the bilingual method, following five stages, namely, two independent translations, synthesis of the Portuguese translations, back translation of the scale into English, and analysis of the questionnaire by a panel of expert judges. The pre-final version was then submitted to pre-testing.

For pre-testing, a sample consisting of 90 Brazilian elderly people living in the community and their respective caregivers or informants was divided into three groups containing 30 individuals each: cognitively normal controls, amnestic MCI patients, and patients with probable early stage AD. The application of the questionnaire was timed.

We included 95 individuals aged 60 years or older with normal cognition, MCI or AD. The diagnosis of probable sporadic AD followed the criteria of Mckhann et al., classified as mild, stage 1 by the Clinical Dementia Rating (CDR).[18,19] For MCI, the criteria defined by Albert et al. and Petersen et al. were used.[5,20] This group only included patients with the amnestic form. The control group consisted of individuals with normal cognition considering the specific cut-off points according to educational level.

Individuals with non-Alzheimer's dementia, moderate or advanced AD, psychiatric illness, Parkinson's disease, delirium and MCI secondary to other causes (psychiatric disorders, endocrine-metabolic diseases, autoimmune diseases, traumatic brain injury, drugs, alcohol and drugs) were excluded. We also excluded subjects with impaired mobility, vision or hearing deficits, and those who did not complete all of the assessments. We did not include individuals whose companion and/or caregiver were not present at the assessment interview.

For an adequate assessment of cognition and allocation of individuals to the groups described, all patients underwent evaluation by geriatricians and neuropsychologists trained in cognitive assessment of the elderly.

All subjects were submitted to the same study protocol. In order to rule out other causes of cognitive decline and to diagnose concomitant diseases, laboratory and structural and functional neuroimaging examinations (nuclear magnetic resonance or computed tomography of the brain and/or positron emission tomography – PET-CT of the brain) were performed. In all cases, the clinical and neuropsychological diagnoses were concordant.

The following tests were used to assess cognition, mood, functionality and caregiver overload: Mini-Mental State Examination[21] (MMSE), verbal fluency test – fruit and animal category,[22] Geriatric Depression Scale – 15-item version,[23] the clock test,[24] word list from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD),[25] Behavioral Pathology in Alzheimer's Disease Scale – BEHAVE-AD,[26] the Pfeffer Instrumental Activities Questionnaire,[27] the List of Figures,[28] Clinical Dementia Rating (CDR),[19] the apathy scale,[29,30] functional stating using the Functional Assessment Staging (FAST),[31] the Neuropsychiatric Inventory (NPI),[32] and the DSM-IV Criteria for Depressive Disorder.[33]

Regarding the neuropsychological assessment, cognitive tests were applied considering the low educational level of the study population, based on the service's protocol, as described below: The Mattis Dementia Rating Scale,[34,35] the Digit Span test,[36] the Corsi Cubes,[37,38] Token Test,[39,40] and Rey's Auditory-Verbal Learning Test – RAVLT.[41-44]

The Shapiro-Wilk test was used for normality analysis. The distribution of the sample was considered normal only for the age of the informant variable. Chi-square, Anova and Kruskal-Wallis tests were used as non-parametric tests. To verify correlations between continuous variables, we used Spearman correlation test.

Descriptive and analytical statistics; quality of clinical trials: sensitivity (Se), specificity (Sp), negative (NPV) and positive (PPV) predictive value, positive (PLR) and negative (NLR) accuracy and likelihood ratio; ROC curve (to establish the cut-off point) and Cronbach's alpha (internal consistency) were performed in order to determine reliability. The data obtained was analyzed using the SPSS statistical software version 19.0, IBM®.

Results

Translation and cultural adaptation of the ADCS-ADL Questionnaire

The process of translation and adaptation of the questionnaire showed satisfactory results, indicating semantic equivalence between the two translations and absence of translation difficulties, verified by the small number of modifications carried out by the expert committee. The changes involved: formatting of the questions (47%), cultural expressions (29%) and vocabulary (17%). Other changes totaled 7%. These items were modified or had their format changed in order to facilitate cultural understanding and appropriateness. These changes did not result in significant change to the scale. One subitem to a question (question 24) was added and the score changed from 78 to 79 points.

During the pre-testing application, a statistical difference was observed between the control and AD groups in the subdomain BADL, composed of self-care and feeding activities. This relation was not expected since the decline in BADL only occurs in the more advanced stages of AD. Analyzing the items in this subdomain, we observed that "select/choose clothes" and "eat using forks and knives" were responsible for this difference, since they obtained lower scores when compared to the other items of the BADL subdomain, probably due to the influence of gender in these tasks.

To minimize this bias, we modified the item "eating using forks and knives" to "eating independently" and removed the item "select/choose clothes," given that even among men in the control group, this activity was performed by a third party, usually the wife or daughter. We observed that for many elderly people the activity of selecting clothes is delegated to the spouse, constituting a pattern of dependence cultivated by personal habits. These modifications to correct the influence of gender did not cause a change in the final score of the questionnaire.

Considering the expert opinions and pre-testing, we constructed the Brazilian version of the ADCS-ADL.

General characteristics of the sample selected for pre-testing

The 95 participants selected were allocated into three groups: 30 controls, 32 MCI and 33 AD. Regarding the MCI group, all of the patients presented the amnestic subtype, with 73% involving multiple domains and 27% a single domain. The sociodemographic data and the comorbidities of the participants are listed in Table 1.

Regarding the characterization of the control, MCI and AD groups, we noted a level of statistical significance and difference among groups in the age (p=0.020) and educational level (p=0.037) variables. The AD group, compared to others, was older (78.6±6.6) and presented lower educational level (3.6±3.2). As for comorbidities, 79.3% of the total sample had high blood pressure (HBP), 38.7% dyslipidemia, 21.5% type 2 diabetes mellitus (T2DM) and 20.4% had major depressive disorder. The depression variable showed a statistical difference among groups (p=0.028). Regarding caregiver characterization, the groups were similar in all of the evaluated variables, except age (p=0.015).

TABLE 1 Clinical and sociodemographic characteristics of the sample and their respective caregivers.

Variables	Control group n=30	Group MCI n=32	Group AD n=33	Total n=95	p-value
Sample data					
Sex					
Female (%)	63.3%	65.6%	51.5%	60.0%	0.461
Male (%)	36.7%	34.4%	48.5%	40.0%	
Education					
(Mean±SD in years)	5.7±4.4	5.2±3.9	3.6±3.3	4.8±3.9	0.037*
Age					
(Mean±SD in years)	73.4±7.9	75.3±7.6	78.6±6.6	75.9±7.6	0.020*
HBP (%)	79.3%	65.6%	84.4%	76.3%	0.190
T2DM (%)	20.7%	18.8%	25%	21.5%	0.824
Dyslipidemia (%)	41.4%	43.8%	31.3%	38.7%	0.554
Depression (%)	6.9%	18.8%	34.4%	20.4%	0.028*
Caregivers' data					
Sex					
Female (%)	74.3%	75.0%	90.0%	80.0%	0.147
Male (%)	25.7%	25.0%	10.0%	20.0%	
Education					
(Mean±SD in years)	9.9±3.8	8.7±3.1	9.2±4.1	9.2±2.6	0.276
Age					
(Mean±SD in years)	52.2±17.1	55.0±13.0	52.1±14.9	53.1±14.9	0.015*
Degree of family relations					
Close relatives (%)**	85.7%	75.0%	87.5%	82.6%	0.285
Other	14.3%	25.0%	12.5%	17.4%	

MCI: mild cognitive impairment; AD: Alzheimer's disease; SD: standard deviation; HBP: high blood pressure; T2DM: type 2 diabetes mellitus.
*significant difference.
**Close relatives: wife, husband, children or siblings.

The control group achieved higher mean scores in the MMSE tests (control: 26.5; MCI: 24.2 and AD: 19.3) and on the Mattis scale (control: 132.5; MCI: 119.1 and AD: 102.6). In relation to the MMSE variable, there was a significant difference only between the AD-MCI and AD-control groups (p=0.001). As for the Mattis scale, there was a significant difference in all groups (p<0.001).

Functionality, assessed by the Pfeffer and ADCS-ADL scales, presented a similar pattern of results to cognitive ability. Regarding the Pfeffer test, we observed greater independence in the control group (0.4±0.7), greater dependence in the AD group (10.6±7.2) and intermediate result in the MCI group (4.3±4.9), with a statistical difference only detected between AD and MCI (p=0.004).

The mean application time of the ADCS-ADL scale was 12 minutes. The control group showed a better score on the scale (72.9), followed by the MCI group, with intermediate performance (65.1). The AD group had the worst performance (55.9) (p<0.001). As for the subitems in the ADCS-ADL scale, AADL and IADL presented a p-value <0.001, while BADL resulted in p=0.004. This difference is shown in Figure 1, which enables the detection of different functional profiles among the control, MCI and AD groups, showing mainly functional decline from the AD group to the MCI group, and from this group to the control group, especially regarding the IADL and AADL subitems.

As for the BADL subitem, despite the statistical difference observed, this was not clinically important due to very close values among the groups, especially considering the standard deviation. The AD group's result was 19.9±2.3, MCI's 20.8±1.5 and the control group's was 21.5±0.7.

Reliability

The reliability of the Brazilian ADCS-ADL scale was obtained by analyzing the internal consistency coefficient of its 23 questions distributed in three subdomains:

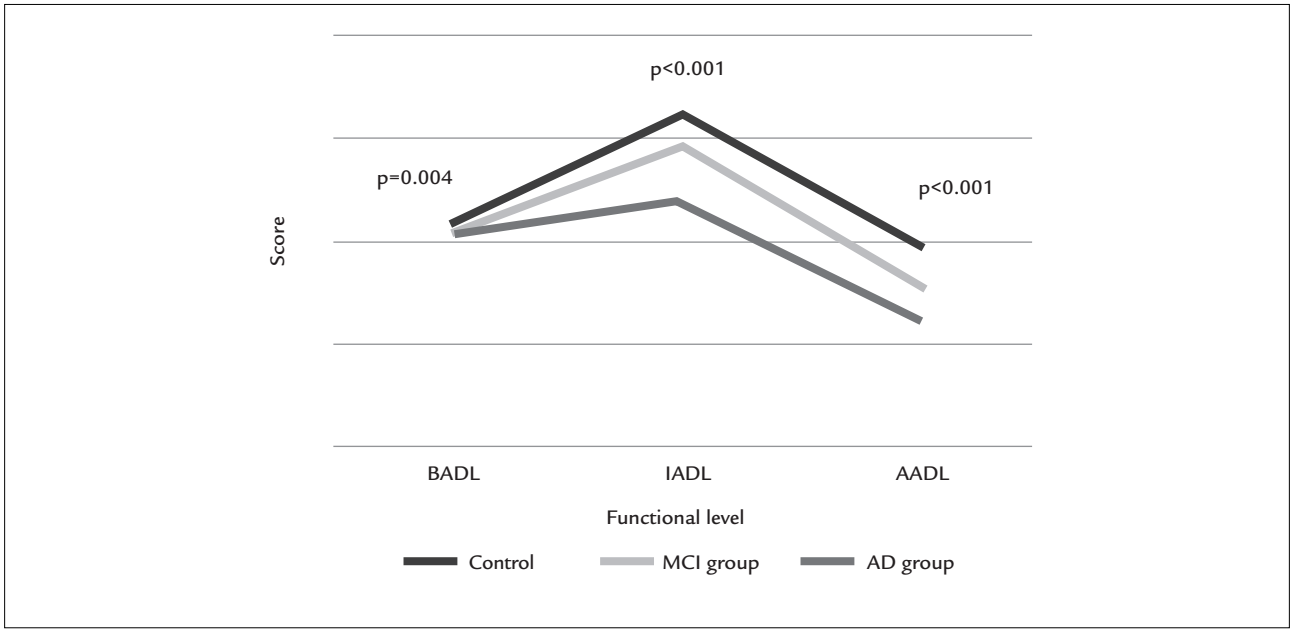

FIGURE 1 Characterization of the functional profile of the groups based on the mean points obtained by subdomain of the ADCS-ADL scale.
MCI: mild cognitive impairment; AD: Alzheimer's disease; BADL: basic activities of daily living; IADL: instrumental activities of daily living; AADL: advanced activities of daily living.

BADL (6 questions), IADL (10 questions) and AADL (7 questions). This analysis was verified by Cronbach's alpha coefficient, yielding 0.89. This value suggests a good correlation among domains. The Cronbach's coefficient was applied question to question rather than by domains (AADL, IADL and BADL), and in all cases the values found were higher than 0.80.

Criterion validity

Our study's hypothesis that the constructs measured by the ADCS-ADL scale and the clinical and neuropsychological diagnoses would be associated and that this could be used as a diagnostic tool for MCI and AD was established and tested.

The results showed a significant association between the total ADCS-ADL scale and the clinical and neuropsychological diagnosis ($p<0.001$) with $ROC_c=0.89$. The AADL subdomain of the total ADCS-ADL scale presented a greater area under the curve ($ROC_c=0.92$) in relation to the reference line (clinical and neuropsychological diagnosis). The results of these variables are close to those in the curve delimited by the Mattis scale ($ROC_c=0.918$), whose study demonstrated greater diagnostic accuracy among study subjects, namely the control, MCI and AD.[44] On the other hand, the Pfeffer IADL scale showed an area under the curve of 0.89.

We established the cut-off point as 71 for the ADCS--ADL scale, to distinguish MCI and AD patients from controls, based on the sensitivity (Se) of 86.2%, specificity (Sp) of 70.0%, PPV of 86.2%, NPV of 70.0% and accuracy of 81.1%. The PLR was 2.9 and the NLR was 0.2.

In order to differentiate the MCI subjects from the controls, the ADCS-ADL scale with a cut-off value of 71 points presents sensitivity of 75% and specificity of 70%. To distinguish individuals with AD from the controls, we observed a sensitivity of 97.0% and specificity of 70%. Finally, to discriminate between AD and MCI, we found a sensitivity of 97.0% and specificity of 25%. The other quality tests of the scale carried out with the subitems IADL and BADL are described in Table 2.

We demonstrated that the AADL subitem of the ADCS-ADL scale shows good accuracy to discriminate subjects from the control, MDI and AD groups, and is superior even to the full results of the scale. We established a cut-off of 18 points, and found the following results: Se: 90.8%; Sp: 73.3%; PPV: 88.1%; NPV: 78.6%; accuracy: 85.3%. PLR was 3.4 and NLR was 0.1.

The subitem AADL with a cut-off point of 18 points presents 84.4% sensitivity and 73.3% specificity to differentiate MCI subjects from controls. To distinguish individuals with AD from the controls, we detected a sensitivity of 97.0% and specificity of 73.3%. To discriminate between AD and MCI, we obtained a sensitivity of 97.0% and specificity of 15.6%. The data relating to IADL and BADL are described in Table 2.

TABLE 2 Analysis of the quality measure of the ADCS-ADL scale.

Analysis of the total ADCS-ADL scale with cut-off value set at 71 points							
	Se	**Sp**	**PPV**	**NPV**	**Accuracy**	**PLR**	**NLR**
Cognitive decline (MCI and AD) versus controls	86.2%	70%	86.2%	70%	81.1%	2.9	0.2
MCI versus control	75%	70%	72.7%	72.4%	72.6%	2.5	0.4
AD versus control	97%	70%	78%	95.4%	84.1%	3.2	0.04
AD versus MCI	97%	25%	42.9%	88.9%	61.5%	1.3	0.1
Analysis of the AADL subitem of the ADCS scale with cut-off value set at 18 points							
	Se	**Sp**	**PPV**	**NPV**	**Accuracy**	**PLR**	**NLR**
Cognitive decline (MCI and AD) versus controls	90.8%	73.3%	88.1%	78.6%	85.3%	3.4	0.1
MCI versus control	84.4%	73.3%	77.1%	81.5%	79%	3.2	0.2
AD versus control	97%	73.3%	80%	95.7%	85.7%	3.6	0.04
AD versus MCI	97%	15.6%	54.2%	83.3%	56.9%	1.1	0.2
Analysis of the IADL subitem of the ADCS-ADL scale with cut-off value set at 32 points							
	Se	**Sp**	**PPV**	**NPV**	**Accuracy**	**PLR**	**NLR**
Cognitive decline (MCI and AD) versus controls	81.5%	76.7%	88.3%	65.7%	80%	3.5	0.2
MCI versus control	68.8%	76.7%	75.9%	69.7%	72.6%	3.0	0.4
AD versus control	93.9%	76.7%	81.6%	92%	85.7%	4.0	0.08
AD versus MCI	93.9%	31.3%	41.5%	83.3%	63.1%	1.4	0.2
Analysis of the BADL subitem of the ADCS-ADL scale with cut-off value set at 21 points							
	Se	**Sp**	**PPV**	**NPV**	**Accuracy**	**PLR**	**NLR**
Cognitive decline (MCI and AD) versus controls	66.2%	63.3%	79.6%	46.3%	65.3%	1.8	0.9
MCI versus control	68.8%	63.3%	66.7%	65.5%	66.1%	1.9	0.5
AD versus control	63.6%	63.3%	65.6%	61.3%	63.5%	1.7	0.6
AD versus MCI	63.6%	31.3%	48.8%	45.5%	47.7%	0.9	1.2

ADCS-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living; MCI: mild cognitive impairment; AD: Alzheimer's disease; Se: sensibility; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; AADL: advanced activities of daily living; IADL: instrumental activities of daily living; BADL: basic activities of daily living.

Discussion

Despite the great amount of knowledge regarding the description and monitoring of functional decline in the population with dementia, there is a gap in the literature with regard to the analysis of impairment of ADL in elderly people with MCI, characterized as a pre-dementia symptomatic stage of AD.[45]

Several studies have aimed to characterize the nature of functional decline in this heterogeneous population, since the inclusion of the criterion "preservation of daily activities with slight impairment in complex activities" as a diagnostic for MCI in 2004. However, the unsystematic use and variability of the functional assessments employed have impaired more accurate results.[46-49]

We know that there are many scales for the assessment of ADL in the elderly. However, they were created with the objective of assessing the functional decline in elderly people with dementia, whose deficit proves to be more significant when compared to elderly people with MCI.[48] This may create a "ceiling effect" in the instrument, masking the functional decline presented by individuals with MCI.[50]

In this context, the concern for early diagnosis is added to the need for instruments adapted and validated for the Brazilian population that assess the risk of dementia and MCI quickly, accurately and at a low cost. Our study aimed to perform a cultural adaptation, initial validation and analysis of the psychometric properties of the ADCS-ADL in view of its applicability and the satisfactory results observed in other studies.[15,16,46,51] To our knowledge, this is one of the few Brazilian studies that describe the functional profile of elderly people with MCI, compared to that of elderly people with normal cognition and initial AD.[16,46,52]

The use of a scale based on information from third parties (caregivers or informants) seems to be the most suitable for assessing the functionality of elderly people with MCI, given that these elderly people often present anosognosia and do not recognize the extent of their difficulties.[53-55]

In our study, we were able to verify that there are different functional profiles among subjects with MCI, AD and controls, with MCI assuming an intermediate pattern between the control group and the elderly with AD. We also noted that elderly people with MCI presented deficits in AADL and IADL when compared to controls with normal cognition for age and educational level. Elderly people with AD also present deficits in these specific areas but functional decline is greater.

Our results resemble those of Perneczky et al. and Pereira et al.[46,56] They found that elderly individuals with MCI presented a functional decline in complex ADL compared to control subjects. The literature on the subject reveals that despite variability in the use of ADL assessment scales, several studies have identified a decline in AADL (exercise of roles and social activities typical of adult life) and IADL (management of domestic and community practical life) in elderly people with MCI.[47-49,57]

It is important to emphasize that this type of instrument can be influenced by factors such as the level of caregiver overload, degree of proximity and the emotional state of the informant.[58] To reduce the chance of error, the ADCS-ADL scale also has a manual with clear and objective explanations for all items. Another positive point is that it assesses the individual's actual performance in a month, and therefore excludes the caregiver's opinion about what the individual could do if they presented conditions to do so, as well as what the caregiver subjectively thinks with respect to the subject assessed.

It was verified that few items were left unanswered (8.7%), which contributes to the high internal validity of the test. Most caregivers were close relatives. However, a small percentage (17.4%) were comprised of other relatives, which may have contributed to the unanswered items.

It is important to emphasize that some items in the IADL and BADL subdomains of the ADCS-ADL scale may be influenced by the gender variable, such as cooking, using cutlery and washing and ironing. Culturally, these activities are carried out by Brazilian women.[59] As previously described, the necessary adaptations were performed after pre-testing applications, adjusting the test to the cultural demands by gender.

Regarding the analysis of the psychometric properties, the ADCS-ADL scale provided good reliability, also verified in the study by Pedrosa et al.[16] In addition, the study presented a moderate Se value in the control-MCI differentiation (75%) and high Se value to differentiate AD-control (97%). However, there were moderate Sp values in both cases (70%).

According to the analyses regarding the differentiation of the MCI-AD group, the scale showed a high Se value (97%) and low Sp value (25%), which indicates that it is effective in the discrimination of this group. It should be noted that our specificity values are lower than those presented in the study by Pedrosa et al.[16]

We can infer from these results that the ADCS-ADL scale constitutes a test with high Se and moderate Sp, presenting greater power to detect people with cognitive impairment, although susceptible to false positives, especially in the differentiation between AD-control and MCI-AD. The scale was reasonable in the distinction between control-MCI. It can be used as a screening instrument for identifying individuals at risk of MCI or AD, requiring further evaluation in order to define the diagnosis.[60]

We believe the ADCS-ADL scale to be a viable instrument as it is easy to apply, and external materials or resources are not required for its completion. Furthermore, it is quick to apply, especially compared to other diagnostic assessment instruments.

When analyzing the psychometric properties of the subitems in the ADCS-ADL scale, we are faced with the fact that AADL, composed of seven questions, presents results superior to the full scale in discriminating between control, MCI and AD patients, especially for differentiating the subjects with MCI from the controls more effectively than the full version of the ADCS-ADL scale. In addition, this subitem presents results only slightly below those obtained using the Mattis scale and above those in the Pfeffer ADL scale, when evaluated using the ROC curve. However, this subitem needs to be evaluated in the future as a reduced version of the ADCS-ADL scale with the same psychometric properties as the full scale.

It should be noted that the AADL subitem presents high sensitivity and a PLR value close to 0.1. These properties point to the potential of using the questionnaire as a screening tool, which reinforces the possibility of it being applied in primary care. This fact is of extreme importance in view of the difficulty in identifying these patients in primary health care, which has an impact on the diagnosis and management of cognitive and functional disorders, especially when considering early diagnosis. It should be noted that the data relating to the AADL subdomain are not comparable, given that no other study with the full scale has adopted this division.

In primary care, initial AD and MCI are often not diagnosed. Data from the literature show that in developed countries only 20 to 50% of patients with dementia are diagnosed, whereas in some underdeveloped countries the rate is less than 10%.[4] These data reinforce the importance of the results found in the AADL subitem. Given the above, we suggest validation studies in primary care, especially

those involving community health agents or nurses at health centers.

The Pfeffer Instrumental Activities Questionnaire presented ROC = 0.89, close to the values shown by the ADCS-ADL scale. It is worth noting that the scale was originally described for functional assessment, and was mainly used to evaluate initial AD with Se: 85% and Sp: 81%.[27] There is no cut-off point defined for MCI in the analysis of all the existing versions of the test in Brazil, with a cut-off point of 3 and 5 points described for functional impairment and functional incapacity, respectively.[61] Studies for screening cognitive impairment in elderly populations with low levels of education, such as in Brazil, indicate that the use of Pfeffer's instrumental activities questionnaire is not sufficient for adequate screening of cognitive decline, and other cognitive tests must be combined to obtain suitable sensitivity and specificity values.[62]

Our study has limitations given that the scale is not yet validated due to the absence of the peer evaluation phase. The validation process for the Brazilian Portuguese version must be completed, despite the existence of a validated version in Portuguese from Portugal.[63] Brazil and Portugal, although adopting the same official language, hold profound cultural and linguistic differences, which justify the need for a separate validation for each country.[64] Furthermore, it is important to highlight the differences resulting from the influence of different levels of education among the elderly population of the two countries.[65] The authors of the original scale have given their authorization for cross-cultural adaptation in Brazil, which did not extend to disclosure in the original format and in the adapted version, therefore the ADCS-ADL scale is not attached to this article.

We conclude that the translated version of the ADCS-ADL adapted to Brazilian Portuguese has satisfactory psychometric properties to differentiate patients with cognitive incapacity from those with MCI. In view of the psychometric properties described for the AADL subitem of the ADCS-ADL scale, we suggest validation of this reduced version as a possible functional screening tool in primary care.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Declínio funcional em idosos com comprometimento cognitivo leve: adaptação cultural da escala ADCS-ADL.

Objetivo: Tradução, adaptação transcultural para o português brasileiro e aplicação da escala Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) como instrumento de triagem cognitiva.

Método: Retrotradução associada ao método bilíngue e de pré-teste. A amostra foi constituída por 95 idosos e seus respectivos acompanhantes, sendo 30 controles, 32 portadores de comprometimento cognitivo leve (CCL) e 33 portadores de demência de Alzheimer (DA) em fase inicial.

Resultados: Um pequeno número de modificações ocorreu na escala. O coeficiente alpha de Cronbach foi 0,89. O grupo controle pontuou 72,9, seguido pelo CCL (65,1) e pelo DA (55,9), valor p<0,001. A curva ROC demonstrou valor de 0,89. Com o ponto de corte de 72, observamos sensibilidade de 86,2%, especificidade de 70%, valor preditivo positivo de 86,2%, valor preditivo negativo de 70%, razão de verossimilhança positiva de 2,9 e razão de verossimilhança negativa de 0,2.

Conclusão: A escala ADCS-ADL apresenta propriedades psicométricas satisfatórias para discriminar entre DA, CCL e cognição normal.

Palavras-chave: comprometimento cognitivo leve, demência de Alzheimer, atividades cotidianas.

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Levels of uric acid and increased diastolic blood pressure: Risk factors for atrial fibrillation in patients older than 60 years

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Summary

Objective: To characterize the maximum P-wave duration (Pmax) and P-wave dispersion (PWD) according to blood pressure (BP) and uric acid (UA) levels in geriatric patients.
Method: An analytical study was performed in 83 patients aged over 60 years treated at the Family Medical Office 5 of the Aracelio Rodríguez Castellón Polyclinic, in Cienfuegos, Cuba between January and December 2015. The sample was divided into two groups (patients with hyperuricemia and patients with normal UA levels).
Results: We found a linear and significant correlation between diastolic BP and Pmax in patients with hyperuricemia (r=0.695; p=0.026), but not in patients with normal UA (r=0.048; p=0.757). A linear and significant correlation was demonstrated between diastolic BP and PWD in patients with hyperuricemia (r=0.657; p=0.039), but not in patients with normal UA (r=0.054; p=0.730).
Conclusion: There is correlation between diastolic BP and Pmax plus PWD in elderly patients with hyperuricemia.

Keywords: atrial fibrillation, risk factor, P-wave, P-wave dispersion, uric acid, geriatrics.

Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. They currently account for approximately 1/3 of global deaths.[1] Atrial fibrillation (AF) is the most frequent cardiac arrhythmia found in clinical practice. Its prevalence is close to 33.5 million people, and it is associated with an increased risk of cardiovascular complications and decline in the quality of life of patients.[2,3] Traditionally, advanced age, high blood pressure (HBP), heart failure, valvular heart disease, ischemic heart disease and diabetes mellitus have been considered risk factors for developing AF. On the other hand, recent studies have shown that increased plasma levels of uric acid (UA) constitute a risk factor for AF. Accumulation of UA in the body increases the action of pro-inflammatory substances, raises the levels of oxidative stress and boosts the activity of the renin-angiotensin-aldosterone system, favoring the development of AF.[4-8]

During the last few years, useful electrocardiographic markers have been developed to predict AF. Some have been proposed, such as maximum (Pmax)[9] and minimum P-wave duration,[10] P-wave terminal force in lead V1[11] and P-wave dispersion (PWD).[12-15]

Although AF has been associated with increased blood pressure (BP) and UA levels, there are still no studies worldwide that address the relation between Pmax plus PWD and BP plus UA in patients over 60 years of age, in whom there is an increased risk of AF. Taking these elements into account, our study aimed to characterize Pmax and PWD according to BP and UA levels in geriatric patients in a health clinic.

Method

An observational and analytical study was performed with patients older than 60 years treated at the Family Medical Office 5 of the Aracelio Rodríguez Castellón Polyclinic, province of Cienfuegos, Cuba, between January and December 2015. The sample comprised 83 patients. The patients were divided into two study groups. The first group included patients with hyperuricemia, while the patients with normal levels of UA were allocated into the second group. Hyperuricemia was defined

by UA > 357 mmol/L in women and > 425 mmol/L in men, according to the reference parameters of the laboratory used for the investigation. Patients using anti-gout drugs, patients with gouty arthritis, acute or chronic renal failure, lymphomas or leukemia or who refused to participate in the study were excluded. In both of the groups, clinical, anthropometric, laboratory and electrocardiographic variables were collected.

Data collection

Each patient underwent a medical interview for collection of the clinical variables of the study that were reflected in a survey designed for this purpose. The individual autonomy of each patient was respected regarding participation in the study. Individuals who were not able to answer the questions or did not meet the inclusion and exclusion criteria were not interviewed. The patients sought medical consultation for three consecutive days, where the clinical and anthropometric variables were obtained. BP was checked for three consecutive days and an average of three readings was obtained. BP was always recorded by the same staff members, either a licensed nurse or the doctor in the practice. The requirements for an appropriate BP check were considered as recommended by current HBP guidelines.[16] A properly calibrated sphygmomanometer KANGJU model KT-A02 distributed by the Ministry of Public Health of Cuba was used.

The weight and height of the patients were obtained using a scale and a stadiometer, respectively. Both were properly calibrated.

Laboratory variables were obtained from a single sample of fasting blood. The conventional method was used for sample analysis, and all values were presented according with the International System of Units.

Each patient underwent an electrocardiogram. Electrocardiograms were conducted with the patients in supine position by an expert who guaranteed their adequate performance. The ECG device was a CARDIOCID BB made in Cuba. All electrocardiograms were recorded at a speed of 25 mm/s and 1 mV voltage = 10 mm. ECG results were digitized for further analysis. The measurements were made using a digital caliper by two experts on the subject. Electrocardiograms with artifacts were excluded, as well as those with measurable P-waves in less than 10 leads. P-wave maximum and minimum duration were obtained from the maximum and minimum values obtained for these parameters, respectively. PWD is defined as the difference between the maximum and minimum P-wave duration, taking into account the 12 ECG leads.

Data analysis and processing

The collected data was analyzed using Statistical Package for the Social Sciences (SPSS) for Windows Version 21.0. The results were displayed in tables and statistical graphs. Qualitative variables were shown as absolute and relative frequencies. Statistical analysis of the qualitative variables was performed using Chi-square.

Quantitative variables were expressed as arithmetic mean ± standard deviation. Kolmogorov-Smirnov test was performed to determine the distribution of the quantitative variables. Variables with a normal distribution were examined using the Student's t-test, while those without a normal distribution were analyzed by the Wilcoxon Test. Pearson's linear correlation test was performed to determine the association between Pmax plus PWD and diastolic blood pressure (DBP) in both groups. Based on the results of the linear regression analysis, the test was adjusted taking into account the following variables: personal history of hypertension, diabetes mellitus and body mass index. A p-value < 0.05 was considered statistically significant.

Our research was approved by the Ethics Committee of the Aracelio Rodríguez Castellón Polyclinic, in Cumanayagua, Cienfuegos, Cuba.

Results

Hyperuricemia was present in 25.3% of patients. Cases with hyperuricemia have a higher frequency of personal history of HBP, ischemic heart disease, diabetes mellitus and smoking (80.95 vs. 62.30%, 23.81 vs. 20.97%, 23.21 vs. 11.29%, 28.57 vs. 25.81%, respectively), although without significant differences. Weight and body mass index are higher in cases with hyperuricemia, although without statistical significance (67.00±16.77 kg vs. 65.31±9.22 kg; p=0.563, and 27.97±5.67 kg/m^2 vs. 25.45±4.12 kg/m^2; p=0.057). Patients with hyperuricemia have higher mean DBP values compared to those with normal UA (81.44±9.30 vs. 75.24±10.49; p=0.042).

Figure 1 shows that there is a linear and significant correlation between mean DBP and Pmax in patients with hyperuricemia (r=0.695; p=0.026), but not in patients with normal UA levels (r=0.048; p=0.757).

Figure 2 shows that there is a linear and significant correlation between the mean DBP and PWD in patients with hyperuricemia (r=0.657; p=0.039), but not in patients with normal UA (r=0.054; p=0.730).

Discussion

Our study is the first to investigate electrocardiographic markers of AF in geriatric patients, and their association with BP and plasma levels of UA.

Table 1 shows the characterization of the sample according to clinical and anthropometric variables in both study groups. It can be observed that certain traditional risk factors such as history of HBP, body mass index and smoking are found more frequently in patients with hyperuricemia compared to those with normal UA. Chuan et al.[8] found that patients with hyperuricemia have a significantly higher body mass index than patients with normal UA (24.5±3.7 kg/m^2 vs. 23.0±3.4 kg/m^2; p≤0.0001). In another study evaluating the risk of AF in patients with and without hyperuricemia, the authors demonstrated that patients in the third quartile of UA levels have a prevalence of HBP of 20.4%, while 13.5 and 12.0%, respectively, were in the lower quartiles.[17] Recently, a study of 1,296 patients over 60 years of age with AF investigating the prevalence of left ventricular hypertrophy showed that hypertension has a higher prevalence among patients with hyperuricemia compared to those with normal UA (77.8 vs. 74.2%).[18]

Hyperuricemia is a recognized risk factor for cardiovascular disease. Increased UA levels have been associated with the development of coronary artery disease, HBP, diabetes mellitus and heart failure,[19] so it is common for cardiovascular risk factors such as HBP, obesity and smoking to be more prevalent in patients with hyperuricemia. Increased UA may also be part of a complex process in which other cardiovascular risk factors are involved. This process could be the cause of higher levels of oxidative stress and systemic inflammation favoring the development of cardiac diseases including AF.

In our investigation, mean systolic blood pressure (SBP), mean DBP, and mean BP are higher in patients with hyperuricemia. These results are consistent with several previous investigations. Sun et al.[20] conducted case-control research on 11,956 patients in China in order to determine the association between UA levels and the risk of AF. They found that among other risk factors, SBP and DBP are significantly higher in patients with hyperuricemia compared to patients with normal UA (145.9±23.8 mmHg vs. 141.2±23.4 mmHg; p<0.01, and 85.7±12.7 mmHg vs. 81.5±11.5 mmHg; p<0.01, respectively). In this investigation, the authors also found that high levels of UA represent a risk factor for developing AF.

High levels of UA have been shown to be a risk factor for HBP.[21,22] Hyperuricemia is equally common in pre-hypertensive patients. Some studies have shown that the prevalence of hyperuricemia is 40-60% in patients with uncontrolled hypertension.[23] In animal models, it has been observed that there is a direct correlation between plasma levels of UA and BP. In these cases, the use of drugs inhibiting the enzyme xanthine oxidase decreases UA levels and BP.[24]

Several pathophysiological mechanisms have been proposed to explain this association. In laboratory rats with hyperuricemia, the development of microvascular renal disease with histological changes similar to atherosclerosis precedes the development of HBP.[25] Experiments

TABLE 1 Clinical variables in patients with hyperuricemia and normal UA.

Variables	Normal UA (n=62)	Hyperuricemia (n=21)	p-value
Age (years), mean±SD	69.69±7.39	67.10±5.49	0.144
Sex – male, N/%	33/53.22	7/33.33	0.115
Skin color – white, N/%	57/91.94	18/85.71	0.404
Weight (kg), mean±SD	65.31±9.22	67.00±16.77	0.563
Height (m), mean±SD	1.60±0.09	1.55±0.12	0.044
BMI (kg/m^2), mean±SD	25.45±4.12	27.97±5.67	0.057
W circum (cm), mean±SD	94.09±10.42	93.76±14.01	0.910
H circum (cm), mean±SD	101.15±8.90	101.14±12.76	0.997
PH-HBP, N/%	38/62.30	17/80.95	0.117
PH-ICM, N/%	13/20.97	5/23.81	0.624
PH-DM, N/%	7/11.29	5/23.21	0.188
Smoking habit, N/%	16/25.81	6/28.57	0.835
HR (bpm), mean±SD	74.25±13.33	74.28±11.82	0.993
mSBP (mmHg), mean±SD	126.12±20.63	126.67±18.07	0.926
mDBP (mmHg), mean±SD	75.24±10.49	81.44±9.30	0.042
MAP (mmHg), mean±SD	92.20±12.65	96.51±11.30	0.236

PH-HBP: personal history of high blood pressure; PH-ICM: personal history of ischemic cardiomyopathy; PH-DM: personal history of diabetes mellitus; HR: heart rate; BMI: body mass index; H circum: hip circumference; W circum: waist circumference; mSBP: mean systolic blood pressure; mDBP: mean diastolic blood pressure; MAP: mean arterial pressure; SD: standard deviation.

developed in cultured cells demonstrate that increased levels of UA induce cell proliferation, inflammation, oxidative stress and activation of the local renin-angiotensin system.[26,27]

The relation between UA and HBP seems to be consistent in numerous investigations and our study supports these results. As previously discussed, hyperuricemia and HBP are risk factors for the development of AF, so the control of these factors may represent a therapeutic alternative for patients with this type of arrhythmia.

Figures 1 and 2 show that there is a significant correlation between mean DBP and Pmax plus PWD in patients with hyperuricemia but not in patients with normal UA. Currently, there are no studies that reproduce these results, so our work is the first to demonstrate the relation between DBP and markers of AF and their relation with UA levels. Increased values of AF predictors associated with DBP makes us reason that there is an increased risk in these patients to develop this type of arrhythmia. This risk is marked in cases with hyperuricemia. A previous study evaluating cardiovascular reactivity and its relation with PWD in normotensive and hypertensive patients demonstrates that there is a correlation between DBP reactivity and Pmax.[28]

Bearing in mind the alterations of HBP in the heart, and the relation between UA levels and the development of AF, the results of our study are justified. High DBP and hyperuricemia lead to atrial changes favoring an increase in electrical pulse duration and heterogeneity in the atria. These changes, in turn, lead to increased Pmax and PWD. Based on these findings, we can hypothesize that regardless of whether or not the person is hypertensive, in patients over 60 years of age with hyperuricemia there is an increase in the values of AF markers that accompany a rise in DBP that, theoretically, predisposes these patients to AF.

The main limitation of our study was the cross-sectional design, which prevented the knowledge of patients who might have developed AF. Similarly, the size of the sample and the absence of variables reflecting the patients' inflammatory status could influence the results.

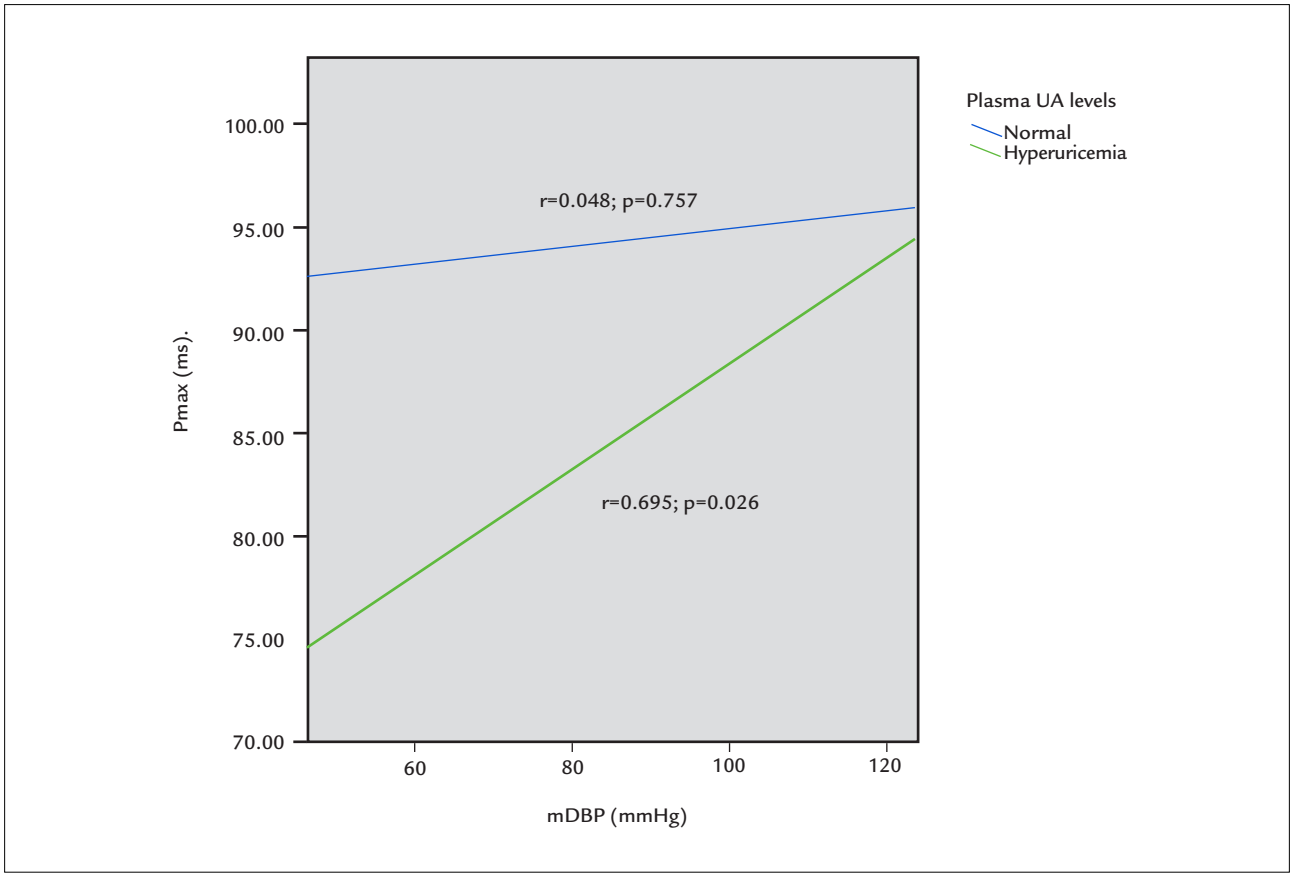

FIGURE 1 Linear correlation between mean DBP and Pmax values adjusted by personal history of high blood pressure, diabetes mellitus and body mass index in patients with hyperuricemia and normal UA.

UA: uric acid; Pmax: maximum P-wave duration; mDBP: mean diastolic blood pressure.

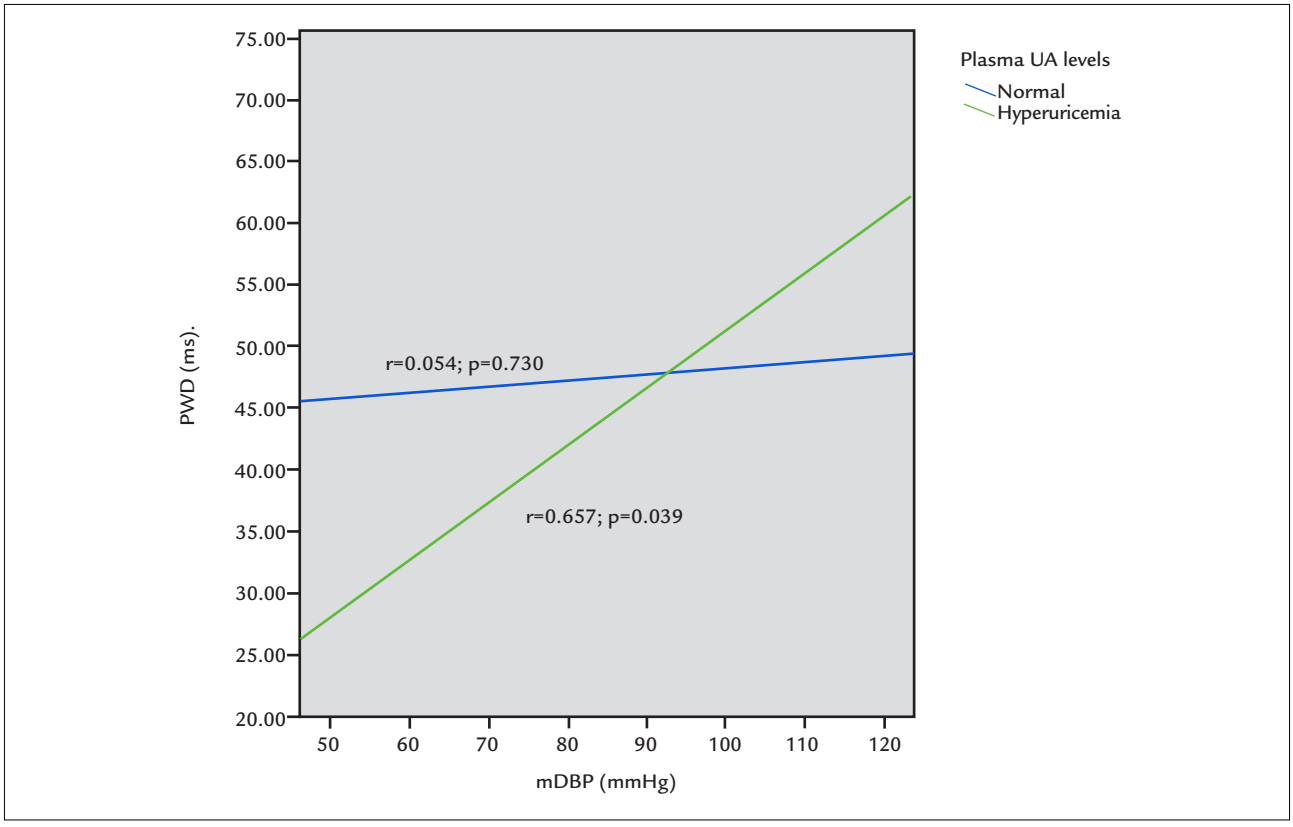

FIGURE 2 Linear correlation between mean DBP and PWD adjusted by personal history of high blood pressure, diabetes mellitus and body mass index in patients with hyperuricemia and normal UA.
UA: uric acid; PWD: P-wave dispersion; mDBP: mean diastolic blood pressure.

Conclusion

There is correlation between Pmax/PWD and DBP values in patients with hyperuricemia.

Resumen

Niveles de ácido úrico y presión arterial diastólica elevada: factores de riesgo de fibrilación atrial en pacientes mayores de 60 años

Objetivo: Caracterizar la máxima duración de la onda P (Pmáx) y la dispersión de la onda P (DP) según las cifras de tensión arterial (TA) y los niveles de ácido úrico (AU) en pacientes geriátricos.
Método: Se realizó un estudio analítico en 83 pacientes mayores de 60 años pertenecientes al Consultorio Médico de la Familia 5 del Policlínico Aracelio Rodríguez Castellón, Cienfuegos, Cuba entre enero y diciembre de 2015. La muestra se dividió en dos grupos (pacientes con hiperuricemia y pacientes con AU normal).

Resultados: Existe correlación lineal y significativa entre la tensión arterial diastólica y la Pmáx en los pacientes con hiperuricemia (r=0,695; p=0,026), mas no en los pacientes con AU normal (r=0,048; p=0,757). Se demuestra correlación lineal y significativa entre la tensión diastólica y la DP en los pacientes con hiperuricemia (r=0,657; p=0,039), aunque no en los pacientes con AU normal (r=0,054; p=0,730), respectivamente.
Conclusión: Existe correlación entre la Pmáx y la DP y las cifras de tensión arterial diastólica en pacientes geriátricos con hiperuricemia.

Palabras claves: fibrilación atrial, factor de riesgo, onda P, dispersión de la onda P, ácido úrico, geriatría.

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Antiretroviral changes during the first year of therapy

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Summary

Introduction: The Brazilian HIV/AIDS management and treatment guideline (PCDT), published in 2013, recommends and standardizes the use of highly active antiretroviral therapy (HAART) in all adult patients, in spite of $LTCD_4$ count. This study aimed to analyze the first year of HAART use in patients from a reference center on HIV/AIDS management in Fortaleza, Ceará.
Method: This descriptive study reviewed all prescription forms of antiretroviral regimens initiation and changes from January to July 2014. All antiretroviral regimen changes that occurred during the first year of therapy were evaluated. Data were analyzed with SPSS version 20. Mean, standard deviation and frequency, Student's t and Mann-Whitney tests calculations were used, with significance at $p<0.05$.
Results: From 527 patients initiating HAART, 16.5% (n=87) had a regimen change in the first year. These patients were mostly male (59.8%; n=52), aged 20 to 39 years, with only one HAART change (72.4%; n=63). Efavirenz was the most often changed drug, followed by tenofovir, zidovudine and lopinavir/ritonavir. Mean time of HAART changes was 120 days, with adverse reactions as the most prevalent cause. HAART was effective in decreasing viral load since second month of treatment ($p=0.003$) and increasing $LTCD_4$ lymphocytes since fifth month ($p<0.001$).
Conclusion: The main cause of initial HAART changes was adverse reaction and most patients had only one change in the HAART regimen. HAART prescription was in accordance to the PCDT from 2013.

Keywords: acquired immunodeficiency syndrome, highly active antiretroviral therapy, human immunodeficiency virus.

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Introduction

Human immunodeficiency virus (HIV) infection spreads to lymphoid tissues and follows initial course with high viremia and immune response, followed by seroconversion and, with replication and elevation in viral load (VL), CD_4^+ T lymphocytes ($LTCD_4$) are destroyed.[1] After a few years, the symptomatic phase of the disease is established, with immunodeficiency and the appearance of coinfections.[2,3]

The Brazilian Ministry of Health recommends 19 drugs for HIV treatment. These drugs are divided into classes, according to their mechanisms of action, namely: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, integrase inhibitors and entry inhibitors (CCR5 co-receptor antagonists).[4,5,8]

The introduction of the highly active antiretroviral therapy (HAART) in people living with HIV/AIDS (PLWHA) led to decreases in VL and increases in $LTCD_4$, thus reducing hospitalizations and HIV transmission. Laboratory tests for $LTCD_4$ and VL counts should be done during the use and change of HAART to verify the immuno-viral effectiveness of the treatment.[6,7]

The Brazilian HIV/AIDS management and treatment guideline (PCDT) recommends introduction of HAART in any $LTCD_4$ count, followed by first-line regimens with combinations of two NRTIs associated with a NNRTI[7] and second-line combinations with two NRTIs plus ritonavir-

-boosted PI (PI/r), in cases of viral resistance, intolerance or toxicity with efavirenz (EFZ) or nevirapine (NVP).[8] If VL remains detectable after six months of initiation or modification of HAART, virological failure may occur, with risk of disease progression, accumulation of antiretroviral (ARV) drug resistance mutations, and less robust and durable elevation of $LTCD_4$ count, i.e., therapeutic failure.[5,9]

In clinical practice, antiretroviral regimens may be changed due to therapeutic failure but also on account of adhesion difficulties, complexity of HAART, and other pharmacological factors (adverse reactions, drug interactions and toxicity).[1,9]

At the São José Hospital for Infectious Diseases (HSJ-CE), approximately 3,944 PLWHA are assisted for treatment with HAART according to PCDT recommendations of 2013. Due to the increasing number of PLWHA using HAART, treatment monitoring for the rational adherence of patients to therapy has become a priority, with improved clinical parameters and less risk of failure, hospitalization, costs, morbidity and mortality, longer survival and positive prevention with the adoption of healthy lifestyle habits.[8-10]

In this context, we aimed to describe the profile of HIV+ patients seen at a reference center in Fortaleza/Ceará, who had their initial antiretroviral regimen modified in the first year of treatment, and the factors involved in the modifications of HAART during this period.

Method

This exploratory, descriptive and retrospective study was performed at the HSJ Pharmacy Center (CENFAR). Application forms for treatment initiation and modification of all outpatients who started HAART between January and July 2014 and who changed therapies during the first year of treatment were analyzed sequentially. These patients were followed for a period of one year after initiation of HAART.[1]

Patients using HAART for prophylaxis, followed in the private health network, in transit from other Brazilian states, pregnant women and children (under 18 years of age) were excluded from the study.

Data were collected from the Medication Logistics Control System (SICLOM), specific forms to justify treatment switch and patient records.

Data regarding patient identification, symptoms, drugs used, $LTCD_4$ counts and VL, reason for the request to change the therapy, and the new requested scheme were amassed.

The analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 20.

Statistical analysis included calculations of means, standard deviation and frequencies. The evolution of numerical variables was analyzed by Student's t-test for those with a normal distribution. For the others, Mann-Whitney test was used. P-value < 0.05 was considered statistically significant.[11]

The study was approved by the Research Ethics Committee of HSJ, with Opinion No. 1,142,439 (Original Project).

Results

After we screened 527 patients who started HAART between January and July 2014, 120 were excluded because they were under medical supervision in the private health network, 11 children, three pregnant women and 306 patients who remained with initial HAART during the first year of treatment. The remaining 87 patients comprised our sample, being the N of the study.

Of these 87 patients, 59.8% (n=52) were male. The predominant age group was 20-39 years (57.5%), followed by 33.3% of patients aged 40-59 years, and 6.9% over 60 years, most of them from the capital of the state of Ceará (59.8%).

Coinfections were reported by 89% (n=77) of the patients, with one coinfection described in 17% (n=15), two coinfections in 31% (n=27), three coinfections in 20%, and more than three coinfections in 21% (n=18). The most frequent coinfections were cytomegalovirus (25%), toxoplasmosis (21%), syphilis (12%), tuberculosis (11%), herpes simplex (6%), histoplasmosis (6%), candidiasis (5%) and pneumocystis (5%). AIDS was diagnosed in 64.4% of the patients (n=56).

The $LTCD_4$ count and VL profile over the course of the treatment is shown in Chart 1. The increase in $LTCD_4$ counts was significant from 5 to 8 months of treatment ($p<0.001$). This increase was significant both in patients who had $LTCD_4$ > 500 cells/dL and in those with > 200 cells/dL at the beginning of treatment. The decrease in VL, in turn, was significant earlier, with 2 to 4 months of HAART (p=0.003).

Initial HAART with two NRTIs combined with one NNRTI was observed in 77% (n=67) of patients, especially the combination of tenofovir (TDF) + lamivudine (3TC) + EFZ, present in 46% (n=40) of the forms. Another widely used regimen was the association zidovudine (AZT) + 3TC + EFZ, present in the forms of 24% (n=21) of the patients.

Initial regimens presenting two NRTIs associated with one PI/r were observed in the forms of 20% (n=17) of the patients, with the following associations predominating: TDF + 3TC with lopinavir (LPV/r), used by 8% (n=7) of patients; and AZT + 3TC + LPV/r, used by 7% (n=6). Analyzing each drug individually, we observed that the most used NRTI was 3TC, present in 100% (n=87) of the regimens,

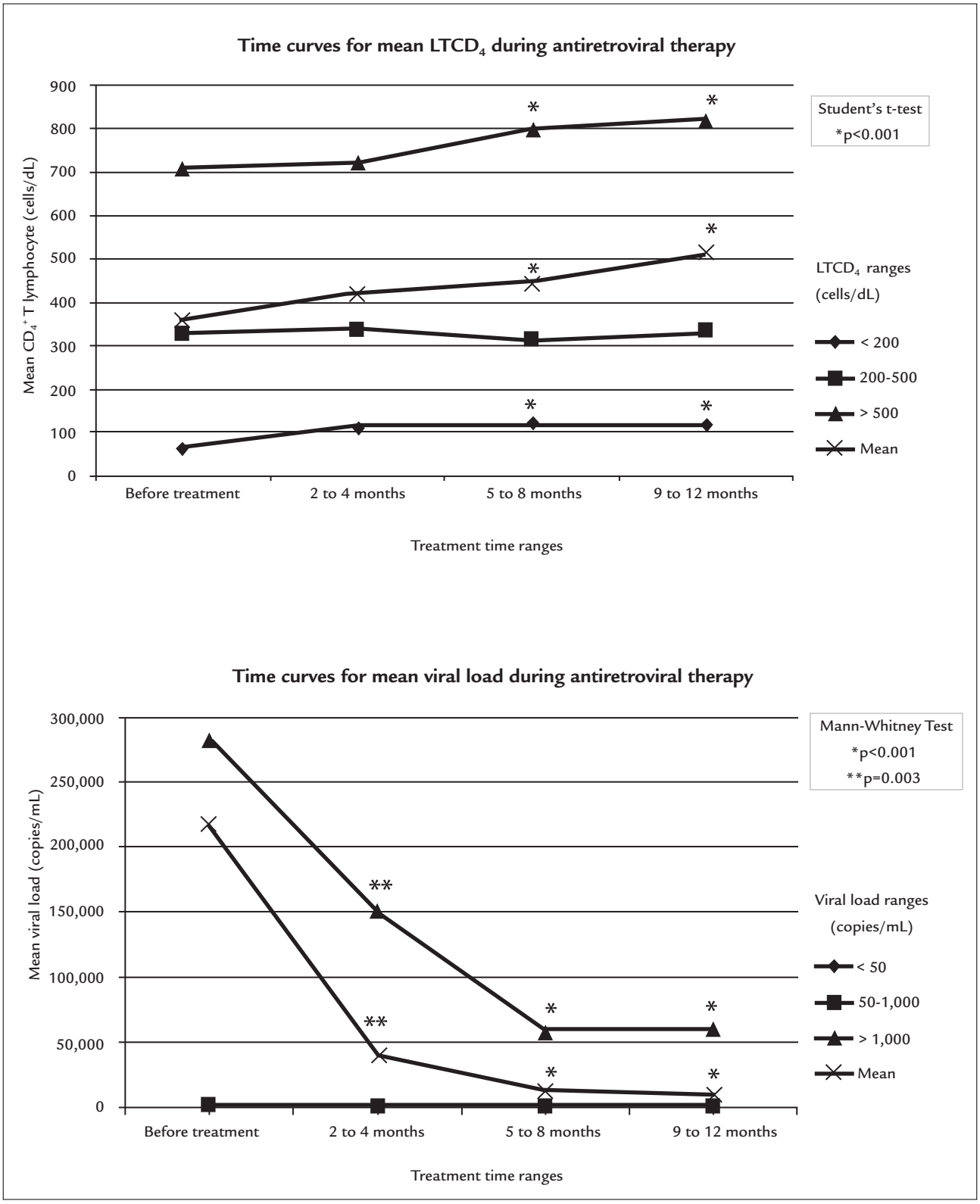

CHART 1 Time curves for mean $LTCD_4$ counts and viral load during antiretroviral therapy.

p-value or level of significance equal to 0.05, p=0.05.

Source: Medication Logistics Control System (SICLOM) and medical records of the São José Hospital outpatient clinic.

followed by TDF, in 62% (n=54). LPV/r was the most used PI/r, present in 17% (n=15), followed by atazanavir (ATV)/r, found in 5% (n=4). In the NNRTI category, EFZ was the drug of choice, being present in 71% (n=62) of the regimens, followed by NVP in 6% (n=5) (Table 1).

Of the 87 patients, 72.4% (n=63) underwent one treatment switch, 21.8% (n=19) two switches, 3.4% (n=3) three switches, and 2.3% (n=2) four switches. In 79% (n=69) of the treatment switches only one drug was changed, whereas in 15% (n=13) two drugs were changed. Three drugs were switched in 3% (n=3) of the patients, and in 2% (n=2) there was a request to add a fourth drug, ATV/r or raltegravir (RAL).

Adverse drug reactions (ADRs) were the main reasons for switching drugs of the initial HAART and were reported as a justification in 70.5% (n=74) of the changes. Therapeutic failure was the reason for drug switching in 11 patients (12.6%) (Table 2).

Of the 54 patients that started HAART with TDF (62.06%, 54/87), 40.7% (n=22) switched medications, 68.2% (n=15) due to kidney dysfunction or nephrotoxicity. Of the 62 patients who used initial EFZ (71.26%, 62/87), 67.74% (n=42) switched the drug, 35.7% (n=15) for psychological reactions and 26.2% (n=11) due to hypersensitivity reactions. LPV/r was associated with drug switching in 47% (n=7) of 15 initial regimens in which it was present, mainly due to gastrointestinal reactions. Table 2 shows the motives for switching drugs and the drugs replaced in the initial schemes.

The only drug that was not changed in the initial HAART was 3TC. Among NRTIs, TDF was replaced 22

TABLE 1 Profile of frequency of use of drugs in initial and modified antiretroviral therapy.

	Initial HAART			Modified HAART		
	Among the drugs		Percentage	Among the drugs		Percentage
ARV drugs used	n	%	among patients	n	%	among patients
3TC	87	33%	100%	87	33%	100%
EFZ	62	24%	71%	29	11%	33%
TDF	54	21%	62%	46	17%	53%
AZT	32	12%	37%	33	12%	38%
LPV/r	15	6%	17%	24	9%	28%
NVP	5	2%	6%	13	5%	15%
ABC	4	2%	5%	11	4%	13%
ATV/r	4	2%	5%	19	7%	22%
RAL	0	0%	0%	3	1%	3%
Total	263	100%	302%	265	100%	305%

HAART: highly active antiretroviral therapy; ARV: antiretroviral; n: number of times the drug was used; %: percentage; 3TC: lamivudine; EFZ: efavirenz; TDF: tenofovir; AZT: zidovudine; LPV: lopinavir; r: ritonavir; NVP: nevirapine; ABC: abacavir; ATV: atazanavir; RAL: raltegravir.
Source: Medication Logistics Control System (SICLOM) and HAART switch request forms.

TABLE 2 Association between the reasons for switching and drugs switched in the initial schemes.

	Drugs switched							
Reason for switching	LPV/r n (%)	AZT n (%)	EFZ n (%)	TDF n (%)	NVP n (%)	ATV/r n (%)	ABC n (%)	Total n (%)
Gastrointestinal reactions	6 (35)	2 (12)	4 (24)	2 (12)	1 (6)	2 (12)		17 (100)
Psychological reactions			15 (100)					15 (100)
Hypersensitivity		3 (20)	11 (73)		1 (7)			15 (100)
Kidney dysfunction			2 (11)	15 (83)		1 (6)		18 (100)
Myelotoxicity		5 (100)						5 (100)
Liver dysfunction					1 (100)			1 (100)
Drug interaction			6 (100)					6 (100)
Dose optimization	1 (10)	5 (50)			1 (10)	1 (10)	2 (20)	10 (100)
Genotyping/Rescue			4 (36)	5 (45)	2 (18)			11 (100)

n: number of times the drug was switched; %: percentage; 3TC: lamivudine; EFZ: efavirenz; TDF: tenofovir; AZT: zidovudine; LPV: lopinavir; r: ritonavir; NVP: nevirapine; ABC: abacavir; ATV: atazanavir.
Source: Medication Logistics Control System (SICLOM), HAART switch request forms and medical records of the São José Hospital outpatient clinic.

times, 64% (n=14) by AZT and 36% (n=8) by abacavir (ABC). As for the NNRTIs, EFZ was replaced 42 times, 40% (n=17) by ATV/r and 33% (n=14) by LVP/r. Among the PI/r, LPV/r was replaced seven times, 71% (n=5) by EFZ.

The initial regimens had an average duration of 100.6 days (±93.4), ranging between 1 and 330 days of treatment. Schemes with 2 NRTI + 1 NNRTI had an average duration of 102 days (±97.6), being mainly represented by the TDF + 3TC + EFZ scheme. Combinations with 2 NRTI + 1 PI/r lasted shorter, with a mean duration of 94 days (±75.7), being more often represented by TDF + 3TC + LPV/r and TDF + 3TC + ATV/r.

Discussion

In our study, the prevalence of male patients was evident, which seems to be in agreement with data in the literature. In recent years, there has been an increase in the number of men with HIV.[12] As of 2009, there was a decline in the number of AIDS cases in women and an increase in men, yielding a sex ratio that in 2014 was 19 cases of AIDS in men for every ten cases in women according to the Epidemiological Bulletin on HIV/AIDS Surveillance (2015).[13] Studies in Spain, Italy, the United States and India also point to an increasing prevalence of HIV infection among men.[14-18]

AIDS was diagnosed in 64.4% of the patients, which can be explained by problems of adherence to HAART and/or late treatment start, according with $LTCD_4$ count and VL profile, which makes immune reconstitution and viral suppression more difficult with onset of resistance, directly reflecting the appearance of AIDS coinfections and symptoms in 15 to 61% of patients.[7,19-22]

In the 87 patients studied, $LTCD_4$ increase was significant between the fifth and eighth month of treatment. In most individuals, the onset of HAART is accompanied by higher $LTCD_4$ counts and immune recovery. Usually, this occurs in the first year of treatment. Then, stability is observed, followed by improvement in the second year.[4,8] However, in spite of a significant increase in $LTCD_4$ counts in our sample, even in patients who initiated HAART with levels lower than 200 cells/dL, in some patients this increase was not enough to reverse the state of severe immunosuppression. This finding may signal adhesion problems[19-21] or partial immunological reconstitution in patients with low initial $LTCD_4$ counts.[6,16,20] This situation occurs due to late onset of HAART in immunocompromised patients, so that initially low levels of $LTCD_4$ are important predictors of the suboptimal recovery response of $LTCD_4$.[23,24]

Effectiveness of HAART on the decrease in VL from the start of treatment (2 to 4 months) was evidenced, with the majority of patients reaching undetectable levels between the fifth and eighth month. Patients who started treatment with VL greater than 1,000 copies/mL had partial viral suppression, since they did not reach undetectable VL six months after starting treatment. However, this does not mean virologic failure, since most HAART changes in these patients occurred before the first six months of treatment. Studies show that about 80% of patients achieve plasma VLs of less than 50 copies/mL after one year of treatment and that viral suppression is maintained over time, whereas virological failure may be characterized with VL counts higher than 50 copies/mL after six months of treatment without interruptions or changes.[4,6-8]

Most of the initial regimens used in this population consisted of 2 NRTI + 1 NNRTI, followed by 2 NRTI + 1 PI/r, with TDF + 3TC + EFZ and TDF + 3TC + LPV/r as the predominant associations in each case, respectively. These findings are in agreement with the 2013 PCDT recommendations.[8]

In most of the initial HAART switches studied, only one drug was replaced in the scheme. Studies indicate that changes within six months usually occur because of intolerance or toxicity.[14,15,25,26] The fact that most of the treatment switches in the present study involved only one drug can be explained by the occurrence of ADR to a specific drug in the scheme in most of the cases (70%).

Among the ADRs presented, gastrointestinal reactions were more often associated with LPV/r, while psychological reactions and hypersensitivity were associated with EFZ, renal alteration with TDF, myelotoxicity with AZT, and hepatic alteration with NVP. These data are in agreement with results obtained by several authors, which show similar correlations between the antiretroviral drugs and their main clinical and laboratory alterations.[14,15,17,25-27]

Other studies also reveal that changes in HAART after six months may also occur after confirmation of immuno-virological failure and low adherence.[16,17,19-21] In our population, therapeutic failure, although not the most prevalent cause for HAART replacement, was the reason for switching drugs in 12.6% of the cases that used initial TDF + 3TC + EFZ and AZT + 3TC + EFZ regimens. Other authors showed that TDF + 3TC + EFZ schemes resulted in viral suppression in 92% of patients and virological failure in 8 and 10.8% of patients.[7,22] Initial regimens with emtricitabine (FTC) + TDF + EFZ had a 3.6% failure.[22] In one study,[21] virological failure combined with viral resistance occurred in 24.1% of patients with interruption and resumption of treatment using stavudine (d4T) + 3TC + NVP, d4T + 3TC + EFZ and AZT + 3TC + NVP regimens. Other studies showed that d4T regimens had virological failure in 16.9%, motivated by predictors such as treatment interruptions, use of NVP, initial $LTCD_4$

< 25 cells/dL, initial VL ≥ 400 copies/mL, and stage of AIDS,[14,16,17,19,20] while only 7.7 and 2.65% obtained treatment failure with the same regimens in other studies.[18,25] These differences may be justified by factors such as ARV classes (NRTI, NNRTI and PI), adherence, toxicity, adverse reactions, incorrect drug combinations in coinfections, and pharmacogenetics of patients.[4,6,10,15,26]

In our study, EFZ was the drug most often switched in the initial regimens. This is possibly due to the significant prevalence of CNS-related adverse events associated with this drug.[4,6,15] It should also be noted that EFZ was one of the most prescribed drugs, since it is part of the preferential scheme for the initiation of HAART in Brazil,[8] which may also have led to a higher prevalence of switching of this drug.

In patients who had to change EFZ, the main drugs of choice were ATV/r and LPV/r. In those who switched TDF, most did so for AZT, followed by ABC. These changes were in accordance with the recommendations of the 2013 PCDT.[8]

The authors identified limitations in the present study. The instruments used for data collection (HAART switch request form, SICLOM drug dispensing record, incomplete laboratory data), together with the retrospective design of the study, have led to difficulties in the analysis of adherence to follow-up and treatment.

Conclusion

The epidemiological profile of patients undergoing changes in initial HAART revealed the prevalence of men in the age group between 20 and 39 years.

The use of HAART led to an immuno-virological response with a significant increase in the mean $LTCD_4$ count and a significant reduction in the mean VL, the former having a later effect when compared to the latter.

The main schemes used to initiate therapy were composed of 2 NRTI + 1 NNRTI. EFZ was most often used in early therapies compared to LPV/r and ATV/r; however, it was also the most often switched drug.

ADRs were the most frequent cause of HAART replacement, most of the times requiring the replacement of only one of the drugs in the initial regimen.

Resumo

Mudanças de terapia antirretroviral durante o primeiro ano de tratamento

Introdução: O Protocolo Clínico e Diretrizes Terapêuticas para manejo da infecção pelo HIV em adultos (PCDT) de 2013 recomenda e normatiza início de terapia antirretroviral (TARV) em pacientes com qualquer contagem de $LTCD_4$. O objetivo do estudo foi analisar o primeiro ano de TARV de pacientes em acompanhamento em um centro de referência em HIV/AIDS de Fortaleza, Ceará.
Método: O estudo descritivo revisou formulários de solicitação de início e modificação de TARV em pacientes que iniciaram tratamento entre janeiro e julho de 2014. Foram avaliadas todas as mudanças que ocorreram durante o primeiro ano de terapia. Os dados foram analisados no programa Statistical Package for the Social Sciences (SPSS) versão 20. Foram calculados médias, desvios padrão, frequências, testes t Student e Mann-Whitney, com significância de $p<0,05$.
Resultados: Dos 527 pacientes que iniciaram TARV, 16,5% (n=87) realizaram troca no primeiro ano. A maioria era do sexo masculino (59,8%; n=52), de 20 a 39 anos, com apenas uma mudança da TARV (72,4%; n=63). Efavirenz foi o fármaco mais substituído, seguido por tenofovir, zidovudina e lopinavir/ritonavir. O tempo médio de ocorrência das modificações da TARV foi de 120 dias, tendo reações adversas como causas principais. TARV foi efetiva na queda da carga viral desde o 2º mês de tratamento ($p=0,003$) e na elevação de $LTCD_4$ desde o 5º mês ($p<0,001$).
Conclusão: Os principais fatores envolvidos em modificações de TARV inicial foram reações adversas, com apenas uma mudança de esquema na maioria dos pacientes. O manejo da TARV estava de acordo com o PCDT de 2013.

Palavras-chave: síndrome da imunodeficiência adquirida, terapia antirretroviral de alta atividade, vírus da imunodeficiência humana.

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Complications of central venous catheter insertion in a teaching hospital

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Summary

Introduction: Central venous catheters are fundamental to daily clinical practice. This procedure is mainly performed by residents, often without supervision or structured training.
Objective: To describe the characteristics of central venous catheterization and the complication rate related to it.
Method: Retrospective cohort study. Adult patients undergoing central venous catheter insertion out of the intensive care unit (ICU) of a teaching hospital were selected from March 2014 to February 2015. Data were collected from medical charts using an electronic form. Clinical and laboratory characteristics from patients, procedure characteristics, and mechanical and infectious complications rates were assessed. Patients with and without complications were compared.
Results: Three hundred and eleven (311) central venous catheterizations were evaluated. The main reasons to perform the procedure were lack of peripheral access, chemotherapy and sepsis. There were 20 mechanical complications (6% of procedures). Arterial puncture was the most common. Procedures performed in the second semester were associated with lower risk of complications (odds ratio 0.35 [95CI 0.12–0.98; p=0.037]). Thirty-five (35) catheter-related infection cases (11.1%) were reported. They were related to younger patients and procedures performed by residents with more than one year of training. Procedures performed after the first trimester had a lower chance of infection.
Conclusion: These results show that the rate of mechanical complications of central venous puncture in our hospital is similar to the literature, but more attention should be given to infection prevention measures.

Keywords: central venous catheters, catheter-related infections, vascular access devices, pneumothorax, ultrasonography.

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Introduction

Central venous catheters are fundamental to daily clinical practice. Its main indications are lack of peripheral access, administration of drugs used exclusively in large veins, administration of parenteral diet, and access for hemodialysis.[1,2] It is estimated that more than 5 million central venous punctures are performed per year in the United States.[3] Although data from Brazil are scarce, in 2015 the Unified Health System authorized the placement of 95,704 catheters, including short and long-term catheters.[4]

The rate of complications of central venous puncture is estimated at 15%.[1,5] Complications related to this procedure are divided into mechanical and infectious. The most common mechanical complications are arterial puncture, hematoma and pneumothorax. Hemothorax, arrhythmia, thoracic duct injury, cardiac tamponade, air embolism or guidewire embolism are more rare but potentially more severe. Using the proper technique for the procedure, a portion of these complications can be avoided.[1,5,6] Infectious complications (especially catheter-relat-

ed bloodstream infection), however, besides being potentially serious, are classically associated with high morbidity and mortality and high hospital costs.[7]

The puncture site is one of the determinants of complications, so that pneumothorax is more common in subclavian approaches, whereas arterial puncture is more common for the femoral and jugular veins.[1] Infectious complications, in turn, appear more common in the femoral and jugular approach.[8] Other variables may also influence the rate of complications, such as the use of ultrasonography to guide the procedure, the time of the procedure and the amount of training of the professional performing it.[1]

Considering the latter, there is no specific training in most Brazilian teaching hospitals. There are also no national guidelines regarding the professional's qualification for such procedure or protocols to make puncture safer. In addition, the American Board of Internal Medicine[9] does not provide clear recommendations on the number of procedures to be performed for a physician being trained to be considered qualified, but recognizes that there is a learning curve that varies between individuals and procedures.[9] It is estimated that 10-20 punctures are required for the training physician to feel comfortable performing the procedure.[10] Unfortunately, it is common for such procedures to be learned in an unsystematic manner, taught in the context of medical education based on the "see one, do one, teach one" model.[2] At the Hospital de Clínicas de Porto Alegre (HCPA), training used to follow this unsystematic model. Despite having a committee for monitoring central venous catheters, most of the learning occurs through observation and supervised performance, with no formal training prior to commencement. Usually, supervision is performed by preceptors of medical residency and more experienced residents (second year or above). After the first few months of training, it is common for procedures to be performed without supervision. The procedures performed by resident physicians of intensive care, on the other hand, are always supervised by preceptors. Considering these problems, the HCPA implemented in 2016 a structured training program for resident physicians focused on central venous puncture techniques outside the intensive care unit and surgical center, with supervised theoretical and practical activities performed on mannequins.

Our study aimed to describe the characteristics of central venous puncture and rate of complications related to this procedure before the implementation of structured training.

Method

This is a retrospective cohort study that evaluated adult patients undergoing central venous puncture outside the HCPA intensive care unit in 2014. We considered the period from March 2014 to February 2015. The study was approved by the Research and Graduate Group and by the Research Ethics Committee of the HCPA under number 15-0048.

Data were collected through electronic form-based chart reviews. All radiological control exams after central venous puncture were identified by searching the HCPA computerized system. This examination is performed routinely in all patients who undergo jugular or subclavian venipuncture procedure. Patients admitted to the intensive care unit and with peripheral central venous catheter were excluded from the initial sample. Then, a random sample (list of numbers generated randomly by computer program) was selected for evaluation. The description of how patients were included in this evaluation is summarized in Figure 1.

The following information was collected: gender, age, platelet count, prothrombin time, presence of heart disease (ischemic disease, heart failure or valvulopathy) or pulmonary (chronic obstructive pulmonary disease, asthma or interstitial disease), infection, cancer, kidney failure (acute or chronic) and diabetes mellitus on insulin. These comorbidities were noted whenever mentioned in the patient's discharge or death records. The following catheter and procedure data were collected: catheter type (mono and double lumen, dialysis and long stay), indication for insertion of the catheter, area of the professional responsible for the procedure (clinical, surgical or other), training time of the professional placing the catheter (grouped as first-year

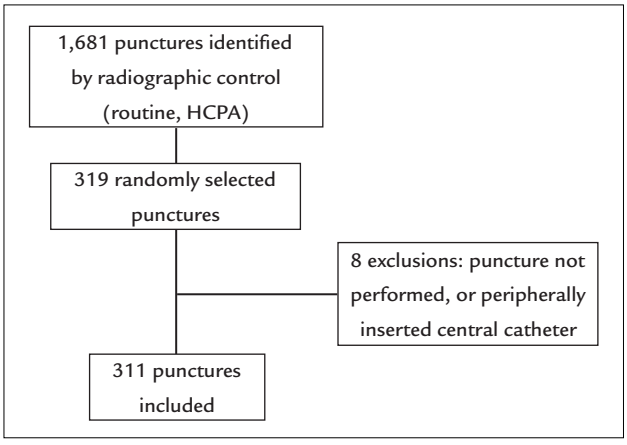

FIGURE 1 Patients flow diagram.

HCPA: Hospital de Clínicas de Porto Alegre.

residents, second-year residents, and third-year or above residents – including in the latter group the hospital's clinical staff – medical staff and professors of medicine), place of the procedure (outpatient surgical center – OSC – or elsewhere), use of ultrasonography and puncture site (jugular or subclavian). Complications related to the procedure were divided into mechanical (arterial puncture, hematoma and pneumothorax) and non-mechanical (catheter-related infection). The data related to the mechanical complications were collected from the systematic review of medical records, with a description of the procedure, radiological examination post-procedure, and subsequent medical and nursing monitoring (7 days). The catheter-related infection data were obtained from the Hospital Infection Control Commission, according to the criteria of the Brazilian Sanitary Surveillance Agency (Anvisa): adult patients with a central venous catheter at the time of diagnosis or up to 48 hours after their removal with 1) one or more blood cultures positive for recognized pathogen unrelated to infection elsewhere, or 2) fever, chills, oliguria and/or hypotension together with at least two blood cultures collected on different occasions positive for skin-contaminant pathogens and unrelated to another site of infection.[11] The incidence of infectious complications was analyzed for the period between insertion of the catheter and hospital discharge or death.

Statistical analysis

Continuous variables were presented as mean and standard deviation or median and 25-75th percentile (variables with non-Gaussian distribution) and the comparison of outcomes was performed using Student's t-test for repeated measures or a Wilcoxon test for paired data (variables with non-Gaussian distribution). The categorical variables were presented in percentages and absolute numbers and the comparisons were performed using Chi-square test. Differences between groups were assessed by residue analysis. Missing data were excluded from all analyzes. These analyzes were performed in SPSS 20.0 software (SPSS, Chicago, IL). Considering the number of procedures in the HCPA as 1,600, and the complication rate being 10-15%, the sample was calculated at 175 procedures with 5% alpha error and power set at 95%.

Results

A total of 1,681 central venous access punctures were identified in adult patients outside the intensive care unit setting during the residency year of 2014. Of these, 311 were randomly selected for evaluation, with 17 patients undergoing two different punctures and two patients undergoing three different punctures due to the need for more than one access during one or more hospitalizations. It should be noted that none of these patients remained with more than one central access simultaneously.

The characteristics of the patients studied are presented in Table 1. We point out that more than half of the patients were diagnosed with active cancer and a quarter of them were being treated for systemic infection. The main indications for the procedure were lack of peripheral access and need for venous access for chemotherapy and severe sepsis/septic shock. The type of catheter most used was double lumen. In addition, most catheters were placed in the setting recommended by the institution (OSC) and by a professional with up to one year of training.

Mechanical complications occurred in 20 patients, representing 6.5% of the procedures. Individually, arterial puncture was the most common complication (12 cases), followed by hematoma (nine cases). Two patients had both arterial puncture and hematoma. Only one case of post-procedure pneumothorax was identified, and no chest drainage was required. There were 35 cases of catheter-related infection (11.1% of the sample). Table 2 presents the characteristics of patients and procedures according to the presence of mechanical complications. In our sample, only thrombocytopenia was associated with an increased risk of complications related to puncture, to the detriment of a higher risk of hematoma, with an odds ratio of 4.9 (95CI 1.27-19.5; p=0.02) for patients with thrombocytopenia compared to patients without this condition. Of the variables related to the procedure, only the performance of the procedure in the second semester of the residency year was associated with a lower risk of complications with an odds ratio of 0.35 (95CI 0.12-0.98; p=0.037). We emphasize that neither the amount of training of the person responsible for the procedure, time of procedure, and use of ultrasonography were associated with risk of complications. Considering the difference found between the training moments, there was a statistical power of 99% to detect it.

As for infection related to the catheter, data are presented in Table 3. Patients with a catheter infection were younger (mean age) and had their procedures performed by second-year residents more frequently. It is also worth noting that the procedures performed after the first trimester of the residency year were associated with a lower risk of complications, with odds ratio of 0.69 (95CI 0.51-0.94; p=0.002) compared to the procedures performed in the first trimester. For this analysis, the statistical power was also 99%. There was no association between infection rate with catheter type, puncture site, use of ultrasonography or the area of the professional.

TABLE 1 Patient's characteristics and procedures.

	N=311
Age (years)	57±17
Male	144/311 (46%)
INR > 1.5	15/165 (9.1%)
Platelets < 100,000	41/281 (14.6%)
Infectious disease	78/311 (25%)
Heart disease	41/311 (13.1%)
Lung disease	32/311 (10.2%)
Cancer	180/311 (57.8%)
Kidney disease	70/311 (22.5%)
DM on insulin	34/311 (10.9%)
Neurological disease with functional limitation	62/311 (19.9%)
Type of catheter	
Mono lumen	88/308 (28.6%)
Double lumen	150/308 (48.7%)
Dialysis	19/308 (6.2%)
Long-term catheters	51/308 (16.6%)
Indication for catheter use	
Lack of peripheral access	85/268 (31.7%)
Sepsis	66/268 (24.6%)
Surgery	23/268 (8.5%)
Dialysis	19/268 (7%)
Chemotherapy	75/268 (27.9%)
Area of professional responsible for the procedure	
Clinical	67/298 (22.5%)
Surgical	231/298 (77.5%)
Amount of training of professional responsible for the procedure	
First-year resident	219/297 (73.7%)
Second-year resident	37/297 (12.5%)
Third-year resident or above	41/297 (13.8%)
Place where procedure was performed	
OSC or surgical unit	239/297 (80.5%)
Other	58/297 (19.5%)
Use of ultrasound	99/308 (32.2%)
Time of procedure	
8-24h	282/309 (91.3%)
24-8h	27/309 (8.7%)
Puncture site	
Right jugular	145/307 (46.9%)
Left jugular	40/307 (12.9%)
Right subclavian	111/307 (35.9%)
Left subclavian	11/307 (3.6%)
Catheterization failure	9/300 (3%)
Mechanical complication associated with puncture	20/308 (6.5%)
Catheter-related infection	35/311 (11.2%)

INR: international normalized ratio of prothrombin time; DM: diabetes mellitus; OSC: outpatient surgical center; data presented as mean and standard deviation or total number and percentage.

TABLE 2 Patient's characteristics and procedures according to the presence of mechanical complications.

	Puncture-related complications		
	Absent (n=291)	**Present (n=20)**	**p**
Age (years)	57.1±17.2	55.5±16.5	0.67
Male	134/291 (46.2%)	8/20 (40%)	0.59
INR > 1.5	14/145 (9%)	1/20 (12.5%)	0.54
Platelets < 100,000	35/291 (12%)	6/20 (30%)	0.04
Infectious disease	74/291 (25.4%)	4/20 (20%)	0.58
Heart disease	38/291 (13%)	3/20 (15%)	0.80
Lung disease	31/291 (10.6%)	1/20 (5%)	0.41
Cancer	169/291 (58%)	11/20 (55%)	0.77
Kidney disease	67/291 (23%)	3/20 (15%)	0.40
DM on insulin	32/291 (10.9%)	2/20 (10%)	0.87
Neurological disease	59/284 (20.7%)	3/20 (15%)	0.50
Professional's area			0.78
Clinical	62/278 (22.3%)	5/20 (25%)	
Surgical	216/278 (77.7%)	15/20 (75%)	
Amount of training of professional responsible for the procedure			0.93
First-year resident	204/277 (73.6%)	15/20 (75%)	
Second-year resident	35/277 (12.6%)	2/20 (10%)	
Third-year resident or above	38/277 (13.7%)	3/20 (15%)	
Place where procedure was performed			0.17
OSC or surgical unit	226/278 (81.3%)	13/19 (68.4%)	
Other	52/278 (18.7%)	6/19 (31.6%)	
Use of ultrasound	91/287 (31.7%)	8/20 (40%)	0.44
Time of procedure			0.56
8-24h	261/286 (91.3%)	19/20 (95%)	
24-8h	25/286 (8.7%)	1/20 (5%)	
Puncture site			0.16
Jugular	170/286 (59.4%)	15/20 (75%)	
Subclavian	116/286 (40.6%)	5/20 (25%)	
Procedures per semester			0.038
First semester	147/288 (51%)	15/20 (75%)	
Second semester	141/288 (49%)	5/20 (25%)	

INR: international normalized ratio of prothrombin time; DM: diabetes mellitus; OSC: outpatient surgical center; data presented as mean and standard deviation or total number and percentage.

TABLE 3 Patient's characteristics and procedures according to the presence of infectious complications.

	Catheter-related infection		
	Absent (n=276)	**Present (n=35)**	**p**
Age (years)	57.7±16.8	51.5±18.4	0.044
Male	129/276 (46.4%)	15/276 (42.9%)	0.69
INR > 1.5	14/141 (9.9%)	1/23 (4.3%)	0.34
Platelets < 100,000	34/246 (13.8%)	7/34 (20.6%)	0.21
Infectious disease	68/276 (24.6%)	10/35 (28.6%)	0.59

(*continues*)

TABLE 3 (cont.) Patient's characteristics and procedures according to the presence of infectious complications.

	Catheter-related infection		
	Absent (n=276)	**Present (n=35)**	**p**
Heart disease	37/276 (13.4%)	4/35 (11.4%)	0.75
Cancer	164/276 (59.4%)	16/35 (45.7%)	0.13
Lung disease	27/276 (9.7%)	5/35 (14.3%)	0.40
Kidney disease	65/276 (23.5%)	5/35 (14.3%)	0.22
DM on insulin	30/276 (10.8%)	4/35 (11.4%)	0.94
Neurological disease	53/276 (19.2%)	9/35 (25.7%)	0.40
Professional's area			0.11
Clinical	56/265 (21.1%)	11/33 (33.3%)	
Surgical	209/265 (78.9%)	22/33 (66.7%)	
Amount of training of professional responsible for the procedure			0.012
First-year resident	201/264 (76.1%)	18/33 (54.5%)	
Second-year resident	28/264 (10.6%)	9/33 (27.3%)	
Third-year resident or above	35/264 (13.3%)	6/33 (18.2%)	
Place where procedure was performed			0.65
OSC or surgical unit	215/266 (80.8%)	24/31 (77.4%)	
Other	51/266 (19.2%)	7/31 (22.6%)	
Use of ultrasound	86/272 (31.6%)	13/35 (37.1%)	0.51
Time of procedure			0.19
8-24h	248/274 (90.5%)	34/35 (97.1%)	
24-8h	26/274 (9.5%)	1/35 (2.9%)	
Puncture site			0.10
Jugular	160/272 (58.8%)	25/35 (71.4%)	
Subclavian	112/272 (41.2%)	10/35 (28.6%)	
Procedures per trimester			0.026
First trimester	59/276 (21.4%)	16/35 (45.7%)	
Second trimester	83/276 (30%)	5/35 (14.3%)	
Third trimester	69/276 (25%)	8/35 (22.9%)	
Fourth trimester	65/276 (23.5%)	6/35 (17.1%)	
Procedures per semester			0.34
First semester	142/276 (51.4%)	21/35 (60%)	
Second semester	134/276 (48.6%)	14/35 (40%)	
Type of catheter			0.26
Mono lumen	80/209 (38.3%)	8/29 (27.6%)	
Double lumen	129/209 (61.7%)	21/29 (72.4%)	

INR: international normalized ratio of prothrombin time; DM: diabetes mellitus; OSC: the HCPA outpatient surgical center; data presented as mean and standard deviation or total number and percentage.

To better understand the relation between procedures performed by second year residents and infectious complications, we evaluated the characteristics of the procedures performed by this group. The main indication for central venous puncture was chemotherapy (40 vs. 31.2% for second and first year residents, respectively, p<0.001). In addition, second-year residents made more punctures earlier that year (80.6 vs. 47.9% of the procedures performed in the first semester by residents of the second and first year, respectively, p=0.001). There was no difference in relation to comorbidities, platelets or prothrombin time among first and second year residents.

After analyzing the cases in which there was at least one complication, either mechanical or infectious, we identified the subclavian puncture site as a factor associated with less risk of complication, with an odds ratio of

0.51 (95CI 0.26-0.97; p=0.04) compared to the jugular site and procedures performed in the second semester, with odds ratio of 0.53 (95CI 0.28-0.97; p=0.04) compared to the procedures performed in the first trimester. There was no association between the rate of grouped complications and the other variables.

Discussion

Our study showed that the rate of mechanical complications related to central venous puncture is infrequent in our setting. Even without structured training, the incidence of mechanical complications is comparable with data published in the literature.[8,9] In turn, the rate of catheter infection in our institution is higher than reported in the foreign literature.[8,12,13]

Arterial puncture, hematoma and pneumothorax are, in this order, the most common complications related to central venous punctures according to the literature.[1,8,9] We point out in particular the fact that pneumothorax, a complication with greater morbidity, is rare, occurring in less than 1% of the jugular approaches and up to 1.5% of the subclavian approaches.[1,8,14] Puncture site, number of punctures and male gender are factors associated with a greater chance of complications.[8,15,16] In our study, we observed that the jugular puncture site had a higher rate of mechanical and infectious complications compared to the subclavian vein. The other associations were not observed in our series, perhaps due to the small number of complications identified. The number of punctures could not be obtained from the records in the medical charts, which is an expected limitation when using secondary data. A study[16] with similar design and heterogeneity of the population (school hospital) demonstrated a rate of mechanical complication approximately three times higher than that found in our study. However, the analysis was performed in an intensive care setting, which may be related to the need for more urgent venous access.

The discrepancy between the rate of central catheter--associated infection identified in the HCPA and in the international literature can be partially explained by different methodologies of data collection and diagnostic criteria for catheter infection. Definitions for central venous catheter-related infection as used in international studies are usually more specific, such as: 1) significant growth of at least one microorganism in catheter-tip culture; 2) 3:1 CFU/mL ratio for the same microorganism of the catheter in relation to the peripheral one; or 3) growth time in the catheter greater than or equal to 2 hours prior to peripheral growth. These criteria are exempted from the definition used by the Brazilian Sanitary Surveillance Agency[11] and are routinely adopted by institutions in the country. Compared to other studies conducted in Brazil, we found higher rates of infection.[17,18] However, the comparison is limited because these studies were performed in specific populations (e.g., chemotherapy, dialysis), and some of them were related to long-term catheters. We did not find Brazilian studies with heterogeneous population samples similar to ours.

Current, unstructured training may partly explain the higher incidence of infectious complications compared to mechanical ones. The training focuses on the puncture, i.e., vessel location and catheter insertion. The infection prevention bundle,[19] including hand hygiene, use of a maximum precautionary barrier during insertion, and daily checking of the need for catheter maintenance, for example, is not part of the training.

The results show that the rate of puncture complications identified in the HCPA is comparable with data from other centers. In addition, we have an indirect finding that unstructured training is capable of promoting a reasonable learning curve for resident physicians, with a reduction in the rate of events (mechanical and infectious) after the first few months of training. This finding may appear to be in disagreement with the absence of a relation between complication rate and the amount of training performed by the person performing the puncture. However, more experienced physicians performed fewer procedures (especially in the second semester) and it is possible that these procedures involved greater technical difficulty and, therefore, did not represent the same group of patients and/or procedures. Second-year residents performed more punctures in patients requiring access to chemotherapy, that is, patients who were immunosuppressed and more susceptible to infections. This finding may partially explain the higher infection rate in the procedures performed by second-year residents and reinforces the impression that these are procedures performed in more severe patients, indicating reverse causality as a probable reason for this result.

Limitations of our study include retrospective design, which may hinder recovery of outcomes and related factors due to underreporting in the medical record. Another limitation is that the study is observational, therefore we cannot exclude the hypothesis that differences may be due to overlooked confounding variables. The low prevalence of procedures performed by more experienced professionals may limit some findings. Finally, failure to evaluate femoral vein procedures partially limits the generalization of our results. As future perspectives, this project also aims to evaluate the effectiveness of the struc-

tured training that will soon be implemented in the HCPA. Considering the low event rate found, confirmation of these findings in a larger sample would also be interesting.

Conclusion

The analysis of the results of the current training practice demonstrates a rate of mechanical complications similar to the data available in the literature. However, our rates of catheter infection appear to be higher than expected. Our results suggest that structured training should focus not only on the technique of vessel location and catheter insertion but also on the bundle of infection prevention measures.

Resumo

Complicações de punções venosas centrais em um hospital de ensino

Introdução: Cateteres venosos centrais são fundamentais na prática clínica diária. Em hospitais de ensino, esse procedimento é realizado por médicos residentes, frequentemente sem supervisão ou treinamento estruturado.
Objetivo: Descrever as características das punções venosas centrais e a taxa de complicações relacionadas.
Método: Estudo de coorte retrospectiva. Foram selecionados pacientes adultos submetidos a punção venosa central fora de unidade de terapia intensiva (UTI) de um hospital de ensino no ano letivo de 2014 (março de 2014 a fevereiro de 2015). Os dados foram coletados por meio de revisão de prontuários com o uso de formulário eletrônico. Foram avaliadas características clínicas e laboratoriais dos pacientes, características do procedimento, taxa de complicações mecânicas e infecciosas relacionadas. Foram comparados os pacientes com complicações em relação àqueles sem complicações.
Resultados: Foram avaliadas 311 punções venosas centrais. Os principais motivos para realização do procedimento foram falta de rede periférica, quimioterapia e sepse. Ocorreram 20 complicações mecânicas (6% dos procedimentos); punção arterial foi a mais comum. Procedimentos realizados no segundo semestre do ano letivo foram associados a menor risco de complicações (razão de chances de 0,35 [IC95 0,12-0,98; p=0,037]). Foram descritos 35 casos de infecção relacionada ao cateter (11,1%). Casos de infecção foram associados a pacientes mais jovens e procedimentos realizados por residentes com mais de um ano de treinamento. Procedimentos realizados após o primeiro trimestre tiveram menor chance de infecção.
Conclusão: Esses resultados mostram que a taxa de complicações mecânicas de punção venosa central em nosso hospital é semelhante à da literatura; porém, maior atenção deve ser dada para medidas de prevenção de infecção.

Palavras-chave: cateteres venosos centrais, infecções relacionadas a cateter, dispositivos de acesso vascular, pneumotórax, ultrassonografia.

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Risk factors and complications in type 2 diabetes outpatients

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Summary

Objective: Our study investigated type 2 diabetes mellitus (T2DM) outpatients attending a university hospital in Montes Claros, MG, to estimate the prevalence of risk factors and their association with diabetes complications.
Method: This was a quantitative, documental, retrospective and analytical study. Medical records of 95 outpatients with T2DM treated in this hospital from 2011 to 2015 were analyzed. Data were collected according to a structured questionnaire surveying sociodemographic, anthropometric and biochemical data and clinical and lifestyle aspects. Regression analysis was used to evaluate the association between risk factor variables and complications.
Results: With a mean age of 54 years, the study population showed irregular blood glucose control, despite the use of hypoglycemic medication, and did not have a healthy lifestyle. The main complication reported was high blood pressure (HBP), occurring in 70.9% of patients. The prevalence of complications was positively associated with patients receiving insulin treatment (p=0.042) and multidisciplinary monitoring (p=0.050).
Conclusion: The associations identified reflect the condition of patients that were already treating diabetes and its complications, especially HBP. The characteristics of the study population indicate the need to improve clinical follow-up and increase motivation for healthy behaviors.

Keywords: diabetes mellitus type 2, diabetes complications, risk factors.

Introduction

In Brazil, socioeconomic transformations have led to an aging population. Some epidemiological changes that result from this phenomenon are a decline in the occurrence of infectious-parasitic diseases and the predominance of chronic non-communicable diseases such as type 2 diabetes mellitus (T2DM).[1,2]

The occurrence of T2DM in the Brazilian population has increased considerably in recent years, and this is currently one of the most prevalent chronic diseases in the country. This increase is probably related to habits of the modern world, such as the consumption of high-energy diets and sedentary lifestyle, as well as increased life expectancy, development of obesity and difficult access to health services. In addition, there are genetic factors that favor the disease, which makes some people more susceptible to it.[2,3]

Diabetes is a pathology that stands out for the potential of developing long-term complications.[4] At a macrovascular level, patients with diabetes may develop ischemic heart disease, cerebrovascular disease and peripheral vascular disease, which often lead to morbidity and mortality.[5,6] At a microvascular level, diabetes can lead to vision impairment (retinopathy), kidney disease (nephropathy) and neuronal damage (neuropathies), which are more common causes of irreversible blindness, chronic kidney disease and non-traumatic lower limb amputations.[6-8] This proves the severity of diabetes, as the reported complications affect different systems in the body and the sequelae can severely compromise the patients' quality of life.[2]

T2DM can be considered one of the chronic diseases of greater impact for the public health system. In addition to causing a high degree of morbidity and mortality, the metabolic control of diabetes and the treatment of its complications have a high cost for health services.[4,9] Considering the prognosis of individuals who develop physiological changes as a consequence of T2DM, our study

investigated patients with T2DM treated at a university hospital in Montes Claros, state of Minas Gerais, Brazil, in order to estimate the prevalence of risk factors and their association with diabetes complications. The knowledge of the local population is important to direct actions to prevent the undesirable consequences of this disease.

Method

This is a quantitative, documentary, retrospective and analytical study. Our study was developed at the outpatient clinic for patients with T2DM linked to the Clemente de Faria University Hospital, in Montes Claros, state of Minas Gerais, Brazil. The target population included all adult patients, of both genders, diagnosed with T2DM and treated at the outpatient clinic from 2011 to 2015. Cases of chronic complications (diabetic nephropathy and secondary hypertension), aged over 65 years, and presenting only one outpatient visit or incomplete data in the medical records were excluded. In all, the records of 95 patients were evaluated.

Data were collected directly from the patients' medical charts, according to a structured script. Data included sociodemographics (age, marital status and gender), as well as anthropometric and biochemical (weight, fasting blood glucose, HbA1c or glycohemoglobin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure) information. Clinical (disease duration, heredity, type of treatment, professional monitoring and presence of complications) and lifestyle (alcoholism, smoking and eating habits) information were also collected. Morbidities identified as complications were those indicated in the medical record, properly diagnosed and resulting from diabetes, including cardiovascular diseases, hypertension, retinopathy and diabetic nephropathy.

Data were analyzed using Statistical Package for the Social Sciences for Windows®, software version 18.0. The results were described as mean±standard deviation (SD), or absolute numbers and percentage.

Statistical analysis of the association between independent factors and the dependent variable "presence of complications" was done using binary, univariate and multiple logistic regression models. For the multiple analysis, variables that presented a descriptive level below 20% were tested. Variables that presented statistical significance of up to 5% were maintained in the final model.

Our study is in accordance with the ethical precepts of Resolution 466/12 of the National Health Council and was approved by the Research Ethics Committee of the University of Montes Claros (Protocol of approval No. 473,558/2013).

Results

The mean age of the 95 patients in our population was 54.21±12.77 years. Almost half were female (52.6%) and most were married (68.4%) (Table 1). According to clinical and lifestyle data, the patients had a median time since the diagnosis of T2DM of 11 years (ranging from one to 30 years). More than three-quarters of the population did not smoke (76.8%) and were not alcohol-dependent (78.9%). Only 23.6% reported consuming a regular diet, and nutritional monitoring was performed by only 17.8%. The use of oral and insulin hypoglycemic agents was reported by approximately half of the patients (Table 2).

TABLE 1 Sociodemographic characterization of patients with type 2 diabetes mellitus.

Variables	N (%)
Sex	
Male	45 (47.4)
Female	50 (52.6)
Age range (years)	
20-30	04 (4.2)
31-40	06 (6.3)
41-50	22 (23.2)
51-60	33 (34.7)
≥ 61	30 (31.6)
Marital status	
Married	54 (56.8)
Common-law partner	11 (11.6)
Single	15 (15.8)
Divorced	7 (7.5)
Widow(er)	3 (3.3)

TABLE 2 Clinical and lifestyle characterization of patients with type 2 diabetes mellitus.

Variables	N (%)
Time since diagnosis (years)	
≤ 5	24 (25.3)
6-10	19 (20.0)
11-15	25 (26.3)
16-20	13 (13.7)
21-25	5 (5.3)
≥ 26	9 (9.4)
Smoker	
No	67 (70.5)
Yes	28 (29.5)
Alcohol abuse	
No	71 (74.7)
Yes	24 (25.3)

(*continues*)

TABLE 2 (cont.) Clinical and lifestyle characterization of patients with type 2 diabetes mellitus.

Variables	N (%)
Family history of diabetes	
No	42 (44.2)
Yes	53 (55.8)
Insulin treatment	
No	53 (55.8)
Yes	42 (44.2)
Dietary control	
Regular	21 (23.6)
Irregular	68 (74.4)
Dietary guidance	
Yes	16 (17.8)
No	74 (82.2)
Multidisciplinary monitoring	
Yes	69 (72.6)
No	26 (27.4)

The mean and standard deviation of the metabolic parameters of patients with T2DM (weight, fasting blood glucose, HbA1c, total cholesterol, HDL-c, LDL-c, triglycerides) are presented in Table 3. The mean fasting blood glucose of the participants was 144.07 mg/dL, with a prevalence of 78% of altered glycemia. Also, 65% presented altered HbA1c results. Regarding lipid profile, 43.2% had total cholesterol levels above 200 mg/dL, 64% had triglycerides > 150 mg/dL, and 63% had low HDL-c.

TABLE 3 Physiological parameters of patients with type 2 diabetes mellitus.

Parameter	Mean±SD	Reference values for diabetics*
Weight (kg)	77.41±19.09	-
Fasting blood glucose (mg/dL)	144.07±60.46	< 110 mg/dL (goal for diabetics) < 130 mg/dL (tolerable for diabetics)
HbA1c (%)	7.81±1.78	Close to 7 (acceptable for diabetics)
Total cholesterol (mg/dL)	177.12±38.74	< 200 (normal)
HDL-c (mg/dL)	47.02±13.85	> 40 (adequate for men) > 50 (adequate for women)
LDL-c (mg/dL)	104.04±31.74	101 a 130 (normal)
Triglycerides (mg/dL)	162.12±85.04	< 150 (adequate)
Systolic blood pressure (mmHg)	134.87±17.90	< 140 (adequate for diabetics)
Diastolic blood pressure (mmHg)	80.63±8.18	< 90 (adequate for diabetics)

*According to the 2015/2016 Guidelines of the Brazilian Diabetes Society.[2]

The main complication among patients with T2DM was high blood pressure (HBP) (70.9%). The frequency of cardiovascular diseases (1.2%), diabetic retinopathy (5.3%) and diabetic nephropathy (6.3%) was low (Figure 1). In our study, considering HBP as the main complication among patients, our association analyses focused on the presence of this specific pathology.

Table 4 shows the result of bivariate regression analysis for factors associated with the presence of HBP in patients with T2DM. At the level of 0.20, the following variables were associated with HBP and were included in the multiple analyses: age, marital status, ethnicity, time since diagnosis, family history of diabetes, insulin treatment, dietary control, nutritional monitoring, multidisciplinary monitoring and HbA1c.

In the multiple analysis, insulin treatment (p=0.042) and multidisciplinary monitoring (p=0.050) were the variables positively associated with the presence of HBP in patients with T2DM. The estimated coefficients for these variables indicate that the adoption of insulin treatment and monitoring by a multidisciplinary team contribute to the increase of 2.88 and 0.335 units, respectively, in the risk of HBP (Table 5).

Discussion

T2DM and its chronic complications have become increasingly common.[1,9,10] Thus, the importance of the survey carried out in our study, which contributes from a clinical point of view to the monitoring of diabetic patients.[11] Monitoring the patient helps to improve adherence to treatment, to detect difficulties in following it, and to guide health professionals to provide continuous support and achieve goals,[1,11] thus avoiding aggravation of chronic diseases such as T2DM.

The mean age of the diabetic patients in our study was 54 years, suggesting a relation between the increase in life expectancy and the presence of chronic pathologies in the population.[1] Considering that patients were not young, the importance of early T2DM screening should be emphasized, since the insidious character means that patients can be affected well before diagnosis.[12] Time since diagnosis is critical as it directly affects the development of comorbidities and the time of adherence to treatment. Thus, the longer the time to obtain a diagnosis, the lower the control of blood glucose and the greater the chance of developing complications.[1,13]

Our sample had a balanced ratio between men and women. We found that most of the patients had a partner, which can be a positive factor since structured families provide subsidies for patients with T2DM, thus contrib-

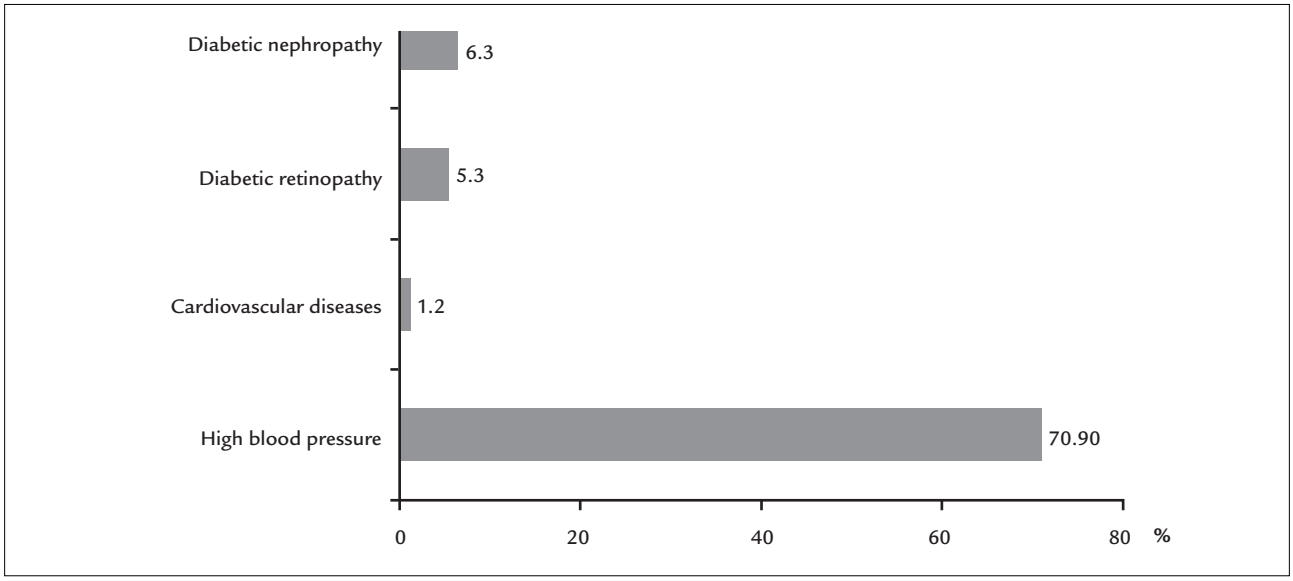

FIGURE 1 Frequencies of complications in patients with type 2 diabetes mellitus.

TABLE 4 Univariate analysis for the factors associated with the presence of high blood pressure in patients with type 2 diabetes mellitus.

Sociodemographics and lifestyle	**HBP**	
	N (%)	**p-value**
Sex		
Male	25 (43.1)	0.297
Female	33 (56.9)	
Age range (years)		
20 to 45	8 (13.8)	0.108
≥ 46	50 (86.2)	
Marital status		
Married/common-law	27 (60.0)	0.066
Single/divorced/widow(er)	18 (40.0)	
Smoker		
No	37 (71.2)	0.955
Yes	15 (28.8)	
Alcohol abuse		
No	42 (82.4)	0.061
Yes	9 (17.6)	
Clinical		
Time since diagnosis (years)		
≤ 10	22 (38.6)	0.022
> 10	35 (61.4)	
Family history of diabetes		
No	29 (50.0)	0.155
Yes	29 (50.0)	
Insulin treatment		
No	25 (43.1)	0.002
Yes	33 (56.9)	

(*continues*)

TABLE 4 (cont.) Univariate analysis for the factors associated with the presence of high blood pressure in patients with type 2 diabetes mellitus.

Sociodemographics and lifestyle	HBP	
	N (%)	p-value
Dietary control		
Regular	10 (18.5)	0.161
Irregular	44 (81.5)	
Dietary guidance		
Yes	7 (12.7)	0.116
No	48 (87.3)	
Multidisciplinary monitoring		
Yes	47 (81.0)	0.021
No	11 (19.0)	
Metabolic		
Fasting blood glucose		
Yes	10 (18.2)	0.589
No	45 (81.8)	
HbA1c		
Yes	24 (41.4)	0.026
No	34 (58.7)	
Total cholesterol		
Yes	31 (53.4)	0.403
No	27 (46.6)	
HDL-c		
Yes	34 (58.6)	0.251
No	24 (41.4)	
LDL-c		
Yes	24 (25.3)	0.341
No	34 (74.7)	
Triglycerides		
Yes	18 (31.0)	0.226
No	40 (69.0)	
Systolic blood pressure		
Yes	39 (67.2)	0.554
No	19 (32.8)	
Diastolic blood pressure		
Yes	37 (63.8)	0.515
No	21 (36.2)	

HBP: high blood pressure.

TABLE 5 Multiple logistic regression analysis for factors associated with the presence of high blood pressure in patients with type 2 diabetes mellitus.

Variables	OR (adjusted)	95CI	p-value
Insulin treatment			
No	1		
Yes	2.88	1.03-8.00	0.042
Multidisciplinary monitoring			
Yes	1		0.050
No	0.335	0.11-1.00	

OR: odds ratio; 95CI: 95% confidence interval.

uting to adherence to treatment.[14] As for family history, 50% of the patients had first-degree relatives with diabetes, proving a genetic basis for the disease, although their prevalence on the environmental factors cannot be affirmed. Although the etiology of T2DM is not fully elucidated, it is known to have a multifactorial composition.[2] Therefore, it is important to investigate the patient's social history and, if possible, to make the family a pillar of care that involves lifestyle change.[14]

Regarding lifestyle, most patients were non-smokers and non alcohol-dependent, which is a satisfactory result, since the association between smoking and limb amputations in diabetic patients is well known.[15] Most did not maintain dietary control and did not follow the guidance of a dietitian. Studies indicate that healthy eating is one of the most difficult practices, in contrast to drug therapy, which, as found in our study, generally has good adherence.[11,15] Non-adherence to diabetes treatment is a problem of known magnitude on the international and national scene that contributes to the low effectiveness of treatment and complications in the medium and long term and, consequently, to an increase in the demand for highly complex health services.[11] It is evident, therefore, that primary care should greatly improve its activities of receiving these patients for multiprofessional treatment.

In our study, 92.6% of diabetic patients had glycemic indexes greater than 91 mg/dL, and the mean in the population was high, reaching 144 mg/dL. Glycated hemoglobin levels were also high, averaging 7.8%. These data indicate that glycemic control was not performed as recommended by the Brazilian Society of Diabetes Mellitus (SBD, in the Portuguese acronym), which establishes the maximum value of 100 mg/dL for fasting blood glucose. There is, therefore, the need for treatment of our population, since adequate metabolic control either prevents the onset of chronic complications or delays their progression, particularly those of microangiopathic nature.[2]

Measures to prevent hypertension and dyslipidemia should be part of the treatment of patients with T2DM because they increase the risk of developing cardiovascular diseases, directly impacting morbidity and mortality rates.[16] In our study, these parameters were altered, which requires attention to indicate the risk of developing a cardiovascular problem. Mortality due to cardiovascular disease progressively increases in a linear, continuous and independent manner with blood pressure values above 115/75 mmHg.[17]

HBP was the main complication described in our population. The Brazilian Society of Diabetes states that T2DM, hypertension and renal function are closely related. HBP can be both a cause and a consequence of kidney disease, and the combination of the two presents a high risk for cardiovascular disease. Thus, appropriate treatment of HBP helps to prevent cardiovascular disease, minimizes the progression of renal disease and diabetic retinopathy. Care involves practices such as regular physical activity, low-sodium diet, decreased consumption of alcoholic beverages and correct intake of prescribed antihypertensive medication.[2]

The combination of complications with the variables insulin use and multidisciplinary monitoring refers to the advanced stage of the disease since patients with T2DM are more susceptible to chronic complications. Thus, T2DM progression time may lead to more risks for the development of microvascular complications in general.[18] It should also be kept in mind that the pathophysiological process of aging alone can cause atherosclerosis, farsightedness and immune changes that may increase the prevalence of complications.[18]

Broadly speaking, the results do not allow the establishment of cause and effect relations but indicate that patients with T2DM in our study, many with HBP, had irregular glycemic control, used hypoglycemic agents but did not make dietary adjustments. These factors directly compromise the quality of life of diabetic individuals and make the pathology difficult to control. Therefore, measures that show patients the severity of diabetes and the possible consequences of a lack of adequate treatment should be adopted in our population.

Since there is no cure for diabetes, its best treatment is primary prevention, encouraging the at-risk population to have healthy lifestyle habits and performing periodic screening. Responsibility for health promotion should not be limited to health professionals. Public policies that need to be implemented include those aimed at improving access to health services, empowering patients to understand the disease and learn self-care skills.[19,20] As for secondary prevention, it is important to monitor and encourage behavioral changes, because even when insulin is used, glycemic control may be unsatisfactory if the individual does not adopt a healthy lifestyle.[2]

A last aspect to be considered refers to the limitations of our study. Some data from the medical records were incomplete or absent, lacking the necessary information to complete the questionnaires. In addition, anamnesis and clinical examination were not standardized, making it difficult to monitor clinical alterations. Finally, there was no specific periodicity for patients attending medical appointments, and in some cases the amount of follow-up data was too low or non-existent. These difficulties led to the exclusion of several medical records, thus reducing the sample.

Conclusion

We identified as the main complication in the diabetic population included in our study the incidence of HBP. In addition, we have shown that the main associated risk factors were, in general, insulin use and multidisciplinary team monitoring. The joint occurrence of these factors may indicate an advanced stage of the disease and greater exposure to chronic complications.

The studied population also showed irregular glycemic control, despite the use of hypoglycemic medication, and irregular diet. Thus, we suggest primary prevention actions for this population, such as strict monitoring of blood glucose and blood pressure, multiprofessional follow-up, adherence to drug therapy, physical exercise and dietary monitoring, in addition to the active participation of the family in the treatment of the disease and a stronger bond with the health unit.

Resumo

Fatores de risco e complicações em pacientes de ambulatório com diabetes tipo 2

Objetivo: O estudo investigou pacientes com diabetes tipo 2 (DM2) atendidos em um hospital universitário de Montes Claros (MG) a fim de estimar a prevalência de fatores de risco e sua associação com complicações da diabetes.
Método: Pesquisa quantitativa, documental, retrospectiva e analítica. Foram analisadas as fichas médicas de 95 adultos portadores de DM2 atendidos no ambulatório do hospital entre 2011 e 2015. Os dados foram coletados de acordo com um questionário estruturado incluindo variáveis sociodemográficas, antropométricas e bioquímicas e aspectos clínicos e de estilo de vida. As análises de associação entre variáveis de fatores de risco e presença de complicações foram feitas por meio da regressão logística.
Resultados: Com média de 54 anos de idade, a população estudada tinha controle glicêmico irregular, fazia uso de hipoglicemiantes e não adotava um estilo de vida saudável. A principal complicação reportada foi hipertensão arterial, presente em 70,9% dos casos. A prevalência de complicações associou-se positivamente com adoção de tratamento insulínico (p=0,042) e acompanhamento multidisciplinar (p=0,050).
Conclusão: As associações encontradas refletem a condição de pacientes que já tratam a diabetes e suas complicações, principalmente a hipertensão arterial. Características da população indicam a necessidade de melhoria do acompanhamento clínico e o incentivo à adoção de hábitos comportamentais saudáveis.

Palavras-chave: *diabetes mellitus* tipo 2, complicações do diabetes, fatores de risco.

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Pregnancy recurrence in adolescents in Southern Brazil

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Summary

Objective: To determine the pregnancy recurrence among adolescents and young people in a city located in the extreme south of Brazil and to identify associated factors.
Method: One hundred and twelve (112) women participated, having delivered their children in 2010, while adolescents. The sample was stratified in two stages, being the first a census of the whole population of the city and the second a convenience sample. For statistical analysis, Pearson Chi-square test was used, with a significance level of 5%.
Results: The recurrence rate was 53.6%, with an average of 28.6 months. At the time of delivery, in 2010, recurrence was significantly associated with level of education (p=0.044) as well as not being in school (p=0.036). In 2014, the factors associated were level of education (p<0.001), transcript of grades (p=0.030) and income (p=0.030).
Conclusion: Recurrence of teenage pregnancy represents a lack of importance given to formal education, a fact that mitigates the opportunities and hinders insertion in the labor market, creating a cycle of social inequality. Multidisciplinary efforts involving schools, health services and the youth in educational activities are thus vital, aiming at critical thinking to transform reality.

Keywords: sexual behaviour, pregnancy in adolescence, recurrence.

Introduction

Pregnancy in adolescence can cause serious health problems affecting both the mother and the newborn[1] including maternal death, abortion, preterm labor and low birth weight infants.[2-4] According to the World Health Organization (WHO), 16 million adolescents between the ages of 16 and 19 and 2 million under the age of 15 have a living child each year. There was a decline in the percentage of live births to adolescent mothers in Brazil between 2000 and 2011 (23.5 and 19.2%, respectively).[5] Nevertheless, the percentage is still high and the situation is more serious when there is recurrence of pregnancy in a period equal to or lesser than 24 months, called rapid recurrent pregnancy (RRP), associated with increased maternal and infant morbidity and mortality.[6-8]

Studies in South Africa and the United States have found recurrent pregnancy rates in adolescents ranging from 17.6[4] to approximately 30%,[2,9,10] respectively. Investigations conducted in Brazil have determined rates varying from 3.7[8] to 29%[11] depending on the region being analyzed.

According to the literature, predictors of recurrence of teenage pregnancy include depression,[12] families with low socioeconomic status, families with many members, adolescents with limited family support and low educational level.[8] In addition to these factors, a family history of recurrence in pregnancy also plays a key role.[8,13]

Recurrence of pregnancy can influence the future of the adolescents and their children. In this context, our study aimed to determine the rate of recurrent pregnancy in adolescents of a municipality in Southern Brazil and to identify associated factors.

Method

Our study is part of a larger project called the "2010 Perinatal Study: Reassessing the Conditions of Assistance to Pregnancy and Childbirth in the Municipality of Rio

Grande." This population-based survey involved interviews of all women who gave birth to their children in this municipality in 2010, totaling 2,446 mothers in the municipality of Rio Grande, which has a human development index of 0.746 and the 4th highest gross domestic product (GDP) in the state.[14]

Our study had a prospective and longitudinal design. In the first phase, all the women who gave birth in 2010, who were between the ages of 10 and 19 years and lived in the urban area were included. As a follow-up, these mothers were re-interviewed in their homes four years later, in 2014, at an age of up to 24 years.[15] Those who did not experience motherhood (either because they were not responsible for raising the child or due to the death of the baby) and those who did not live in Rio Grande were excluded.

At baseline, in 2010, the data were collected by means of a semi-structured questionnaire with questions about demographic characteristics, formal education, occupation, reproductive history and life habits of the mothers, socioeconomic status, housing and sanitation conditions, and use of health services. The pregnant adolescents were identified from self-reported information and confirmed by the entry of the babies, data in the hospital's birth registry book, with interview conducted within 48 hours after delivery.

The second questionnaire applied in 2014 was also semi-structured and repeated the same questions. The interviewers contacted the mothers by telephone to schedule the visit. When the contact was not successful, they were actively tracked at the addresses provided at the time of delivery in 2010, in the vicinity of those addresses, and in the records of the Medical and Statistical Archive Service (SAME). The interviews were conducted from July to December 2014, at the participants' homes. The outcome was pregnancy recurrence, defined as the birth of another child or children, with gestational age greater than 20 weeks and birth weight greater or equal to 500 g, and the number of recurrences.

The independent variables of the first stage of the study were: age in full years, later categorized as up to 16 and 17 years or older; self-reported skin color, categorized as white, black or other; marital status during pregnancy, categorized as with or without partner; years of formal education, categorized as up to seven years and more than eight; if the participant was enrolled in school when she became pregnant; if she stopped studying during pregnancy; education at the end of pregnancy, categorized as continued to study, did not study at the time or stopped studying; the per capita income at the date of delivery, categorized as less than or equal to a minimum wage and more than a minimum wage; if the participant worked before getting pregnant; and variables containing prenatal, labor and newborn weight data. In the second stage, the same socioeconomic variables were collected, except for age, which in 2014 was categorized as up to 20 or 21 years or older.

The sample size was calculated using the Epi Info 6.04®[16] statistics software. For an estimated 40%[17] pregnancy recurrence rate, with a 10% variation and 95% confidence interval, in a total pregnant population estimated at 2,395, the minimum number required is 101 participants. At this number, 10% was added to compensate for any losses. Thus, the minimum number of subjects required to assess recurrence was 111 participants.

The data previously collected from 2010, already coded, were entered into a database created using Epi Info 6.04®[16] software. The 2014 questionnaires were coded and entered in the same database, being typed twice in reverse order and independently. Subsequent data cleaning was performed to identify coding errors.

Data analysis was carried out using SPSS software version 20®.[18] Pearson's Chi-square test, Student's t-test and Linear Trend test were used, adopting a p-value < 0.05 of a two-tailed test. The multivariate analysis was performed using non-conditional logistic regression, calculating the prevalence ratio (PR) and its respective 95% confidence intervals. Adjusted analysis was performed according to a three-level hierarchical analysis model defined by the researchers.[19] The first, more distal level comprised the demographic variables of the adolescent. At the second level, the variables of school status, income and work during pregnancy were included. At the third level, the most proximal, variables related to prenatal care were included. The variables were selected for the final model using the backward method. At each level, only the variables with a p≤0.20 value were maintained, in order to evaluate the possibility of negative confusion. The p-value to establish a significance level was 0.05 for two-tailed tests.

The 2010 Perinatal survey was approved by the Research Ethics Committee (CEPAS) of the Federal University of Rio Grande (FURG), Opinion no. 117/2009, and the CEPAS of Santa Casa de Misericórdia Charitable Association of Rio Grande, Opinion no. 09/2009. The 2014 survey was approved by the CEPAS/FURG, Opinion no. 90/2011.

Results

A total of 112 women who gave birth in their adolescence, now aged 17-24 years (mean of 22 years plus standard deviation [SD] ± 1.5) participated in this study. Of the 445 eligible women, 284 (63.8%) were not found, 22 (4.9%)

refused to participate in the study and 27 (6.1%) were excluded. It should be noted that, according to the data collected in 2010, there was no significant statistical difference regarding socioeconomic and prenatal factors among re-interviewed and non-interviewed mothers in the present study (Table 1).

The pregnancy recurrence rate was 53.6% (60/112). The mean recurrence time was 28.7 months (SD±12.7), and two years after the first birth, half of these adolescents (30/60) were pregnant again, while after three years, the rate increased to 80% (46/60).

Regarding the characteristics of the adolescents obtained in the perinatal study of 2010, it is observed that the sample was predominantly formed by women over 17 years of age at delivery (81.2%), with skin color self-reported as white (70.5 %), and who lived with a partner during pregnancy (68.8%). The age of the child's father ranged from 16 to 45 years (mean of 23.2 years, SD±5.1). Regarding education, 60 women (53.6%) studied seven years or less, most did not study when they became pregnant (56.2%) and of the 49 women who studied, 27 (55.1%) stopped studying. After analyzing these variables simultaneously, we observed that almost five out of six participants (80.4%) were no longer studying or interrupted their studies. The majority of the participants (57.7%) had income equal to or less than one minimum wage. We found a predominance (69.6%) of young women who did not perform paid work at the time of delivery. The age of the mother of the participant when their first child was born ranged from 13 to 32 years (mean of 19.4 years and SD±4.2). We found that 95.5% of the women had prenatal care, 77.4% of them started in the first trimester,

TABLE 1 Comparison of socioeconomic and prenatal factors among adolescent mothers interviewed a second time and those not interviewed for the study "Recurrence in gestation and associated factors in adolescents in Southern Brazil," according to data provided in 2010.

Variables	Second interview	Not interviewed	p-value
Age (Mean)			0.12[a]
Skin color	17.70 (SD±1.28)	17.31 (SD±1.48)	
White	72.3%	63.4%	0.08[b]
Non-white	27.7%	36.6%	
Education			
Up to 8 years	69.6%	73.3%	0.50[b]
9 years or more	30.4%	26.7%	
Education (mean)	7.71 (SD±2.15)	7.32 (SD±2.17)	
Income in MW			0.71[a]
Less than 1 MW	24.1%	23.7%	0.43[b]
1 to 1.9 MW	38.4%	44.7%	
2 MW or more	37.5%	31.5%	
Mean income	957.84 (SD±875.17)	907.99 (SD±889.37)	
Prenatal care			0.55[a]
SUS – public system	74.8%	80.6%	0.19[b]
Private healthcare plan	25.2%	19.4%	
Prenatal care performed			
Yes	95.5%	94.6%	0.69[b]
No	4.5%	5.4%	
Number of consultations			
5 or less	79.2%	69.7%	0.06[b]
6 or more	20.8%	30.3%	
Trimester in which prenatal care was initiated			0.25[b]
First	76.5%	70.8%	
Second or third	23.5%	29.2%	

[a]Student's t-test.
[b]Chi-square.

with a mean of 2.7 months (SD±1.1) of pregnancy and 7.7 (SD±2.5) medical consultations, on average. According to Takeda's criteria, prenatal care was considered adequate in 80 (76.2%) of the participants. Vaginal delivery was the most prevalent (54.5%), and the mean weight of the newborn was 3.0 kg.

In Table 2, after the adjusted analysis, it is clear that adolescents with seven years or less of formal education presented twice the risk of conceiving again than those with a longer education (PR 2.26; 95CI 1.02-5.01), whereas those who did not study before becoming pregnant or who left school during pregnancy had a three times greater risk of a new pregnancy compared to those who never left school (PR 2.96; 95CI 1.07-8.19).

The data in Table 3 refer to the characteristics of participants after the second interview in 2014. In 2014, the mean age was 22 years with SD±1.53. As for marital status, 89.3% have a spouse or partner who is the father of the child in 59.8% of cases. The proportion of women with a per capita income less than a minimum wage increased to 82.1% over the four years of follow-up. The proportion of participants who did not perform paid work fell to 59.9%. Young mothers who had 4 to 7 years of education in 2014 had a two-fold increased risk of another pregnancy, whereas participants with three years or less of study had a three-fold higher risk compared to mothers who studied for 8 years or more. After the adjusted analysis for demographic data (age and color) and socioeconomic status (income), we found that, for each year studied, there is a 16% protection against a new pregnancy (PR 0.84; 95CI 0.79-0.88 and p-value<0.001). Participants classified in the 2nd and 3rd quartiles of income had two times greater risk of new pregnancy compared to women of the highest income quartile.

Discussion

The recurrence of gestation in adolescents presents contrasts in different regions of the world.[8] The recurrence rate in our study, 53.6%, is higher than the 31.5% (58/193) found in a study conducted in the United States with adolescents aged 13 to 19 years who were interviewed immediately after delivery.[12] Mphastswe et al.,[4] while investigating 341 South African adolescents aged 13 to 19 who were in the postpartum period, found that 60 (17.6%) of these women had had recurrent pregnancies after a minimum of 12 months and a maximum of 60 months. In Brazil, Silva et al.[11] analyzed all the statements of liveborn children of adolescents between 10 and 19 years old, in the city of Rio de Janeiro in 2005, and found that 29.1% (3,542/12,168) of these births were the result of recurrent pregnancy.

Our study evaluated the recurrence of pregnancy in adolescents over a four-year period, unlike most studies, which include two-year periods.[2,6,8,20,21] Thus, it is possible to affirm that most of the studies only evaluate rates of RRP. It is estimated that between 10 and 50% of adolescents become pregnant again 24 months after a previous birth.[12] In our sample, the mean time to a new pregnancy was 28.9 months, with an RRP rate of 26.8% (30/112). This value is similar to the 25.9% (120/464) found by Nery et al.[20] in young mothers aged between 17 and 22 years in the city of Teresina (capital of the state of Piauí) and the 35.4% (62/175) detected by Nery et al.[21] in five municipalities in the state's countryside. A study with data from the declarations of live births in the city of Rio de Janeiro, for the year 2002, identified an RRP rate of 5.2% (809/15,636) in adolescents aged between 10 and 19 years.[8] On the other hand, a study conducted in the United States with adolescents aged 15 to 19 found an RRP rate of 67.1% (89/133).[2] It is important to note that, in our study, the longer investigation allowed us to find twice as many pregnancy recurrences as we would have if follow-up was limited to two years. In three years of analysis, this rate increased from 50 to 80%. Thus, we hypothesize that the minimum interval of two years between pregnancies is not adequate for the adolescents, requiring a longer study time to investigate the recurrence of gestation in youth.

In relation to the characteristics collected in the year 2010, school dropout was significantly associated with recurrence of pregnancy. This is corroborated by other studies that point to formal education as the main factor associated with recurrence of pregnancy or lack thereof.[8,11,20,21] A study conducted in the United States with 193 adolescents between the ages of 13 and 19 years found that 77% of the girls had not finished high school.[12] Similar to these data, our study showed that 75% of the adolescents with recurrence had up to eight years of study in the previous pregnancy. It was also observed that adolescents who did not study or stopped studying at the end of gestation were three times more likely to have a recurrent pregnancy compared to adolescents who remained studying. With the responsibilities of motherhood arising, many adolescents dropped out of school after getting pregnant.[21] Thus, it is possible to assume that young people who drop out of school early do not present the autonomy necessary to avoid a recurrent pregnancy. In addition, the lack of academic aspirations can be one of the factors causing school dropout and, indirectly, the recurrence of pregnancy in adolescents.[10]

Regarding the characteristics collected in 2014, education and income were the variables significantly associated

TABLE 2 Analysis of factors associated with recurrence of pregnancy up to 2014 in relation to variables collected immediately after delivery in 2010 among adolescents in Southern Brazil (N=112).

Variable	Description of the sample	Pregnancy recurrence n (%)	p-value[a] PR (95CI) bivariate	p-value[a] PR (95CI) adjusted
Age at child birth (112)[1st]			0.544	
≤ 16	21 (18.8)	10 (47.6)	1.0	
≥ 17	91 (81.2)	50 (54.9)	1.16 (0.73-1.85)	
Self-reported skin color (112)[1st]			0.894	
White	79 (70.5)	42 (53.2)	1.0	
Black or other	33 (29.5)	18 (54.5)	1.03 (0.66-1.60)	
Marital status during pregnancy (112)[1st]			0.261	
Single	77 (68.8)	16 (45.7)	1.0	
Spouse or partner	35 (31.2)	44 (57.1)	1.27 (0.85-1.89)	
Education (years) (112)[2nd]			0.050	0.044
8 or more	52 (46.4)	27 (45)	1.0	1.0
0-7	60 (53.6)	33 (63.5)	1.51 (0.98-2.30)	2.26 (1.02-5.01)
Was studying when she became pregnant (112)[2nd]			0.215	
Yes	49 (43.8)	23 (46.9)	1.0	
No	63 (56.2)	37 (58.7)	1.29 (0.87-1.91)	
Stopped studying (49)[2nd]			0.055	
No	22 (44.9)	7 (31.8)	1.0	
Yes	27 (55.1)	16 (59.3)	1.67 (0.98-2.86)	
Education status by the end of pregnancy (112)[2nd]			0.022	0.036
Continued to study	22 (19.6)	7 (31.8)	1.0	1.0
Did not study or dropped out of school	90 (80.4)	53 (58.9)	1.66 (1.14-2.42)	2.96 (1.07-8.19)
Per capita income at the time of child birth (111)[2nd]			0.354	
>1 minimum wage	47 (42.3)	23 (48.9)	1.0	
≤1 minimum wage	64 (57.7)	37 (57.8)	1.21 (0.81-1.81)	
Worked prior to becoming pregnant (112)[2nd]			0.462	
No	78 (69.6)	40 (51.3)	1.0	
Yes	34 (30.4)	20 (58.8)	1.18 (0.75-1.88)	
Mother's age during the first pregnancy (96)[2nd]			0.560	
≥ 20	38 (39.6)	18 (47.4)	1.0	
≤ 19	58 (60.4)	31 (53.4)	1.13 (0.75-1.70)	
Prenatal care (112)[3rd]			0.768	
Yes	107 (95.5)	57 (53.3)	1.0	
No	5 (4.5)	3 (60.0)	1.17 (0.39-3.48)	
Number of prenatal consultations (106)[3rd]			0.856	
6 or more	84 (75.0)	44 (52.4)	1.0	
Up to 5	22 (19.6)	12 (54.5)	1.05 (0.63-1.74)	
Adequate prenatal care according to Takeda (105)[3rd]			0.759	
Adequate	80 (76.2)	42 (52.5)	1.0	
Inadequate	25 (23.8)	14 (56.0)	1.08 (0.66-1.78)	
Type of delivery (112)[3rd]			0.377	
C-section	51 (45.5)	25 (49)	1.0	
Vaginal	61 (54.5)	35 (57.4)	1.20 (0.80-1.78)	
Birth weight (112)[3rd]			0.669	
≥ 2,500 g	102 (91.2)	54 (52.9)	1.0	
≤ 2,449 g	10 (8.9)	6 (60)	1.18 (0.54-2.58)	

[a]Pearson's Chi-square.
Minimum wage in 2010: BRL 511.00.
1st, 2nd, 3rd = levels of the hierarchical model in the adjusted analysis.

TABLE 3 Analysis of factors associated with recurrence of pregnancy up to 2014 in relation to variables collected over four years of study among adolescents in Southern Brazil (N=112).

Variable	Description of the sample	Pregnancy recurrence n (%)	p-value PR (95CI)
Age difference			
3 years	6 (5.4)	2 (33.3)	
4 years	68 (60.7)	37 (54.4)	
5 years	38 (33.9)	21 (55.3)	
Marital status			
Single/Single	7 (6.2)	2 (28.6)	
Single/Spouse or partner	28 (25.0)	14 (50.0)	
Spouse or partner/Spouse or partner	72 (64.3)	41 (56.9)	
Spouse or partner/Single	5 (4.5)	3 (60.0)	
Formal education in years			<0.001[b]
≥ 8 years	56 (50.0)	18 (32.1)	1.0
4 to 7 years	45 (40.2)	31 (68.9)	2.14 (1.40-3.29)
≤ 3 years	11 (9.8)	11 (100)	3.11 (2.13-4.55)
Education progression			0.030[b]
Studied for 2 years or more	57 (50.9)	25 (43.9)	1.0
Studied for 1 year	41 (36.6)	25 (61)	1.39 (0.95-2.04)
Did not study	14 (12.5)	10 (71.4)	1.63 (1.05-2.54)
Income history			
Income increase	57 (51.4)	28 (49.1)	
Income loss	54 (48.6)	32 (59.3)	
Income quartile			0.030[a]
4th (highest)	27 (24.3)	9 (33.3)	1.0
3rd	28 (25.2)	19 (67.9)	2.04 (1.13-3.68)
2nd	27 (24.3)	18 (66.7)	2.00 (1.10-3.63)
1st (lowest)	29 (26.1)	14 (48.3)	1.45 (0.75-2.78)
Works			0.164[a]
Yes/Yes	18 (16.1)	9 (50.0)	1.0
Yes/No	16 (14.4)	11 (68.8)	1.38 (0.78-2.43)
No/Yes	27 (24.1)	10 (37.0)	0.74 (0.38-1.45)
No/No	51 (45.5)	30 (58.8)	1.18 (0.70-1.97)

[a]Pearson's Chi-square.
[b]Linear Trend test.
Minimum wage in 2014: BRL 788.00.

with recurrence of pregnancy. As mentioned above, low formal education is a risk factor for recurrent teenage pregnancy.[8] Similarly to our investigation, Silva et al.,[11] after analyzing the pregnancy rate in 12,168 adolescents in the city of Rio de Janeiro, also found a linear trend between education and the number of recurrences, so that girls with less education were more likely to have recurrent pregnancies. Therefore, formal education is presented as the main variable to solve the social problem of teenage pregnancy.[21]

Our research has shown that every additional year of study in a girl's life provides increased protection against recurrence of pregnancy. This finding is in agreement with the scientific literature that assumes that the longer the girls continue to study, the more topics related to sexuality are addressed, allowing their empowerment regarding contraceptive methods.[8] In addition, it was not only the years of study that influenced the rate of recurrence, but also school progression in those four years. The more years of study these girls have after delivery, the lower the risk of recurrence, reinforcing the hypothesis that continuing to study is imperative to avoid new pregnancies.

Similarly to other studies,[21,22] the recurrence of pregnancy in our population was higher among low-income participants. It is observed that the participants belong-

ing to the second and third income quartiles are twice as likely to have recurrence compared to the young women classified in the highest quartile. However, these data are contradictory, since the increase in expenses after the birth of a second child increases the pressure for increasing income. One possible explanation for this is the fact that young women from lower socioeconomic backgrounds may desire family stability that they associate with pregnancy as an alternative to the absence of other projects.[23]

The fact that formal education (or lack of it) is clearly associated with recurrence reinforces this proposition. In our study, 56.2% of the analyzed group was no longer in school when they became pregnant, and 57.7% had studied for eight years or less, suggesting that school really is the first barrier against teenage pregnancy. Legally, pregnant adolescents have the support of Law No. 6,202 of 1975, which stipulates that from the eighth month on, or before that, depending on medical orders, these girls have a right to be home-schooled, being assured a rest period before and after delivery without interfering with their final exams.[24] Thus, school and teachers should provide conditions to ensure the continuation of studies of pregnant adolescents in accordance with the legislation, as well as strengthen the discussion about consequences of a recurrent pregnancy.

In addition to the family and school, health professionals also have a responsibility to address this issue with adolescents and fail to do so. In our study, 79% of these girls had more than six medical visits during prenatal care, with a mean of 7.7. Health professionals need to recognize moments such as puerperal and pediatric consultations and children's immunization days as opportunities for comprehensive care, debating and instructing these young women about the importance of studying and working, as well as discussing contraception. Health workers can help reduce recurrent teenage pregnancy because they have more interaction with the community, so they are essential in identifying vulnerable, low-income youth who are not studying or working. These professionals have the opportunity to focus their actions and their dialogues on contraception according to the reality of life of these young women.

Limitations of the study included difficulties in tracing participants due to address changes and/or loss of contact by the researchers, which may result in selection bias. Although telephone contact is a simple and virtually universal form of access, it is common to change numbers, not to mention incorrect numbers or blocked line, which is a problem faced in several studies.[22,25] Finally, the sample size calculation was performed only for recurrent pregnancy rate, so that non-significant associations may be a result of the lack of statistical power of the sample. Nevertheless, it is important to highlight that the recurrent pregnancy rate was higher than that described in other articles that also had this limitation,[21,22] highlighting the epidemiological importance of this data.

Despite the above limitations, we can conclude that recurrence of pregnancy in adolescence and youth represents the low value given to formal education, a fact that mitigates the experience of opportunities and hinders insertion in the labor market, creating a cycle of social inequality. It is imperative to join multidisciplinary efforts in schools and health services, including young people in educational actions aimed at favoring critical thinking to transform reality.

Resumo

Recorrência de gestação em adolescentes do extremo sul do Brasil

Objetivo: Determinar a recorrência de gravidez em adolescentes de um município no extremo sul do Brasil e identificar os fatores associados.
Método: Participaram 112 mulheres que tiveram filho em 2010, quando eram adolescentes. A amostra foi estudada em dois estágios, sendo no primeiro por meio de um censo do município e no segundo por uma seleção de conveniência. Para análise estatística, foi utilizado o teste Qui-quadrado de Pearson com nível de significância de 5%.
Resultados: A taxa de recorrência de gravidez encontrada foi de 53,6% com tempo médio de 28,6 meses. No momento do parto, em 2010, estiveram significativamente associados à recorrência a escolaridade (p=0,044) e o fato de não estar estudando (p=0,036). Em 2014, foram a escolaridade (p<0,001), o histórico escolar (p=0,030) e a renda (p=0,030).
Conclusão: A recorrência de gravidez na adolescência representa a pouca valorização da educação formal, o que mitiga a vivência de oportunidades e dificulta a inserção no mercado de trabalho, criando um ciclo de desigualdade social. É imprescindível unir esforços multidisciplinares nas escolas e nos serviços de saúde, em conjunto com os jovens, em ações educativas que visem a uma relação crítica reflexiva transformadora da realidade.

Palavras-chave: comportamento sexual, gravidez na adolescência, recidiva.

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Use of SGLT-2 inhibitors in the treatment of type 2 diabetes mellitus

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Summary

Introduction: Diabetes mellitus is one of the most common chronic diseases in the world, with high morbidity and mortality rates, resulting in a greatly negative socioeconomic impact. Although there are several classes of oral antidiabetic agents, most of the patients are outside the therapeutic goal range.
Objective: To review the use of SGLT-2 inhibitors in the treatment of type 2 diabetes mellitus, focusing on their favorable and unfavorable effects, as well as on cardiovascular profile.
Method: A literature search on Pubmed database was performed using the following keywords: "SGLT-2 inhibitors," "dapagliflozin," "empagliflozin," "canagliflozin."
Results: SGLT-2 inhibitors are a class of oral antidiabetic drugs directed to the kidney. Their mechanism of action is to reduce blood glucose by inducing glycosuria. Extra-glycemic benefits have been described, such as weight loss, decline in blood pressure and levels of triglycerides and uric acid, and they can slow the progression of kidney disease. Genitourinary infections are the main side effects. There is a low risk of hypotension and hypoglycemia. Diabetic ketoacidosis is a serious adverse effect, although rare. Empagliflozin has already had its cardiovascular benefit demonstrated and studies with other drugs are currently being performed.
Conclusion: SGLT-2 inhibitors are a new treatment option for type 2 diabetes mellitus, acting independently of insulin. They have potential benefits other than the reduction of blood glucose, but also carry a risk for adverse effects.

Keywords: SGLT-2 inhibitors, type 2 diabetes mellitus, kidney, glycosuria, review.

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Introduction

Diabetes mellitus (DM) is currently considered a public health problem, with increasing incidence and prevalence worldwide. The global estimate of DM patients in 2013 was greater than 381 million, projected to increase to approximately 592 million by 2035.[1,2] Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders, accounting for 90-95% of adult diabetes.[3]

The pathophysiology of T2DM is complex and multifactorial. Ralph DeFronzo was responsible for the concept of ominous octet – a broader theory, which identified different organs in addition to the pancreas, as well as eight problems, which play a key role in the pathogenesis of T2DM. The main defects include pancreatic beta cell failure and insulin resistance in muscles and liver. Furthermore, incretin deficiency, accelerated lipolysis, hyperglucagonemia, insulin resistance in the brain, and increased renal reabsorption of glucose also participate in the development of the disease[4] (Table 1).

TABLE 1 DeFronzo's ominous octet.

Pancreatic beta cells	Insufficient insulin secretion
Pancreatic alpha cells	Excess glucagon
Fat cells	Increased lipolysis
Muscles	Reduction of peripheral glucose uptake
Liver	Greater hepatic glucose production
Gastrointestinal tract	Decline of incretin activity
Brain	Dysfunction of brain neurotransmitters
Kidneys	Greater renal reabsorption of glucose

The identification of the ominous octet was important, as it provided a paradigm shift in the treatment of DM. DeFronzo proposed the association of drugs to act in all pathophysiological defects of the disease, and not only reduce glycated hemoglobin.[4] Although there are several therapeutic options, it is still common to find poorly controlled patients with blood glucose levels outside of the target range. One of the causes that contribute to this is therapeutic inertia of physicians, who end up delaying the association of drugs.[5]

Complementing the therapeutic arsenal currently available for the treatment of T2DM, a new class of drugs called SGLT-2 inhibitors has been approved in recent years by the Brazilian Agency for Sanitary Surveillance (Anvisa, in the Portuguese acronym), with a focus on kidney treatment. They reduce blood glucose by increasing the urinary excretion of excess glucose that would be reabsorbed by the kidneys.[6]

The aim of this article was to review the state of the use of SGLT-2 inhibitors in the treatment of T2DM, focusing on its favorable and unfavorable effects, and its cardiovascular profile.

Method

Bibliographical and transversal search for scientific articles was carried out in the Pubmed (National Center for Biotechnology Information) database. The following keywords were used: "SGLT-2 inhibitors," "dapagliflozin," "empagliflozin," "canagliflozin". The inclusion criteria were: scientific articles in human beings or animals, written in English, Portuguese or Spanish. There was no date restriction for the articles. Scientific articles related to the subject were selected after title and abstract analysis. Articles such as letters to the editor, communications, editorials, comments, articles in other languages and those with partially published data were excluded. The references of the articles selected were also analyzed to identify other articles relevant to the subject.

The kidney as a treatment target

The kidney contributes to glucose homeostasis by filtering plasma glucose through glomeruli and reabsorbing it in the segments 1 (S1) (90%) and 3 (S3) (10%) of the proximal tubule. In healthy subjects, the kidneys filter approximately 180 g of glucose per day. Due to reabsorption, glucose in the urine is either absent or present at very low concentrations (0.03 to 0.30 g/dL).[7,8]

The sodium and glucose linked transporter (SGLT) is a sodium/glucose cotransporter membrane protein. Type 2 (SGLT-2) is present in S1 of the proximal convoluted tubule and is the main glucose transporter, whereas type 1 is found in S3 of the proximal convoluted tubule and the small intestine.[6,9]

That is why, in recent years, the kidney has become a target organ for the treatment of DM. The class of SGLT-2 inhibitors (SGLTi-2), approved for T2DM, then emerged. SGLT-2 inhibitors, by inhibiting glucose reabsorption in the kidneys, increase urinary glucose excretion, reducing glycemic levels (Figure 1) in an insulin-independent manner, with positive effects on various glycemic parameters, such as glycated hemoglobin, fasting and postprandial levels of blood sugar.[10-12] They can then be used at any stage of the disease in both newly diagnosed and long-term diabetes,[13] since they do not depend on insulin secretion or peripheral insulin sensitivity.[14]

Three drugs have been approved in Brazil by the regulatory agency Anvisa: dapagliflozin, empagliflozin and canagliflozin (Table 2). These drugs can be used both as monotherapy or combined with other oral antidiabetic drugs (OAD) or insulin.[12] Dapagliflozin and empagliflozin have a greater sensitivity for SGLT-2, while canagliflozin is the only one that has a significant effect on SGLT-1, but only at high doses (greater than 200 mg). For this reason, it has been suggested that canagliflozin can reduce the levels of blood glucose by double action, both in the kidneys and in the intestine.[15] Nevertheless, more studies are needed to confirm this hypothesis.

TABLE 2 SGLT-2 inhibitors.

Active ingredient	Comercial name	Presentation
Canagliflozin	Invokana®	100 and 300 mg
Dapagliflozin	Forxiga®	10 mg
Empagliflozin	Jardiance®	10 and 25 mg

SGLT-2 inhibitors have demonstrated several beneficial extra-glycemic effects in patients with DM. Just like any other drug, they present risks and side effects that should not be overlooked.

Positive effects of SGLTi-2

Several studies have already shown that SGLTi-2 can reduce body weight in patients with T2DM, since the elimination of glucose through urine leads to a loss of calories (around 200-300 cal/day), resulting in a negative energy balance.[16-18] A study with dapagliflozin showed a significant reduction in waist circumference, which is consistent with a reduction in fat mass.[19] Studies evaluating body composition suggested that most of the weight loss associated with SGLTi-2 was due to a reduction in visceral or subcutaneous fat.[20,21] This is a beneficial effect for dia-

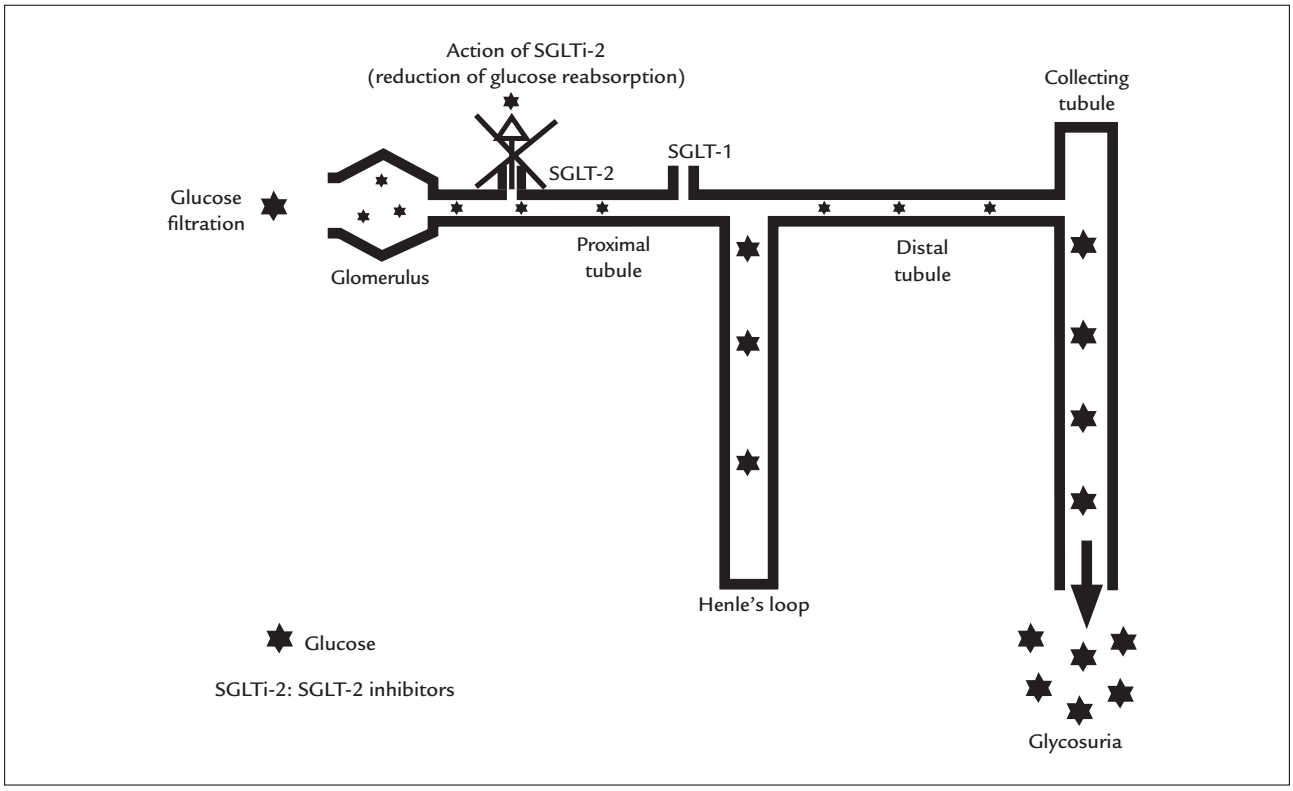

FIGURE 1 Action of SGLT-2 inhibitors.

betic patients, since most are overweight and thus present greater insulin resistance. In addition, these drugs differ from other OADs, such as sulfonylurea and insulin, which cause weight gain.[22]

Decreased blood pressure (BP), both systolic (SBP) and diastolic (DBP), was observed with SGLTi-2, without compensatory increase in heart rate. This is because, by causing glycosuria, osmotic diuresis occurs, reducing circulating volume and, consequently, BP levels. Weight reduction and sodium depletion also contribute to this finding.[23,24] In addition, a direct vascular effect, with reduced arterial stiffness, leads to BP change.[25]

The effect of this class on serum lipid levels is mild. Small increase in HDL and LDL levels, but no change in HDL/LDL ratio and a mild reduction in triglyceride levels were found in clinical trials. It is not yet known if these changes are clinically relevant, and further studies are needed on the subject.[19,24]

DM is a major risk factor for cardiovascular disease (CVD) and CVD is the leading cause of morbidity and mortality in diabetics.[26] It is also known that DM is one of the main risk factors responsible for cognitive deficits, such as Alzheimer's disease and vascular dementia.[27]

In a study of obese diabetic rats, administration of empagliflozin was able to significantly improve cardiac fibrosis and inflammation, coronary artery remodeling, vascular dysfunction, and cognitive dysfunction. These benefits were associated with significant attenuation of oxidative stress in cardiovascular and brain tissues.[28]

Uric acid is the end product of purine metabolism. Hyperuricemia, in addition to causing gout, is associated with chronic kidney disease, DM and metabolic syndrome, and is considered a marker of cardiovascular (CV) risk. Reduction of serum uric acid levels has been seen with SGLTi-2 due to increased urinary excretion.[29,30] No increase in kidney uric acid stones was observed with SGLTi-2.[30]

This new class of drugs has already been shown to reduce glycemic levels in animals and humans with type 1 DM (T1DM), in addition to allowing a reduction in insulin dosage.[31-33] These drugs could, thus, be used as an adjuvant therapy in the treatment of DM1, with low risk of hypoglycemia and without weight gain. However, this is not yet an approved therapy for T1DM, and further studies are needed to assess the safety of SGLTi-2 in this group of patients.[33]

Studies in animal and human models have demonstrated that the use of SGLTi-2 has improved markers of renal damage, such as albuminuria, hyperfiltration/hypertrophy, inflammation and expansion of the mesangial matrix, suggesting the possibility of preventing diabetic nephropathy. There can be a slight reduction in glomerular filtration rate at the onset of use, which normalizes after a few weeks.[34,35] A large study with empagliflozin combined with standard treatment in patients at high CV risk showed an improvement in the progression of kidney disease compared to placebo.[36] Since the drug's effect depends on renal function, its benefits will be reduced in patients with this type of dysfunction.[37]

Negative effects of SGLTi-2

There is a risk of hypoglycemia with SGLTi-2, but at a lower rate. Such a low risk is justified by the fact that these drugs have an insulin-independent mechanism of action. The risk increases when these drugs are associated with insulin or insulin secretagogues.[13]

The main side effects related to the class are urinary and genital infections (vaginal moniliasis, vulvovaginitis, balanitis), attributed to the higher concentration of glucose in the urine. Infections are usually resolved with conventional treatments.[17] In order to avoid such complications, it is recommended to instruct patients about proper hygiene.

Osmotic diuresis caused by SGLTi-2 is responsible for the small rise in hematocrit levels, due to hemoconcentration, but without significant clinical effect verified so far.[13]

The risk of systemic arterial hypotension is low, since the reduction of SBP and DBP is not as marked. SGLTi-2 may increase the effect of thiazide diuretics and loop diuretics, with increased risk of dehydration. Greater attention should be given to the elderly, who are more sensitive to the risk of hypotension, especially those who use diuretics.[23,24]

A more serious and potentially fatal but uncommon adverse effect is the risk of diabetic ketoacidosis (DKA), rare in T2DM but more common in T1DM. These drugs are being used in addition to what has been approved by Anvisa, as an adjunct to insulin treatment in T1DM. There have been reports of atypical presentation, with mild increase in blood glucose and even normoglycemic DKA. This may delay diagnosis and treatment, and thus compromise the patient's prognosis. Some cases were secondary to the occurrence of triggers, such as infection, reduction of water intake or low adherence to insulin therapy. The mechanism involved in this situation is not yet known. If DKA is suspected, the drug must be discontinued immediately, ketone levels should be investigated and appropriate treatment initiated.[38,39]

Canagliflozin was associated with another side effect: bone fracture. A study with this drug demonstrated a significant decline of bone mineral density (BMD) in the hip, raising the hypothesis that it would be secondary to weight loss.[40] Reducing BMD can accelerate the osteoporosis process and increase the risk of fractures.[41] More studies are needed for a more detailed investigation of this risk.

Cardiovascular profile

In recent years, for new OADs to be registered and maintain such approval, drug regulatory agencies now require a CV safety study in patients at high risk.[42] The least expected is that it has a neutral effect over placebo.[43,44]

The results of the EMPA-REG OUTCOME study were published in September 2015 at the 51st Congress of the European Association for the Study of Diabetes (EASD), which was considered a positive milestone in the history of DM, as the first study to demonstrate cardiovascular superiority with an OAD.[45]

This was a randomized, multicenter, double-blind, placebo-controlled trial that evaluated the effects of standard treatment-associated empagliflozin on the occurrence of CV events. The study included more than 7,000 individuals with T2DM and CVD, either treated or being treated, for a mean period of 3.1 years. There was a significant reduction in the risk of major CV events (CV death, non-fatal acute myocardial infarction [AMI] and non-fatal stroke) by 14%. There was also a significant decrease in CV death rate (38%), in the rate of hospitalization due to heart failure (35%) and death from any cause (32%).[45]

Other effects were found in this study, including reductions in weight and waist circumference, decrease in uric acid levels, decrease in SBP and DBP without any increase in heart rate, and modest increases in LDL and HDL cholesterol.[45] It is not yet known, however, what mechanism provided such benefit. It may have been a multifactorial effect that included an osmotic diuretic factor, a lower rate of hypoglycemia, good cardiac performance (BP decline without tachycardia), change in arterial stiffness, weight loss, and reduction in albuminuria and uricemia.[43,45]

Further studies are underway to show the CV profile of the other SGLTi-2. These are: the Canagliflozin Cardiovascular Assessment (CANVAS) and the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58). They will clarify whether this CV benefit is a class effect or restricted to empagliflozin, and may contribute by providing more information regarding this new class. [43]

Final remarks

Although there are several drugs available to treat DM, glycemic control is still not ideal and leads to a significant increase in morbidity and mortality.

SGLTi-2 are the latest oral agents for lowering blood sugar levels, targeting the kidneys, causing glycosuria. They offer the potential to improve glycemic control with a low risk of hypoglycemia, regardless of insulin secretion. These drugs have several favorable effects, such as reductions in weight, BP, uric acid and triglyceride, in addition to reducing the progression of kidney disease, and a proven CV benefit for empagliflozin. Its main adverse effects are: more frequent genitourinary infections, low risk of hypotension, and rare and severe risk of DKA. There is much more to be uncovered about this class of drugs, with promising prospects for the history of diabetes.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Uso dos inibidores da SGLT-2 no tratamento do *diabetes mellitus* tipo 2

Introdução: O *diabetes mellitus* é uma das doenças crônicas mais frequentes no mundo, com altas taxas de morbimortalidade, resultando em um grande impacto negativo socioeconômico. Apesar de existirem diversas classes de antidiabéticos orais, a maioria dos pacientes acometidos está fora da meta terapêutica.

Objetivo: Revisar o uso dos inibidores da SGLT-2 no tratamento do *diabetes mellitus* tipo 2, com enfoque nos efeitos favoráveis, desfavoráveis e no perfil cardiovascular.

Método: Foi realizada uma pesquisa bibliográfica transversal com artigos científicos obtidos da base de dados Pubmed, utilizando os descritores: "SGLT-2 inhibitors", "dapagliflozin", "empagliflozin", "canagliflozin".

Resultados: Os inibidores da SGLT-2 são uma classe de antidiabéticos orais com atuação no rim. O mecanismo de ação é reduzir a glicemia induzindo glicosúria. Benefícios extraglicêmicos já foram descritos, como redução de peso, pressão arterial, triglicerídeos e ácido úrico, além de retardar a progressão da doença renal. O principal efeito colateral é a infecção geniturinária, com baixo risco de hipotensão e hipoglicemia. Cetoacidose diabética é um efeito adverso grave, mas infrequente. A empagliflozina já teve seu benefício cardiovascular demonstrado, e estudos com outras drogas estão em andamento.

Conclusão: Os inibidores da SGLT-2 são uma nova opção de tratamento do *diabetes mellitus* tipo 2, que atua de forma insulino-independente e com potenciais benefícios adicionais, além da redução da glicemia, mas também com risco de efeitos adversos.

Palavras-chave: inibidores da SGLT-2, *diabetes mellitus* tipo 2, rim, glicosúria, revisão.

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Pelvic floor muscle training protocol for stress urinary incontinence in women: A systematic review

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Summary

Introduction: Strengthening exercises for pelvic floor muscles (SEPFM) are considered the first approach in the treatment of stress urinary incontinence (SUI). Nevertheless, there is no evidence about training parameters.
Objective: To identify the protocol and/or most effective training parameters in the treatment of female SUI.
Method: A literature research was conducted in the PubMed, Cochrane Library, PEDro, Web of Science and Lilacs databases, with publishing dates ranging from January 1992 to March 2014. The articles included consisted of English-speaking experimental studies in which SEPFM were compared with placebo treatment (usual or untreated). The sample had a diagnosis of SUI and their age ranged between 18 and 65 years. The assessment of methodological quality was performed based on the PEDro scale.
Results: Seven high methodological quality articles were included in this review. The sample consisted of 331 women, mean age 44.4±5.51 years, average duration of urinary loss of 64±5.66 months and severity of SUI ranging from mild to severe. SEPFM programs included different training parameters concerning the PFM. Some studies have applied abdominal training and adjuvant techniques. Urine leakage cure rates varied from 28.6 to 80%, while the strength increase of PFM varied from 15.6 to 161.7%.
Conclusion: The most effective training protocol consists of SEPFM by digital palpation combined with biofeedback monitoring and vaginal cones, including 12 week training parameters, and ten repetitions per series in different positions compared with SEPFM alone or a lack of treatment.

Keywords: training, pelvic floor, urinary stress incontinence, women.

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Introduction

The International Continence Society (ICS) and the International Urogynecological Association define urinary incontinence (UI) as a symptom, namely "the complaint of any involuntary loss of urine."[1] UI is classified according to the record of signs, symptoms and results from urodynamic study (UDS).[1] Stress urinary incontinence (SUI) is "the complaint of involuntary urine loss on effort or physical exertion, or on sneezing or coughing."[1]

Worldwide, SUI is predominant in females, and the mean prevalence in the various studies is 25%.[2,3] It can, however, range from 10% in young women[3] to 45% among the elderly.[3]

UI has a devastating effect on women's quality of life in the physical, social, sexual and psychological spheres.[4] Women restrict or diminish their activity and social participation, with serious implications.[5]

In SUI, there is an association between physical exertion and urinary loss.[6] Increased intra-abdominal pressure triggered by physical exertion leads to increased intravesical pressure and, if it exceeds intraurethral pressure, in the absence of contraction of the detrusor muscle, the resulting urinary leakage is referred to as SUI.[6-8] The pathophysiology underlying this condition follows two mechanisms: hypermobility of the urethra and bladder neck, and intrinsic deficiency of the urethral sphincter.[7-9]

The recommendations of the Agency for Health Care Policy and Research suggest that the first intervention in the treatment of SUI should be conservative. Pelvic floor rehabilitation includes behavioral modifications and advice on everyday life hygiene, intravaginal manual reeducation, strengthening exercises for pelvic floor muscles (SEPFM), electrical stimulation, biofeedback and vaginal cones.[10] Rehabilitation of pelvic floor muscles (PFM) may be active and/or passive, but reeducation depends on a request of voluntary muscle contraction. Active exercises include SEPFM, intravaginal manual reeducation, vaginal cones and biofeedback, while passive exercise refers to electrical stimulation.[10] Investigations[11-13] demonstrated similar effectiveness of different SEPFM programs, but no evidence of a specific, standardized program. These investigations differ regarding the parameters used in the training programs: eight[14-16] to forty repetitions;[17] two[15] to five series;[16] submaximal[14,18] to maximum contractions;[15,16] duration of five weeks[16] to six months;[14] three times a week[14] to daily;[19] instruction on muscle contraction using digital palpation;[18] biofeedback[19] or perineal ultrasound;[20] individual[20] or group sessions;[21] supervised training[14] or home practice.[10,19,22] In general, SEPFM is effective in the treatment of female SUI; however, there is a great heterogeneity of programs, not allowing identification of the most effective protocol.

The objective of our review was to identify the most effective protocol and/or PFM training parameters to treat female SUI.

Method

The structural and content organization of our systematic review was based on the recommendations of the PRISMA statement.[23,24]

Eligible studies were of an experimental nature comparing SEPFM to placebo, usual treatment or lack of treatment. They presented high methodological expressiveness (score ≥ 5 on the PEDro scale) and were written in English.

The participants were female, aged between 18 and 65 years, diagnosed with SUI based on subjective perception (symptom) and/or clinical evaluation (signal) and/or UDS (uroflowmetry and cystometry). Exclusion criteria included diagnosis of SUI triggered by factors external to the lower urinary tract (neurological pathologies, cognitive deficits), pregnant and postpartum women, ≥ stage 2 prolapse in the Pelvic Organ Prolapse Quantification (POP-Q), and other types of UI (mixed and urgent).

Search strategy

The search covered five databases: PubMed (Medline), Cochrane Library, PEDro, Web of Science and Lilacs. In addition, we conducted a manual survey from the bibliography of the articles, systematic reviews and meta-analyses included, as well as on the ICS website, in order to reduce publication bias.[25] Studies included were published between January 1992 and March 2014. The Medical Subject Headings (MeSH) of the National Library of Medicine enabled the identification and the combination of keywords pertaining to: the pathology (urinary stress incontinence), interventions (pelvic floor muscle training; pelvic floor muscle exercise; physical therapy; program; protocol; rehabilitation), population (women; female), and study design (randomized controlled trial; controlled clinical trial; comparative study; research design).

The final search choice included the following keywords: (pelvic floor muscle) AND ("education" OR "training" OR "education"[MeSH Terms] OR "training") OR (pelvic floor muscle exercise) AND physical therapy OR physiotherapy OR protocol OR program OR rehabilitation AND (stress urinary incontinence) AND women AND female AND (randomized controlled trial OR controlled clinical trial OR comparative study OR research design) NOT (pregnancy OR animals).

Methodological quality

The methodological quality of the studies was analyzed by three independent researchers using the PEDro scale. This assessment tool has 11 items, with a maximum score of 10 points.[26] For each criterion presented in the scale (except for the first one), a score of 1 or 0 points can be attributed.[26] The PEDro scale was created by Moseley et al. in 1999 based on the *Delphi List*, and was translated and adapted for the Portuguese population by Costa in 2011.

Results

Search strategy results

The search in the databases led to the identification of 591 potentially relevant studies (Figure 1).

Methodological quality results

The mean score for methodological quality evaluation was 5.7±1.28 (min/max: 5/8) out of 10 points (Table 1).

The items that most contributed for the decrease of the total score were the 5 (blind study regarding the participants) and 6 (blind study regarding therapists) (Table 1).

Description of the studies

Our systematic review identified seven experimental studies. The studies were conducted between 1996 and 2013, with a total sample of 331 women.

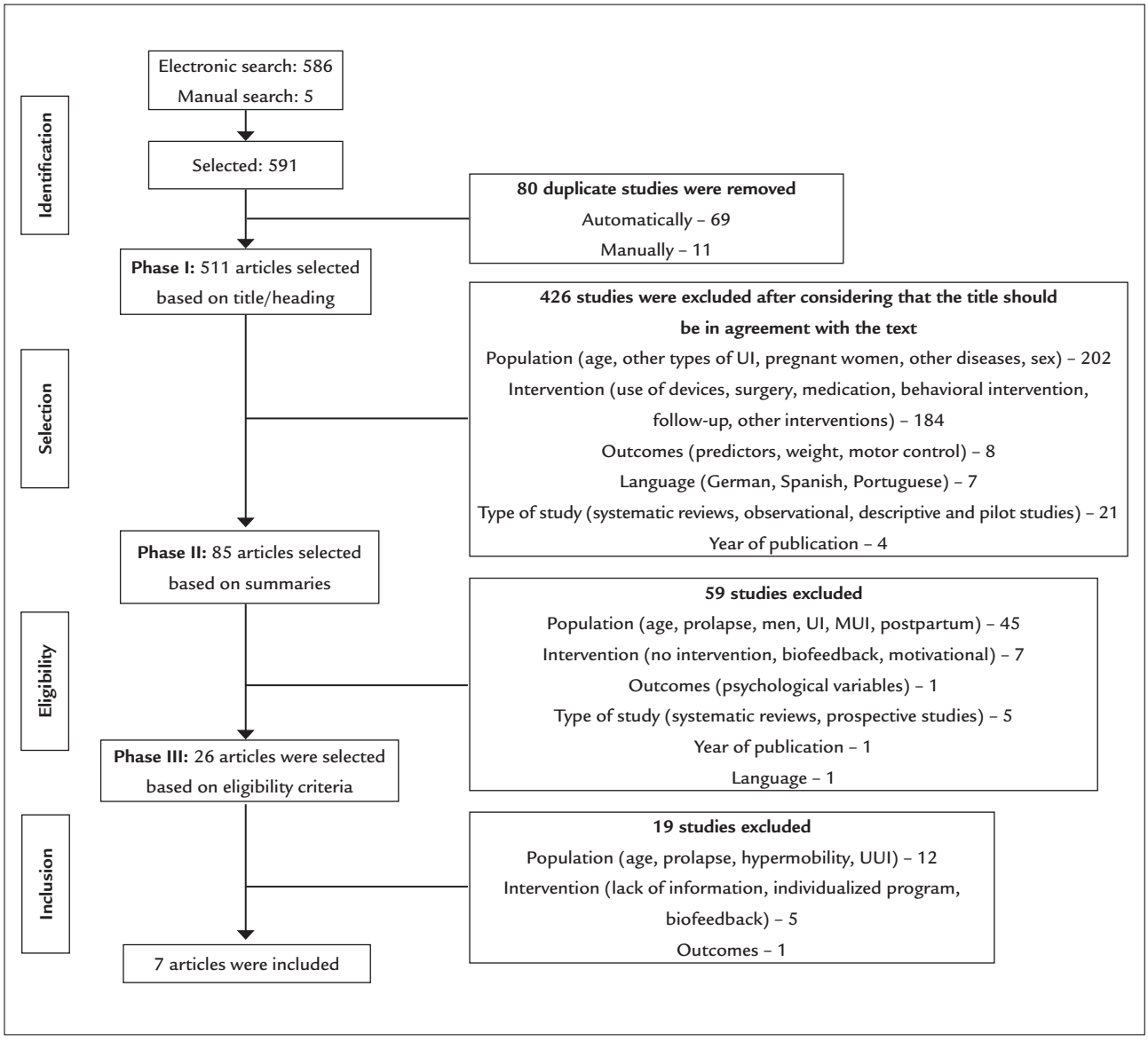

FIGURE 1 Study selection flowchart.

TABLE 1 Classification of the methodological quality of studies according to the PEDro scale.

Studies	1	2	3	4	5	6	7	8	9	10	11	Total
Glavind et al.[30]	1	1	1	1	0	0	0	1	0	1	1	6
Arvonen et al.[29]	1	1	0	1	0	0	0	1	0	1	1	5
Aksac et al.[19]	1	1	1	1	0	0	0	0	1	1	0	5
Zanetti et al.[18]	1	1	1	1	0	0	0	1	0	1	1	6
Felicíssimo et al.[31]	1	1	1	0	0	0	0	1	0	1	1	5
Sriboonreung et al.[28]	1	1	1	1	0	0	0	1	0	1	0	5
Kamel t al.[27]	1	1	1	1	0	0	1	1	1	1	1	8

Note: 1. Eligibility criteria have been specified; 2. Participants were randomly assigned to groups; 3. The distribution into groups was blinded; 4. The groups were initially similar in relation to the most important prognostic indicators; 5. Blind study regarding the participants; 6. Blind study regarding therapists; 7. Blind study regarding evaluators who measured at least one key result; 8. Measurements of at least one key outcome were performed on more than 85% of participants initially allocated to groups; 9. All participants for whom outcome measures were presented received treatment or control intervention as planned or, whenever this was not the case, data were analyzed for at least one of the key outcomes by "intention to treat"; 10. The results of the inter-group statistical comparisons were described for at least one outcome; 11. The study presents measurement points and variation measurements for at least one key result.

Characteristics of the studies

Sample size varied between 30[27] and 68[28] women, with a mean age of 48.8±5.51 years, ranging from 25 to 65 years.[27-30] The mean duration of urine loss was 64±5.66 months[18,29,31] with severity ranging from mild[19,27] to severe (even though the definition of the severity of UI is not expressed).[30]

The diagnosis of SUI was demonstrated through subjective evaluation/symptoms (questionnaire, interview),[19,27,29,31] physical examination/signs (pad test, gynecological evaluation)[19,27-31] and/or UDS.[18,19,27,31]

Interventions

In most studies, the program began with instructions for contracting PFM. Methods most often used were digital palpation[19,27,31] and teaching of the anatomy and function of PFM.[29-31] Only one study used biofeedback,[19] while two omitted the teaching of contraction.[18,28]

Two studies combined SEPFM and biofeedback,[19,30] one combined the exercises with vaginal cones,[29] two compared SEPFM supervised or not,[18,30] and other two compared the exercises with and without the activation of abdominal muscles.[27,28] SEPFM program parameters included length of contractions, which ranged from 1 s[28] to 20 s[29], length of rest from 1 s[18] to 20 s[19,27] and number of series, ranging from 2[27] to 40.[19]

Three studies used maximum contractions[27,28,31] and two applied a combination of submaximal and maximum contractions.[18,29] As for training positions, the one most often used was supine,[18,19,27,30,31] followed by standing,[18,29-31] seated[18,29-31] and lateral decubitus position.[31] Two studies, however, did not specify a training position.[19,28]

Regarding the frequency of sessions, the minimum applied was two sessions per week,[30] while daily treatment was the most frequent.[18,19,28,29,31]

The analyzed programs lasted between 8[19,31] and 16 weeks,[29] and most opted for a 12-week duration.[18,27,28,30]

Instruments used to measure outcomes

Almost all of the studies (6 out of 7) assessed the amount of urine leakage based on 1-hour and 24-hour pad tests.[18,19,28-31] PFM strength was assessed by digital palpation[19,29,31] and perineometry (vaginal squeeze pressure)[19,27,28] while intrinsic sphincter was assessed by UDS.[27] Other outcomes included a subjective assessment based on a visual analogue scale,[19] quality of life scales (QV-I-QOL, QV-ICIQ-SF)[18,31] and voiding diaries.[18]

Cure rate results

Six studies[18,19,28-31] displayed their assessments of cure rates measured by pad test ranging between < 1 g[19,30] and < 2 g.[18,29,31] The results of cure rate according to the type of intervention were: 50% (cones) versus 26% (PFM Training – PFMT);[29] 36.6% (supervised PFMT) versus 34.5% (unsupervised);[31] 58% (PFMT+biofeedback) versus 20% (PFMT);[30] 48% (PFMT+supervision) versus 9.5% (unsupervised);[18] 75% (PFMT+palpation) versus 80% (PFMT+biofeedback) versus 0% (no treatment).[19] For intervention periodicity, cure rates were 28.6% (daily PFMT) versus 21.2% (PFMT three times weekly) versus 20% (abdominal training)[28] (Table 2).

On perineometry, PFM strength increased to 84.7% (PFMT+palpation) versus 161.7% (PFMT+biofeedback) versus 7% (no treatment);[19] 15.6% (SEPFM) versus 4.7% (abdominal muscle strength)[27] and 63.4% (daily) versus 48.4% (three times weekly) versus 59.7% (SEPFM+abdominal, three times weekly).[28] On digital palpation, PFM strength reached 37.5% (digital palpation) versus 48.9% (biofeedback) versus 0% (no treatment);[19] 33% (SEPFM) versus 0% (vaginal cones);[29] and 50% (supervised) versus 50% (unsupervised).[31] On UDS, intraurethral pressure increased 16% (abdominal muscle strength) versus 9.1% (SEPFM)[27] (Table 2).

Subjective perception of cure increased from 23.8[18] to 75%.[28]

Discussion

Our systematic review confirmed the diversity in study designs, measurement instruments, cure rate definitions, and intervention outcomes.

Zanetti et al.[18] found that supervised SEPFM were more effective than unsupervised SEPFM, unlike another study,[31] which demonstrated the equal efficacy of both. The heterogeneity of the results may derive from the different manners of measuring the pad test (24-h and 1-h) and the duration of the interventions (8 and 12 weeks), respectively.[18,31] The pad test is an instrument that reveals the amount of urinary leakage in grams, in addition to being inexpensive and non-invasive.[32] According to Jørgensen et al.,[33] the correlation coefficient varies between 0.68 and 0.93.[33] The investigations are inconsistent regarding pad test application duration (1-h or 24-h), although some guidelines recommend the long-duration pad test (24 hours) as it allows the reproduction of urine losses during daily activities according to an individual's bladder capacity, compared with the 1-hour pad test, which requires a standardized bladder volume and provokes urine leakage in distinct physical activities.[32]

In our review, combined therapy with SEPFM and abdominal muscle strengthening training significantly increased PFM strength, as proven by perineometry ($p<0.05$).[27,28] However, there were no statistically significant differences in reducing the amount of urine leakage.[28]

TABLE 2 Summary of the description of the studies according to intervention, results and conclusions.

Study	Groups	Severity	Outcomes	Results		Inter-groups	Definition of cure	Rate of cure	Main conclusions
				Pre-intervention	Post-intervention				
Glavind et al.[30]	G1: SEPFM + biofeedback G2: SEPFM	Mild to severe	Pad test 1h (g)	G1: 9.0 (5-22); G2: 12.8 (9-44)	G1: 0.8 (0-4); G2: 10.0 (2-27)	p=0.02	Pad test ≤ 1 g	G1: 58% G2: 20%	Combined treatment of biofeedback with SEPFM showed a significant reduction of urinary loss compared to SEPFM alone.
Arvonen et al.[29]	G1: SEPFM G2: Vaginal cones	NR	Pad test 1h (g)	G1: 20; G2: 30	G1: 5; G2: 1	p=0.03	Pad test < 2 g	G1: 26% G2: 50%	Treatment with vaginal cones has significantly reduced the amount of urinary loss compared to SEPFM.
			Digital palpation (0-5)	G1: 3; G2: 3	G1: 3; G2: 4	p=0.05			
			Subjective assessment of cure (0-100%)	NR					
Aksac et al.[19]	G1: SEPFM via digital palpation G2: SEPFM via biofeedback G3: no treatment	Mild and moderate	Pad test 1h (g)	G1: 19.9±2.5; G2: 20.5±0.7; G3: 29.1±3.2	G1: 2.1±0.4; G2: 1.2±0.2; G3: 28.2±3.7	p<0.001	Pad test < 1 g	G1: 75% G2: 80% G3: 0%	SEPFM combined with digital palpation or biofeedback are effective compared to the untreated group.
			Perineometry (cmH_2O)	G1: 20.3±6.2; G2: 19.1±4.8; G3: 18.7±4.9	G1: 37.5±8.7; G2: 50.0 ±11.5; G3: 20.0±3.9	p<0.001			
			Digital palpation/Oxford scale (0-5)	G1: 3.5±0.5; G2: 3.3±0.4; G3: 3.3±0.4	G1: 4.8±0.4; G2: 4.9±0.2; G3: 3.3±0.6	p<0.001			
			Subjective assessment – VAS (0-10 points)	NA	G1: 7.5±1.2; G2: 8.1±0.8; G3: 3.6±0.6				
Zanetti et al.[18]	G1: Supervised SEPFM G2: Unsupervised SEPFM	NR	Pad test 1h (g)	G1: 20.1; G2: 24.7	G1: 3.2; G2: 15.0	p=0.002	Pad test < 2 g	G1: 48% G2: 9.5%	The supervised SEPFM group improved significantly compared to the unsupervised SEPFM group.
			QV-I-QoL	G1: 69.0; G2: 82.0	G1: 89.0; G2: 79.0	p=0.046			
			Voiding diary	G1: 7.0; G2:	G1: 1.0; G2: 10.0	p<0.0002			
			Subjective assessment	NA	G1: 66.7%; G2: 23.8%				

(*continues*)

TABLE 2 (cont.) Summary of the description of the studies according to intervention, results and conclusions.

Study	Groups	Severity	Outcomes	Results		Inter-groups	Definition of cure	Rate of cure	Main conclusions
				Pre-intervention	Post-intervention				
Felicíssimo et al.[31]	G1: Supervised SEPFM G2: Unsupervised SEPFM	NR	Pad test 24h	G1: 4.5 (3.0-15.7); G2: 9.3 (3.3-36.1)	G1: 3.2 (1.2-8.0); G2: 2.8 (1.5-8.5)	p=0.78	Pad test < 2 g	G1: 36.6% G2: 34.5%	Supervised and unsupervised SEPFMs were equally effective, with prior teaching of the correct contraction of PFM.
			Digital palpation/Oxford scale (0-5)	G1: 2.0 (2.0-3.0); G2: 2.0 (2.0-3.0)	G1: 3.0 (3.0-4.0); G2: 3.0 (2.0-4.0)	p=0.20			
			QV-ICIQ-SF (0-21)	G1: 14.0 (9-16); G2: 14.0 (10-16)	G1: 8.0 (6-12); G2: 8.0 (5-13)	p=0.76			
			Subjective assessment of cure (0-100%)	NA	G1: 69%; G2: 70%				
Sriboonreung et al.[28]	G1: Daily SEPFM G2: SEPFM, three times weekly G3: SEPFM + abdominal muscle strength, three times weekly	NR	Pad test 1h (g)	G1: 4.0±0.9; G2: 4.0±1.5; G3: 4.7±1.6	G1: 1.4±0.7; G2: 1.7±0.7; G3: 4.7±1.6	p>0.05	Pad test	G1: 20% G2: 21.2% G3: 28.6%	Daily SEPFM significantly increased PFM strength compared to the three times weekly frequency group and the abdominal training group. However, all groups reduced the amount of urine leakage.
			Perineometry (cmH_2O)	G1: 29.0±10.2; G2: 28.7±13.1; G3: 29.0±7.4	G1: 47.4±9.6; G2: 42.6±12.4; G3: 46.3±8.2	p<0.001			
			Subjective assessment of cure (0-100%)	NA	G1: 75%; G2: 68.4%; G3: 66.7%				
Kamel et al.[27]	G1: Abdominal muscle strength G2: SEPFM	Mild	Perineometry (cmH_2O)	G1: 49.9±4.85; G2: 50.3±6.06	G1: 57.73±6.39; G2: 52.60±7.60	p>0.05	NR	NR	Abdominal training significantly increased PFM strength compared to SEPFM.
			Valsalva LPP (cmH_2O)	G1: 80.00±5.52; G2: 78.00±4.49	G1: 92.80±13.57; G2: 87.33±9.07	p=0.058	NR	NR	

According to Sapsford et al.,[34] training of deep abdominal muscles triggers the co-contraction of PFM, causing an increase in the strength of PFM and an improvement in urinary continence. A systematic review by Kari Bø et al.[35] concluded that the results are ambivalent because, to date, there is no strong clinical evidence of benefit with abdominal muscle training in women with UI.

In the studies included in the review, PFM training programs including adjuvant therapies such as biofeedback, digital palpation and vaginal cones reach high rates of cure (80, 50 and 58%, respectively).[19,27,31] A systematic review by Neumann et al.[36] demonstrated that SEPFM combined with adjuvant therapies were effective in the treatment of SUI, reaching a cure rate of 73%. These PFM strengthening techniques allow identification, awareness of correct muscle contraction, and inhibition of synergistic muscles, enhancing results.[37]

The PFM training programs differed in the following parameters: type of muscle contraction, number of repetitions and series, rest time between each contraction, time of contraction and progressivity of the exercises. Nevertheless, most of the studies that were analyzed showed consistency in the repetition frequency parameter (ten initial repetitions), except for the study by Kamel et al.,[27] who initiated the SEPFM program with 15 repetitions. This parameter corroborates the parameters of strength training to obtain muscular hypertrophy advocated by the American College of Sports Medicine,[38,39] which recommends 8 to 12 contractions per series.

The frequency of SEPFM was predominantly intensive (one to three times per day), but the study by Sriboonreung et al.[28] failed to verify significant differences in reducing the amount of urine leakage by using different frequencies of SEPFM. The current evidence for the principles of strength training recommends that the frequency of three times weekly is sufficient for muscle hypertrophy.[38,39]

In most studies,[18,27,28,30] the training program duration was 12 weeks, except for two studies[19,31] that applied SEPFM for 8 weeks. According to the recommendations of the American College of Sports Medicine, strength training programs should last at least 15-20 weeks.[38] PFM are skeletal muscles and, therefore, the recommendations of strength training are not different from other skeletal muscles.[12] In the first 8 weeks of training, the changes are essentially neural (increased number and frequency of motor unit activation), followed by muscle hypertrophy due to increased volume and number of myofibrils, essential for morphological or structural adaptations.[36] In our systematic review, training programs of 8 to 12 weeks seem to reduce the amount of urine leakage, and/or to increase PFM strength, inferring that short-term training is equally effective in the treatment of SUI. However, these results should be analyzed with caution, because the gain of muscular strength in this period was sustained by an increase in number and synchronism of the motor units,[36] without any mention of patient follow-up after training, in addition to the fact that the studies included in the analysis used different designs, eligibility criteria and measuring instruments. Also, some of the studies[28,29] in our review demonstrated that increasing the strength of PFM in this short period of time may not be related to a significant reduction in the amount of urine loss. This suggests that the increase in PFM strength and urethral resistance does not seem to guarantee the mechanism of urinary continence.[28,29] According to some authors, coordination between early contraction of PFM and increased intra-abdominal pressure may be the most relevant factor in reducing urine leakage compared to the strength gain of PFM, which may justify the positive results of short training programs.[7,40]

We found in our review that five studies used different positions to perform the exercises, so that the most commonly applied ones were the standing, seated and lateral decubitus positions.[18,27,29-31] One of the ways to promote the progression of the exercises is to create different levels of difficulty (without and against gravity).[11] According to Kari Bo et al.,[41] a standing position increases pressure on the bladder and PFM, and may decrease the effectiveness of PFM contraction, affecting the reduction of muscle strength.

According to recent studies,[42,43] the PFM contraction reflex to increased intra-abdominal pressure may be inherent to the mechanism of urinary continence, but coordination of the different patterns may be acquired as a learned behavior and is currently considered complementary to SEPFM, a determining factor in any PFM reeducation protocol.

The literature cites cure rates ranging from 44 to 70%.[13,18,44] In our systematic review, the objective cure rate varied between 20[28,30] and 75%,[19] while the subjective cure rate ranged between 23.8[18] and 75%.[28] The low cure rate can be justified by different definitions of cure using pad test (< 1 g or < 2 g). On the other hand, variations in cure rates also depend on different levels of severity of SUI,[45] training program duration,[22] initial PFM strength[42] and patient adherence to treatment.[22,46]

Conclusion

SEPFM combined with digital palpation, biofeedback and vaginal cones, as well as 12-week duration training

parameters, with ten repetitions per series and in distinct positions seemed more effective to reduce the amount of urine leakage, also providing a subjective perception of cure compared with SEPFM alone or a lack of treatment. The limited number of studies and the heterogeneity of the intervention protocols did not allow us to identify the most effective PFM training protocol.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Protocolo de treino dos músculos do pavimento pélvico em mulheres com incontinência urinária de esforço: revisão sistemática

Introdução: Os exercícios de fortalecimento dos músculos do pavimento pélvico (EFMPP) são considerados a primeira intervenção no tratamento da incontinência urinária de esforço (IUE); porém, não existe evidência sobre os parâmetros de treino.
Objetivo: Identificar o protocolo e/ou os parâmetros de treino mais eficazes no tratamento da IUE feminina.
Método: A pesquisa bibliográfica foi realizada entre janeiro de 1992 e março de 2014 nas bases de dados PubMed, Cochrane Library, PEDro, Web of Science e Lilacs. Os artigos incluídos eram de língua inglesa, estudos experimentais, comparando EFMPP com tratamento placebo, usual ou sem tratamento, com idade compreendida entre 18 e 65 anos e diagnóstico de IUE. A avaliação da qualidade metodológica foi realizada por meio da escala PEDro.
Resultados: Sete artigos de elevada qualidade metodológica foram incluídos na presente revisão. A amostra foi constituída por 331 mulheres, com idade média de 44,4±5,51 anos, duração média das perdas urinárias de 64±5,66 meses e gravidade da IUE variando entre ligeira e grave. Os programas de EFMPP eram distintos relativamente aos parâmetros de treino dos MPP. Alguns estudos incluíram treino abdominal e técnicas adjuvantes. A taxa de cura da quantidade de perda urinária variou entre 28,6 e 80%, enquanto o aumento da força dos MPP variou de 15,6 a 161,7%.
Conclusão: O protocolo de treino mais eficaz consiste nos EFMPP por palpação digital e supervisão combinados com *biofeedback* e cones vaginais, incluindo os parâmetros de treino de 12 semanas de duração, dez repetições por série e em distintas posições comparados com os EFMPP isolados ou sem tratamento.

Palavras-chave: treinamento, assoalho pélvico, incontinência urinária de esforço, mulheres.

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Mild cognitive impairment and progression to dementia of Alzheimer's disease

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Summary

The increase in life expectancy in the Brazilian population raises questions about the preparation of the public health system in identifying elderly patients with signs of cognitive impairment. Currently, as a consequence of the long duration of preclinical phase of Alzheimer's disease, efforts of early detection have been emphasized. Clinical dementia presents an important impact on the individual's caregivers, family, society and economy. Identifying individuals who already have some cognitive impairment, despite remaining functional, as well as analyzing associated comorbidities, constitutes an opportunity to analyze possibilities for future interventions. Dementias are clinical conditions that impose a burden on the health system with its high costs, whereas the identification of individuals with cognitive impairment without dementia can aid patients and their families to plan the future and mitigate costs. This narrative revision can provide general practitioners with more information on the subject.

Keywords: elderly, cognitive deficits, mild cognitive impairment, general practice, Alzheimer's disease, diagnosis.

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Introduction

In the last decades, Brazil has undergone rapid demographic transition with an increase in the population of elderly. The Brazilian life expectancy has reached 73 years and, currently, the elderly represent approximately 10% of the general population. In 2030, they will be 36%.[1,2]

Along with the aging of the global population, there is an increase in the incidence and prevalence of diseases associated with senility including mild cognitive impairment (MCI) or, according to DSM-5, mild neurocognitive disorder.[3] Subjects aged 60 years or older with subjective cognitive complaints corroborated by an informant show an increased conversion rate to MCI or to dementia.[4] The risk of elderly individuals with subjective cognitive complaints to progress to MCI or dementia is 1.5 to 3 higher than in those without it.[5] According to Petersen et al.[6] the annual conversion rate of amnestic-type MCI to clinical dementia ranges from 10 to 15%.

The term "mild cognitive impairment" was first suggested in 1980 by Reisberg et al.[7] The first paper on MCI was published in 1994 by Petersen;[8] but only in 1999 Petersen et al.[6] further developed the concept by proposing criteria based on an observational study on ageing. The concept of MCI defines an early but abnormal stage of cognitive harm, no longer considered a normal part of aging, and therefore a diagnostic entity and pathological condition. The initial criteria were: a) subjective impairment of the memory, preferentially confirmed by an informant; b) objective impairment of the memory compared with a group paired by age and education level (below 1.5 standard deviations from the mean); c) normal global cognitive functioning; d) independence in daily life activities; and e) absence of dementia. This concept is based on the observation that Alzheimer's disease (AD) progresses insidiously, usually initiating with a memory deficit that is well characterized, and may allow the diagnosis of AD in the phase of pre-dementia.[9]

At a Key Symposium held in Stockholm in the year 2003, MCI was defined as a heterogeneous entity divided into three categories: amnestic MCI with greater risk of AD; MCI of multiple cognitive domains; and MCI with impairment of a single cognitive function different from memory.[10] Main diagnostic points of MCI were redefined: the individual being neither normal nor demented; evidence of cognitive decline measured objectively or based on subjective perception combined with objective cognitive impairment; preservation of basic living and complex instrumental activities or minimally compromised.[10] A task force of American authorities, led by the National Institute of Aging and the Alzheimer's Association, proposed a review of the criteria used for the classification of MCI in 2011.[11] Despite the basic clinical criteria being similar to those for MCI diagnosis, this review opened the focus on the probable etiological mechanisms that lead to cognitive impairment, with emphasis on early diagnosis of AD, via the utilization of biomarkers.

The term "mild cognitive disorder" was included in the International Classification of Diseases (ICD) to be applied to patients that presented a decline in cognitive performance, usually accompanied by abnormalities in objective tests for cognitive functions, but not sufficiently to fulfill the diagnostic criteria of dementia.[12]

Epidemiology

The first population-based study on the prevalence of MCI and its subtypes (Figure 1)[13] was based on a cardiovascular health study.[14] The researchers applied the criteria for MCI retrospectively in a cohort and found a prevalence of 22%, of which 6% referred to the amnestic subtype and 16% to multiple domains in patients aged 65 years or older.[15] Other studies demonstrated an incidence rate from 1 to 6% per year and a prevalence of 3 to 22%.[15] The prevalence and incidence of MCI found in Brazil was similar to rates observed in other countries.[16] In a riverside-dwelling population with low education and practically no vascular risk factors, MCI prevalence was 7.7%.[17] A systematic review and meta-analysis on the prevalence of dementia among individuals aged 60 years or older found a narrow range of 5-7% in most world regions, with a higher prevalence in Latin America (8.5%), and a distinctively lower prevalence in the four sub-Saharan African regions (2-4%).[18] In this study, 35.6 million people lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. Yet, in 2010, 58% of all people with dementia lived in countries with low or middle incomes, with this proportion expected to rise to 63% in 2030 and 71% in 2050.[18]

Progression to AD (Figure 2)[19]

Several authors observed an increased rate of progression toward dementia in patients with MCI.[8,20-25] However, studies have not been replicated by other researchers. One explanation for this fact may arise from the observation that memory complaints appear to have little correlation with the performance of individuals on objective cognitive tests.[26]

On the other hand, longitudinal studies revealed that elderly individuals with recent complaints of impaired memory performed worse in memory tests than those who had not had such a complaint in one year of follow-up. They suggest that memory complaints from the elderly must be taken even more seriously when accompanied by objective signals of cognitive deterioration.[27,28] Despite some discrepancies among studies, the researchers agree that individuals diagnosed with MCI develop dementia at a faster rate than the rest of the population.

Evaluation of memory problems

The initial evaluation must rely on careful obtainment of patient history and of memory complaint, always comparing to previous functional state of cognitive complaint,[29] establishing a chronology for the initiation of symptoms, as well as habits and comorbidities; investigation of mood symptoms and behavioral alterations. Questions on dietary and sleep habits must be posed.[30,31] Detailed neurological and general physical exam must be carried out, with thorough observation of gait and verification of motor signals (alterations of reflexes, rigidity, bradykinesia, tremor, slowness).[32] The laboratory exams that must be performed to rule out reversible dementia syndromes include:

- Thyroid hormone tests to investigate underactive thyroid.
- Vitamin B12 blood test to check vitamin deficiency.
- Complete blood count to investigate infections.
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) blood tests that check liver function.
- Chemistry screening to check the level of electrolytes in the blood and to check kidney function.
- Glucose test to check the level of sugar in the blood.
- VDRL and HIV.
- Erythrocyte sedimentation rate, a blood test that investigates signs of inflammation in the body.
- Toxicology screening, examining blood and urine.
- Antinuclear antibodies, a blood test used to diagnose autoimmune diseases.
- Investigation of heavy metals in the blood, such as a lead test.[33]
- A lumbar puncture to test for certain proteins in the spinal fluid.

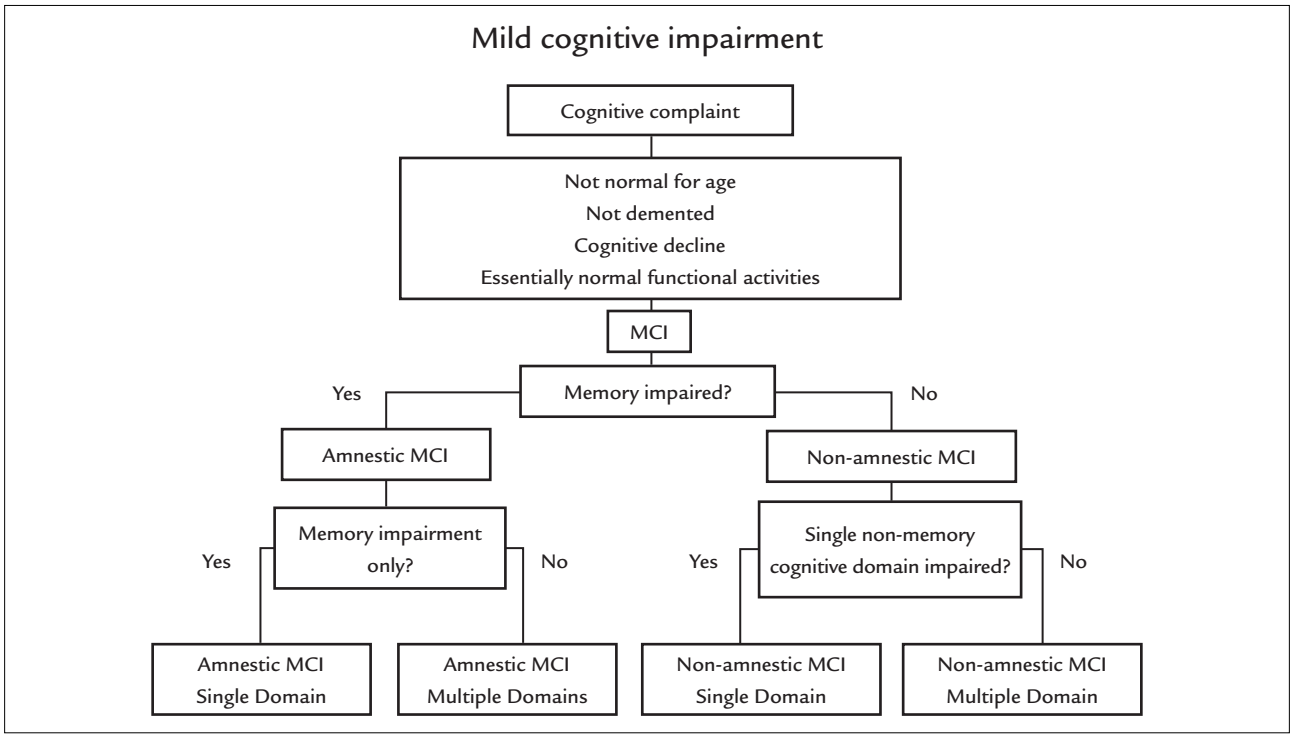

FIGURE 1 Current algorithm used to classify the subtypes of mild cognitive impairment (MCI).
Source: Petersen R.[13]

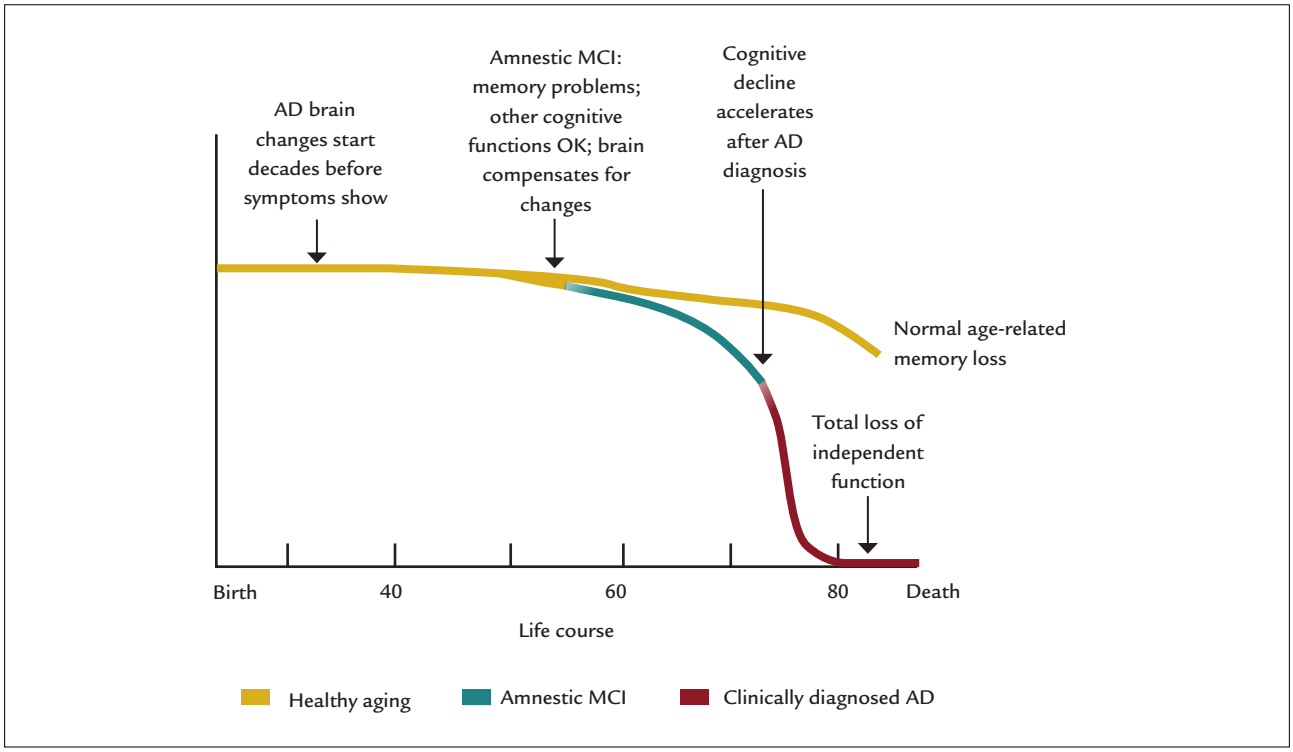

FIGURE 2 Charting the Course from Healthy Ageing to AD.
MCI: mild cognitive impairment; AD: Alzheimer's disease.
Source: National Institute On Aging – NIH.

Neuroimaging exams must be requested, including CT or MRI scans, not only to verify the limbic structures but also to rule out other diseases, particularly vascular cognitive impairment.[34]

Screening tests such as the mini-exam of the mental state,[35] clock-drawing test, verbal fluency and a questionnaire on instrumental and basic daily life activities, as well as the geriatric depression scale (GDS) questionnaire, must be applied.[36,37]

Neuropsychological testing

Longitudinal studies investigating the usefulness of neuropsychological tests to identify subjects at high risk of developing dementia reported that, by measuring recall, delayed recall, verbal fluency and visual-motor skill, they were able to identify 85% of the individuals that developed dementia and 95% of those that remained stable, in four years of accompaniment.[23] The results suggest that individuals with increased risk of developing dementia, or in a preclinical state of AD, can be identified by neuropsychological tests, which evaluate mainly memory (measures of late evocation) and other cognitive functions, such as attention, language and thought.[23] The standardized application of tests to elderly individuals with cognitive complaints is a manner of rendering the concept of cognitive impairment both valid and reliable.[38]

Neuroimaging

In the initial stages of the disease, cranial MRI might not present abnormalities. In some cases, a SPECT or PET scan can be considered.[30] In SPECT a decline in blood flow is noted whereas in PET a reduction of glucose utilization is observed. PIB and FDG PET are employed in some research studies to compare controls with patients suffering from AD and MCI.[39]

Treatment

Currently, there is no evidence for the utilization of drugs for the treatment of individuals with MCI.[40] Nonetheless, several clinical trials have been conducted in an attempt to slow down the appearance of dementia.[41] There was a large clinical trial involving 70 medical centers in North America.[42] The study was randomized, double-blind and placebo-controlled and aimed to verify the safety and efficacy of vitamin E (2,000 IU per day) and donepezil (10 mg per day). A decrease, although not significant, was noted in the conversion rate of MCI to AD from 45 to 30% in a three-year period. Among 769 randomized individuals, the annual conversion rate of MCI to AD was approximately 16%. Donepezil reduced the risk of AD in the first 12 months of the trial, but there was no drop in the progression to AD in 36 months. Vitamin E had no therapeutic effect.[43]

Conclusion

Aging of the population is making the cases of chronic degenerative diseases more frequent, including AD. In MCI, a loss of memory for recent facts with relative preservation of functionality is observed. A general practitioner must know that individuals with MCI constitute a group of great risk for AD. Early identification of individuals in the beginning of clinical dementia provides a possibility of intervening in the progression of the disease and providing support to patients and their family members. Upon encountering elderly patients with memory complaints, the physician must perform a detailed anamnesis and complete physical exam, ruling out reversible causes of cognitive alterations. Mood symptoms such as depression and anxiety, if identified, need to be treated. Laboratory exams must include a complete blood count, fasting blood glucose, electrolytes, renal, liver and thyroidal function, lipidogram, folic acid and vitamin B12. An imaging exam such as cranial CT or MR should also be performed. Cognitive testing must include a mini-exam of the mental state (mini-mental), clock-drawing test and verbal fluency for fruits and animals. The Brazilian Public Health System (SUS, in the Portuguese acronym) is responsible for a great portion of patient healthcare in the country. The Family Health Team of Basic Health Units must serve as both the first contact and the longitudinal contact with SUS users, enabling the recognition of the patients' cognitive impairment and potential progression to AD.

Resumo

Comprometimento cognitivo leve e progressão para a demência da doença de Alzheimer

O aumento da expectativa de vida da população brasileira faz surgir questões sobre o preparo do sistema de saúde pública na identificação de pacientes idosos com sinais de alteração cognitiva. Atualmente, como consequência da longa duração da fase pré-clínica da doença de Alzheimer (DA), existe maior ênfase sobre a detecção precoce. A demência apresenta um importante impacto sobre a família, os cuidadores, a sociedade e a economia. Identificar indivíduos que já apresentam algum comprometimento cognitivo, embora eles mantenham a funcionalidade, bem como analisar as comorbidades associadas constituem oportunidades para direcionar futuras intervenções. Demências são doenças que impõem sobrecarga ao sistema

público de saúde, com altos custos. A identificação de indivíduos com alteração cognitiva sem demência pode adicionar planejamentos futuros por parte do próprio doente, da sua família e dos cuidadores, resultando em menor sobrecarga física e emocional para todos os envolvidos. Esta revisão narrativa tem como objetivo ajudar os clínicos gerais a atuar na detecção dos idosos que se encontram em risco de desenvolver demência.

Palavras-chave: idoso, déficit cognitivo, comprometimento cognitivo leve, clínico geral, doença de Alzheimer, diagnóstico.

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Urinary EN-2 to predict prostate cancer: Systematic review and meta-analysis

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Summary

Introduction: Prostate cancer is the second type of cancer diagnosed and the fifth cause of death in men worldwide. Early diagnosis helps to control disease progression. Currently, prostate specific antigen is the standard biomarker, as it has a broad scope of identification and, thus, new and more specific biomarkers must be studied.
Objective: To evaluate the accuracy of engrailed-2 protein (EN2) in urine as a prostate cancer biomarker.
Method: A comprehensive search was conducted in the period from January 2005 to July 2016 using the following electronic databases: Medline (PubMed), Embase, Cochrane Library and Lilacs. The keywords used in the databases were: "engrailed-2," "EN2," "prostatic neoplasms." The search was limited to humans and there was no language restriction. Critical appraisal of the included studies was performed according to Quadas-2. Statistical analysis was performed using Meta-DiSc® and RevMan 5.3 softwares.
Results: A total of 248 studies were identified. After title and abstract screening, 231 studies were removed. A total of 17 studies were read in full and two studies were included in the meta-analysis. The pooled sensitivity was 66% (95CI 0.56-0.75) and specificity was 89% (95CI 0.86-0.92). The DOR was 15.08 (95CI 8.43-26.97).
Conclusion: The EN2 test showed high specificity (89%) and low sensitivity (66%).

Keywords: prostatic neoplasms, biomarker, EN2, systematic review, meta-analysis.

Introduction

Prostate cancer (PCa) is the fifth most frequent type of cancer in the world and the second most diagnosed non-cutaneous cancer in men in the United States according to the International Agency for Cancer Research.[1]

The disease has good prognosis when diagnosed at an early stage, since it is responsive to various treatments. Patients diagnosed with PCa at stage I, II, or III have a high 5-year survival rate; however, patients with stage IV cancer have a low 5-year survival rate of < 27%, highlighting the importance of early detection.[2]

Early stage PCa is often asymptomatic and the gold standard test is prostate biopsy, which is usually indicated in case of one or more of the following factors: family history, abnormal lumps within the prostate by physical digital rectal examination, or an elevated serum prostate-specific antigen (PSA).[3]

PSA started to be used 30 years ago, and it is the most common biomarker to diagnose and manage PCa. Despite being used globally, it is important to mention that the blood levels of PSA are often high in men with prostatic benign conditions as well.[4]

A recent systematic review of randomized controlled trials of PSA screening for PCa concluded that screening did not significantly decrease PCa-specific or overall mortality, and showed that PSA can result in a high number of false-positives, leading to overdiagnosis and overtreatment.[5] Low specificity of PSA and unnecessary biopsies are the most common problems of balancing benefits and risks in tests.[6]

Recently, engrailed-2 (EN2), a protein found in the urine of patients with PCa, proved to be a potential biomarker for the diagnosis of PCa compared to ELISA.[7]

The identification of cancer biomarkers that can be measured in a noninvasive way should improve the specificity of PSA in the detection of PCa. Thus, we performed a systematic review and meta-analysis to verify the accuracy of EN2 as a potential biomarker of PCa.

Method

Data sources and searches

The study protocol was registered at PROSPERO 35417 and included a systematic review according to protocol and PRISMA-statement guidelines.[8]

We searched the Medline (PubMed), Embase, Cochrane Central Register of Controlled Trials, Ibecs, Biosis, Web of Science, Scopus, Conference Abstracts and Grey Literature (Google Scholar; British Library) databases from January 2005 to July 2016. We used the following terms, both as text words, Medical Subjects Heading (MeSH) or equivalent subject heading/thesaurus terms: "Prostate cancer" and "prostatic neoplasms." These terms were combined with "engrailed-2." The search had no language restrictions. The reference list of all available primary studies was reviewed to identify additional relevant studies. A copy of the complete search strategy is available on request.

For this review, we used the definitions: Index test – The diagnostic test consisted of the urine EN2 analysis and Reference standard – The diagnostic reference was the result of the histological analysis of standard paraffin-embedded sections.

The inclusion criteria for this systematic review were: studies measuring EN2 levels in at least two histological diagnoses comparing with PCa, benign or normal prostate tissue.

Study selection

The abstracts/titles identified from the search were screened by two reviewers (E.R.D. and M.C.M.A.). Disagreements about the inclusion or exclusion of studies were resolved by consensus, and, if consensus was not possible, disagreements were resolved by a third reviewer (M.I.R). The final inclusion or exclusion of a study was made with a standard checklist. We included case-control and cohort studies, both prospective and retrospective.

Data extraction and quality assessment

We extracted data in duplicate (E.R.D. and M.C.M.A) with a standard form. We extracted information about study design, participants' description, index test description, reference test description, and total number of participants. A 2x2 table was created for each study comparing EN2 levels and the histologic diagnosis.

The eligibility criteria of all articles were assessed using Quality Assessment of Diagnostic Accuracy Studies (Quadas-2). This tool comprises four domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of the risk of bias, and the first three domains are also assessed in terms of concerns regarding applicability. Signaling questions are included to help judge the risk of bias.[9] The quality assessment of the studies was independently performed by two authors (E.R.D. and M.C.M.A). Any disagreement was resolved by consensus.

Data synthesis and statistical analysis

For each study, 2x2 contingency tables were constructed so that all cases were classified as PCa or benign lesions. We calculated the true-positive rate (TPR; sensitivity), specificity, and false-positive rate (FPR; 1 – specificity). Bivariate analysis was used to calculate the pooled estimates of sensitivity, and specificity with 95% confidence intervals (95CI) for the summary estimates.[10] The diagnostic odds ratio (DOR) can relate to different combinations of sensitivity and specificity. The DOR describes the odds of positive test results in participants with disease compared with the odds of positive test results in those without disease.

Statistical analysis was performed using Meta-DiSc® (Clinical Biostatistics Unit, Ramón y Cajal Hospital, Madrid, Spain) (version 1.4) and RevMan 5.3 software.[11,12]

Results

The searches identified a total of 248 studies, of which 17 were potentially relevant after initial assessment. Of these, 15 full-text studies were excluded. Two primary studies (Morgan et al. and Killick et al.)[7,13] involving 597 participants met the criteria for inclusion and were analyzed (Figure 1).

The main characteristics of the included studies are shown in Table 1. Both were conducted in the UK and used ELISA assay for diagnosis.

Methodological quality of included studies

The risk of bias for patient selection, index test, reference standard, flow and timing, as well as the concerns for applicability related to the first three domains, are shown in Figure 2. The Quadas-2 items for Morgan study had low risk of bias in all domains. The second study by

TABLE 1 Characteristics of primary diagnostic studies on prostate cancer measuring urinary levels of EN2.

Author/ Year	Mean age	Age control	Design and settings	N Control	N PCa	Sensibility (%)	Specificity (%)	TP	FP	FN	TN	EN2 cut-off (µg/L)
Morgan et al.[7]	67 (44-83)	63 (42-86)	Case-control	102	82	66	88.2	54	12	28	90	42.5
Killick et al.[13]	53 (40-69)	54.3 (40-69)	Cross-sectional	392	21	66.7	89.3	14	42	7	350	42.5

PCa: prostate cancer; TP: true positive; FP: false positive; FN: false negative; TN: true negative.

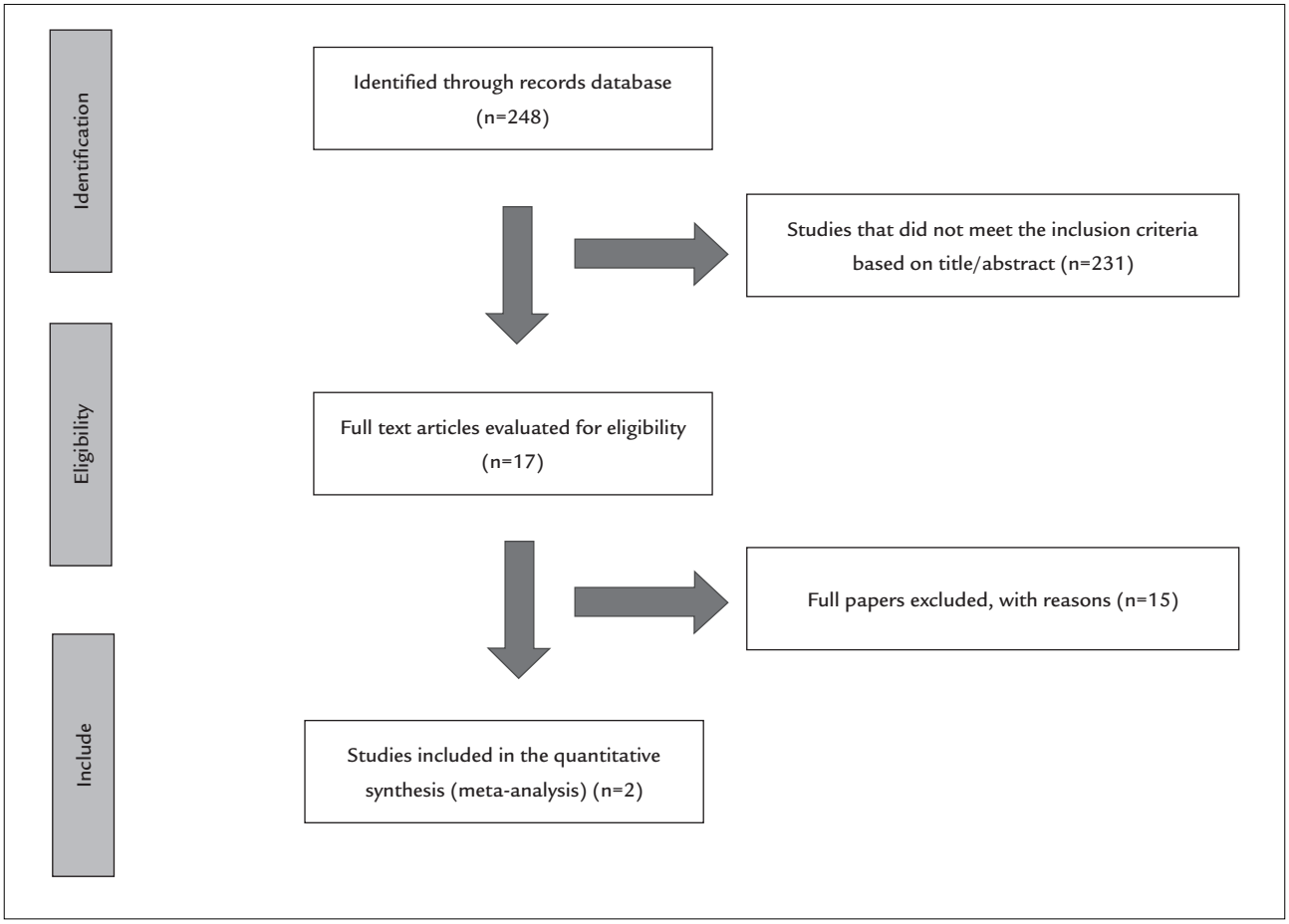

FIGURE 1 Flow diagram of the study selection process.

Killick et al.[13] showed unclear risk of bias to the reference standard (prostate biopsy), since it is unclear whether all participants underwent prostate biopsy, flow and time (patient flow and time between the completion of the EN2 test and biopsy). These criteria resulted in a high risk of bias for the reference standard, with respect to applicability criteria.

EN2 test vs. biopsy

The two studies had a combined sensitivity (Figure 3A) of 66% (95CI 56-75) and a combined specificity (Figure 3B) of 89% (95CI 86-92). The DOR (Figure 3C) was 15.082 (95CI 8.432-26.977).

Begg's funnel plot and Egger's test were not performed to assess the publication bias of the literature in all comparison models since only two studies were included.

Discussion

PCa is becoming a public health concern worldwide and PSA test is not being recommended by its own creator, Professor Richard J. Ablin, who always say "PSA testing cannot detect prostate cancer." This is the first systematic review

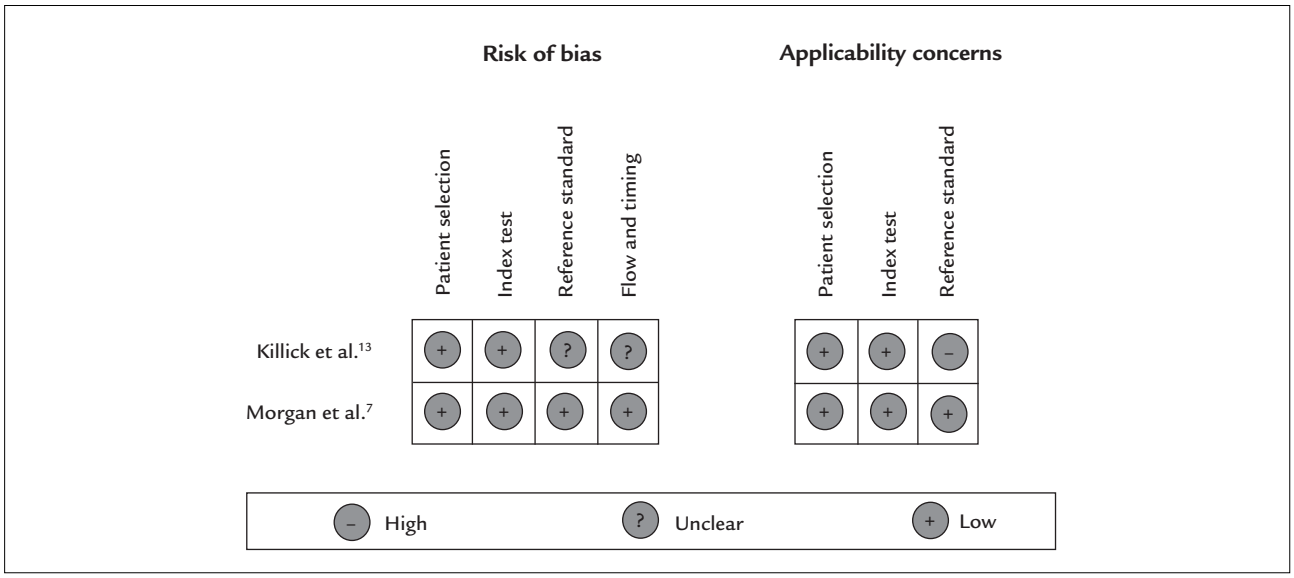

FIGURE 2 Results of the evaluation of each study according to Quadas-2.

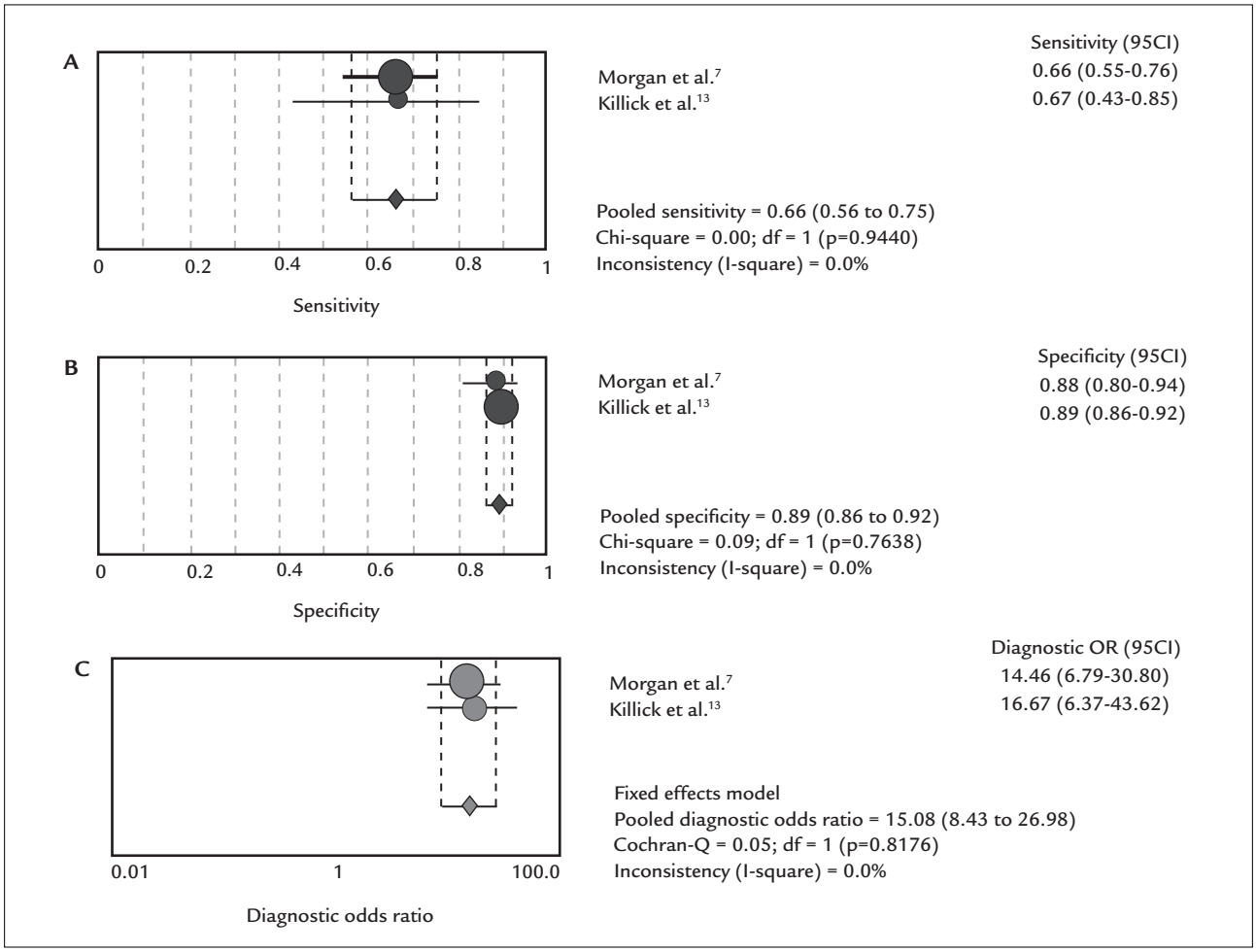

FIGURE 3 Florest plot showing of sensitivity (A), specificity (B) and odds ratio diagnostic (C).

and meta-analysis to specifically investigate and compare EN2 as a possible biomarker for PCa.

According to Pandha et al.,[14] EN2 test can lead to faster diagnosis, saving thousands of lives, and has the potential to reduce the cost of disease. However, it has the disadvantage of not providing disease progression or predicting tumor recurrence.

To date, the PSA is the most widely used tumor biomarker to detect, track and monitor PCa. In the literature, there are still differences regarding the use of PSA indicative of biopsy to confirm cancer. There is a lack of consensus among the authors on the ideal point. This contributes substantially to the great heterogeneity between the studies.[15]

Interestingly, there are few published studies assessing EN2 protein in PCa because it is a relatively new subject. It is thus necessary to conduct further studies so that we can understand the actual link between the EN2 protein and PCa, as well as in other types of neoplasias, such as breast cancer. Certainly, the development of new studies on this subject is essential to come up with a fast, accurate and primary diagnosis in cancer evaluation.

Considering the high specificity of EN2 and the high sensitivity of PSA, we hypothesize that using both tests together would increase the likelihood of PCa diagnosis. Thus, we suggest future studies to investigate if this occurs in the practice.

We used the GRADE approach to assess the quality of the evidence produced in this study, classifying it as low, which means that "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate or any estimate of effect is very uncertain." The evidence was downgraded due to risk of bias (limitations in the study design and execution) and indirectness (differences in patients, time and flow of tests) across the included studies.

A limitation of this study is that some of the included control patients did not undergo prostate biopsy. The study protocol includes annual PSA screening for 5 years, at which point recruits are offered an optional prostate biopsy; approximately half of the 392 individuals with PSA 3.0 ng/mL will undergo prostate biopsy. However, we decided to include this study because all PCa patients included were diagnosed by biopsy and did not present heterogeneity between the studies.

Conclusion

The low sensitivity and high specificity must be analyzed carefully, since there are few studies analyzing EN2 and the quality of evidence is low. It is too early to recommend EN2 for detection and/or screening of PCa.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Proteína EN2 urinária no diagnóstico do câncer de próstata: revisão sistemática e metanálise

Introdução: O câncer de próstata é o segundo tipo de câncer diagnosticado e a quinta causa de morte em homens em todo o mundo. O diagnóstico precoce é fundamental para o prognóstico da doença. Atualmente, o antígeno específico da próstata (PSA) é o biomarcador mais utilizado; porém, biomarcadores mais específicos devem ser estudados.
Objetivo: Avaliar a acurácia da proteína engrenada-2 (EN2) na urina como biomarcador de câncer de próstata.
Método: Foi realizada uma busca abrangente no período de janeiro de 2005 a julho de 2016, utilizando as seguintes bases de dados eletrônicas: Medline (PubMed), Embase, Cochrane Library e Lilacs. As palavras-chave utilizadas foram: "engrailed-2", "EN2", "prostatic neoplasms". A busca foi limitada a humanos e não houve restrição de idioma. A avaliação da qualidade dos estudos incluídos foi realizada de acordo com Quadas-2. A análise estatística foi realizada usando o software Meta-DiSc® e RevMan 5.3.
Resultados: Foram identificados 248 estudos. Após a triagem dos títulos e resumos, foram excluídos 231. Um total de 17 foram lidos na íntegra e dois, incluídos na metanálise. A sensibilidade combinada foi de 66% (IC95% 0,56-0,75). A especificidade foi de 89% (IC95% 0,86-0,92). O DOR foi de 15,08 (IC95% 8,43-26,97).
Conclusão: O teste EN2 mostrou alta especificidade (89%) e baixa sensibilidade (66%).

Palavras-chave: câncer de próstata, biomarcador, EN2, revisão sistemática, metanálise.

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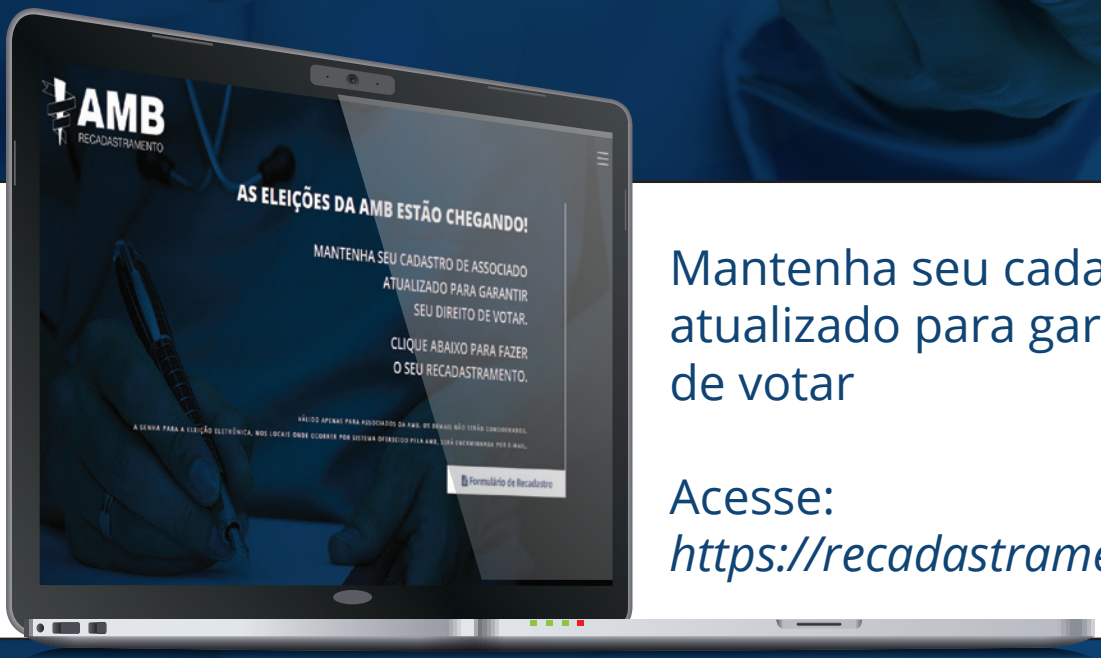

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