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SECTIONS

ORIGINAL ARTICLES

REVIEW ARTICLES

Hoping for something new

A esperança do novo

Florentino Cardoso[1]

[1]President of the Brazilian Medical Association

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A new light was lit with the change of government. Will this flame be kept burning, illuminating a better future? We shall soon see. Things cannot continue as they are, failing to meet the expectations of the vast majority of Brazilians. Brazil's script must be revised, especially with better education and health care for our population.

We lived a time of "more" without any concern for quality – more doctors, more specialists; these are examples of the folly of a government drenched in corruption, which led the country to bankruptcy. We need more doctors in certain specialties and in some places because doctors are heavily concentrated in capitals and larger cities. What incentives do medical doctors have to work in places of difficult access and provision? What are the working conditions for them? The population, even the poor and needy, has no doubt that health care in Brazil is chaotic.

Medical specialties were also threatened when the previous government sponsored the "more" program, with zero quality, a lure to the people. They tried to "make specialists" out of those who undertook low-quality courses approved by the Ministry of Education, in many cases with reduced hours, taught through distance education and without practical activities. These courses are traps designed for people to waste money; they threaten proper medical training and endanger health care. This cannot thrive, and urgent measures need to be adopted by the new government.

Health care is bad, even in sectors of supplementary health and education. The authorities continue to give their approval for the opening of medical schools that do not present the proper conditions to educate good doctors. It is the race of deputies and senators "sponsoring" medical schools in cities devoid of good health conditions, where there is a lack of professionals in various specialties. They say we stand for the training of medical experts. We do! The unwary who say this are talking about something they do not know; for example, they do not know that family and community physicians are medical specialists. "One can only recognize what one knows" is an always current saying.

And clinical research in Brazil crawls trailing other countries that invest in research (United States, several European countries, Japan, South Korea, and more). We know that research leads to development, resources, and opportunities for both researchers and the public. How many Brazilians miss opportunities to participate in new and better treatments for different health problems due to the incompetence and sluggishness of our bureaucratic CEP-Conep-Anvisa system? The National Health Surveillance Agency (Anvisa) has shown signs of improvement and we hope that it will help to "untie the knot," so we can create a new reality.

In this scenario (care, teaching, and research in health), we can imagine the situation of health care management, another mainstay of the area. Why continue to choose managers who are committed to politics and elections at the expense of merit, focus on goals, results and outcomes? Why don't we move further in the work grounded in strong scientific evidence? When a patient needs treatment, we should treat them at the right time, in the right place and with the right professional. The invasion of other health professionals who have not had adequate training to perform certain activities is frightening, and puts people's lives at risk. How many deaths have occurred in esthetic procedures performed by non-specialists?

Our uncompromising defense of merit, competence, and the truth is intended to protect the population, because we take care of our greatest asset: health. And in order to have a better future, we must think beyond diagnosis and treatment (do not care much for rehabilitation). Let us work to improve early diagnosis, focusing on prevention, on health promotion, and especially on health education, which can truly change the sad current scenario for the next generations. Too bad that such immeasurable politicization only sees the short term (term of office and re-election). We must see and work for Brazil's future, planning the next 5, 10, 20 years, that is, the new generations.

What should we expect from this new government? Show its good intentions with structural and major course changes, thinking about the people, not about a party or a government. Enough!

We are ready to help without any political ideology, seeking quality in our services. And if the high ranks do not meet our expectations, let us pray for better choices in the upcoming elections. Health is our greatest asset and we deserve respect.

Nutrition assessment – Modal ergometry

Avaliação nutrológica – Ergometria modal

Authorship: Associação Brasileira de Nutrologia (ABRAN)
Participants: Ribas DF[1], Kelman G[2], Buzzini RF[2], Simões RS[2], Bernardo WM[2]
Final draft: March 11, 2016

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

Evidence collection method

This policy followed the pattern of a systematic review with retrieval of evidence based on the principles of evidence-based medicine (EBM), according to which clinical experience is integrated with the ability to critically analyze and rationally apply scientific information, thus improving the quality of medical care. EBM uses existing scientific evidence available at the time, with good internal and external validity, applying its results to the clinical practice.[1,2]

Systematic reviews are considered today as level I evidence for any clinical question as systematically summarize information on a particular topic based on primary studies (clinical trials, cohort studies, case-control or cross-sectional studies). The methodology used for this is reproducible, and integrates information on effectiveness, efficiency, efficacy, and safety.[1,2]

We ask the questions in a structured way, summarized by the acronym PICO, where P is the patient or population, I intervention or indicator, C is comparison or control, and O is the outcome. Based on a structured question, the keywords or descriptors that will form the basis of the search for evidence in the various available databases are identified[1,2] (Annex I).

Clinical question

What is the role of modal ergometry in the measurement of muscle strength in children, adolescents or adults?

Grade of recommendation and strength of evidence

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

Objective

To determine the role of modal ergometry in the measurement of muscle strength while assessing the nutrition status of children, adolescents and adults.

Conflict of interest

No conflict of interest was declared by the participants in the development of this guideline.

Introduction

Impairment of muscle strength is a well-known phenomenon that occurs in diseases related to poor nutrition. A reduced nutritional supply results in compensatory loss of body protein, mostly from the muscles. Decline in muscle protein synthesis can also occur in diseases related to poor nutrition. Reduced muscle strength is, in turn, associated with a loss of physical functionality and a negative impact on the recovery of acute diseases or surgery, which partly explains a high predictive power of muscle function tests. The palmar gripping force test reflects the maximum strength derived from the contraction of intrinsic and extrinsic muscles that support the contraction of the joints in the hands. Despite its good correlation with other muscle function tests, such as the knee extension test and the peak expiratory flow test, it cannot be used to replace the evaluation of lower-limb muscle function.[3] (**D**)

Approximately 9 to 35% of patients admitted with a diagnosis of acute stroke, either ischemic or hemorrhagic, are malnourished. Dysphagia contributes to poor di-

etary intake and is present in over 50% of patients with acute stroke, further increasing the risk of malnutrition in these patients. Neurological, emotional, and cognitive changes can also affect the nutrition of these patients. Elderly patients (n=170) with diagnosis of stroke who presented malnutrition or nutritional risk [body mass index (BMI) ≤ 20 kg/m^2, or unintentional loss of weight greater than 5% in the last 3 to 6 months, or decreased dietary intake in the last 5 days] were randomized to receive personalized nutrition combined with supplementation or routine care (control). Weight loss after 3 months of follow-up was higher in the control group, but the difference was not statistically significant. There was a significant increase in palmar gripping force in the intervention group, and decreased strength in the control group (73.2 *vs.* 44.6%, p=0.001).[4] (**B**)

In cancer patients, malnutrition is common and is associated with worse quality of life, increased morbidity and mortality. One hundred and thirty patients aged 19 to 95 years, with malnutrition (22.3%) or risk of malnutrition (42.3%), were followed during hospitalization in a cancer hospital. One hundred and eleven (111) patients had solid tumors and 19 hematopoietic neoplasms. Patients with less palmar gripping force on admission, which accounted for more than half of the total, were discharged later (> 15 days of hospitalization), while those with higher values for strength stayed in the hospital for a shorter period (discharged earlier than 15 days). Patients malnourished or at risk of malnutrition and those with low palmar gripping force values on admission were associated with increased risk of death during hospitalization, regardless of age. This allowed us to distinguish who would have a long hospital stay (Table 1).[5] (**B**)

TABLE 1 Palmar gripping force.

Palmar gripping force	Length of hospital stay-IQR	p-value hospital discharge
High	6 (4.0-11.0)	<0.001
Intermediate	12 (7.3-23.3)	<0.001
Low	17 (7.0-32.0)	<0.001

IQR: interquartile range.

In order to assess palmar gripping force as a screening method for the identification of patients (18 to 96 years old) considered malnourished in hospital environment, 314 individuals with diseases including cardiovascular, gastrointestinal, respiratory, neurologic, surgical, and more were evaluated. All patients underwent the palmar gripping force test, performed using a mechanical dynamometer. The Nutritional Risk Screening (NRS-2002) protocol was applied to assess the nutritional risk.

Patients identified as malnourished according to the NRS-2002 (37.9%) had low values of palmar gripping force (p<0.001). When patients with decreased palmar gripping force were compared with those with greater force, this parameter showed good specificity (70.2%) and sensitivity (86.7%), and positive and negative predictive values, respectively, 69.9 and 86.8%, with 77.4% agreement, k=0.56. Thus, it proved to be an appropriate tool for nutritional screening in hospitals.[6] (**B**)

The liver is an essential metabolic organ for energy--protein control in the body. Patients with liver disease show a greatly affected nutritional status, and energy--protein malnutrition is found in most patients with cirrhosis. Prevalence of ascites, postoperative mortality, and post-transplant prognosis are all related to energy-protein malnutrition. One hundred and forty-five (145) patients were followed up; they were divided into three groups (group 1 with 50 patients with cirrhosis; group 2, 46 patients with hypertension; and group 3, 49 patients with functional gastrointestinal disease, which is the control group). According to the gold standard Subjective Global Assessment (SGA), malnutrition was found in 28% of patients in group 1, 13.1% in group 2, and there were no malnourished patients in group 3. The palmar gripping force test led to the detection of 63% of the malnourished patients in group 1, 12.7% in group 2, and 4.08% in group 3. The sensitivity of the palmar gripping force test was 100%, while specificity reached 48.6%, positive predictive value amounted to 37.9%, and negative value to 100%; k test = 0.31 compared with the gold standard (SGA).[7] (**B**)

Assessing the palmar gripping force of 787 healthy children from 6 to 10 years old, we identified a difference in mean gripping force between the malnourished and the well-nourished children, which was more noticeable among the older children. Of the 116 boys and 112 girls classified as malnourished using weight for age, only 24 and 22.3%, respectively, had low values for grip strength.[8] (**B**)

When grip strength and height for age were used to assess the prevalence of malnutrition, only 26.7% of the boys and 22.9% of the girls with short stature presented low values for gripping force. Similar results were observed in children considered malnourished based on height for weight.[8] (**B**)

Sensitivity of the muscle strength test as a nutritional status index was not as high for both sexes, and 39.3% was the highest value when the strength test was compared with the height for age among the girls. Specificity of the strength test was 94% compared with weight for age, and

94.3% when compared to height for age in boys. The positive predictive value of the strength test compared with the two methods was 70%. However, in the case of weight for height, it reached low values (25.5% for girls and 35.5% for boys) (Table 2).[8] (**B**)

TABLE 2 Sensitivity, specificity, and PPV of the muscle strength test for both sexes.[8] (B)

	Weight/Age		Height/Age		Weight/Height	
	M	F	M	F	M	F
Sensitivity (%)	24.7	27.3	26.7	39.3	23.9	25.9
Specificity (%)	94.0	87.8	94.3	76.5	87.4	85.1
PPV	70.0	43.9	70	22.9	31.5	21.5

PPV: positive predictive value; M: male; F: female.

Recommendations

The palmar gripping force test is an appropriate tool for nutritional assessment and screening of adult and elderly individuals hospitalized due to cardiovascular, gastrointestinal, respiratory, neurologic, surgical, and other diseases. The test also allows the estimation of hospital stay and risk of death during hospitalization of patients with cancer. In patients with liver cirrhosis, the palmar gripping force test is a good method to predict increased incidence of major complications. In children, the palmar gripping force test proved to be specific to measure lean body mass; however, sensitivity was low when compared to weight for age, height for age, and weight for height, which suggests that only children with decreased lean mass could be identified as malnourished.

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Annex I

Clinical question

What is the role of modal ergometry in the measurement of muscle strength in children, adolescents or adults?

Structured question

- P: Children, adolescents or adults
- I: Modal ergometry
- C: ----------
- O: Measurement of muscle strength

Strategy for search of evidence

- #1 – (Nutrition Disorder OR Nutritional Disorders OR Nutritional Disorder OR Nutritional Status OR Nutrition Status OR Nutrition Assessment OR Nutrition Disorders OR Malnutrition OR Deficiency Diseases OR Overnutrition OR Obesity OR Avitaminosis OR Ascorbic Acid Deficiency OR Vitamin A Deficiency OR Vitamin B Deficiency OR Vitamin D Deficiency OR Vitamin E Deficiency OR Vitamin K Deficiency OR Magnesium Deficiency OR Potassium Deficiency OR Protein Deficiency OR Protein-Energy Malnutrition OR Swayback OR Scurvy OR Choline Deficiency OR Folic Acid Deficiency OR Hyperhomocysteinemia OR Pellagra OR Riboflavin Deficiency OR Thiamine Deficiency OR Beriberi OR Wernicke Encephalopathy OR Vitamin B 12 Deficiency OR Anemia, Pernicious OR Subacute Combined OR Degeneration OR Vitamin B 6 Deficiency OR Rickets OR Osteomalacia OR Renal Osteodystrophy OR Steatitis OR Kwashiorkor OR Overweight OR Obesity, Abdominal OR Obesity, Morbid OR Wasting Syndrome) = 753,330
- #2 – (Hand Strength OR Muscle Strength OR Muscle Weakness OR Ergometry OR Ergometer OR Modal Ergometry OR dynamometer) = 146,656

Modal ergometry = #1 AND #2 = #3 = 6,750

Methodological search filter = #4 = ((specificity[Title/Abstract]) OR random* OR ((prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])) = 2,045,824

1st Retrieval = #3 AND #4 = 1,434

- (((Nutrition Disorder OR Nutritional Disorders OR Nutritional Disorder OR Nutritional Status OR Nutrition Status OR Nutrition Assessment OR Nutrition Disorders OR Malnutrition OR Deficiency Diseases OR Overnutrition OR Obesity OR Avitaminosis OR Ascorbic Acid Deficiency OR Vitamin A Deficiency OR Vitamin B Deficiency OR Vitamin D Deficiency OR Vitamin E Deficiency OR Vitamin K Deficiency OR Magnesium Deficiency OR Potassium Deficiency OR Protein Deficiency OR Protein-Energy Malnutrition OR Swayback OR Scurvy OR Choline Deficiency OR Folic Acid Deficiency OR Hyperhomocysteinemia OR Pellagra OR Riboflavin Deficiency OR Thiamine Deficiency OR Beriberi OR Wernicke Encephalopathy OR Vitamin B 12 Deficiency OR Anemia, Pernicious OR Subacute Combined OR Degeneration OR Vitamin B 6 Deficiency OR Rickets OR Osteomalacia OR Renal Osteodystrophy OR Steatitis OR Kwashiorkor OR Overweight OR Obesity, Abdominal OR Obesity, Morbid OR Wasting Syndrome) AND (Hand Strength OR Muscle Strength OR Muscle Weakness OR Ergometry OR Ergometer OR Modal Ergometry) AND ((diagnosis/broad [filter]) OR random* OR ((prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])))) NOT (((((ergometry OR ergometer OR model ergometry) AND (strength OR muscle OR weakness) AND (diagnosis/broad [filter] OR prognosis/broad [filter] OR random*))) OR ((hand strength OR muscle strength OR muscle weakness) AND (ergometry OR ergometer OR modal ergometry) and ((diagnosis/broad [filter]) or random* or ((prognos*[title/abstract] or (first[title/abstract] and episode[title/abstract]) or cohort[title/abstract])))))

Studies retrieved

The number of studies retrieved until the last day of searching (03/11/16) according to the final search strategy was 3,292.

Exclusion criteria

Articles that did not meet the specificities of PICO, that were not available for access in full, and those written in languages other than English, Portuguese or Spanish were excluded.

Image-guided pancreatic biopsy; can we trust it as a diagnostic alternative?

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Introduction

Most pancreatic adenocarcinomas are unresectable at the time of diagnosis,[1] or present image limitations in the case of non-adenocarcinomas,[2] thus posing a challenge for adequate histological sampling without the aid of laparoscopy. The American Joint Committee on Cancer considers the endoscopic ultrasound-guided diagnostic puncture as a procedure of choice.[3] In recent years, with advances in imaging methods, computed tomography (CT) and percutaneous ultrasound have become a diagnostic alternative in case of failure diagnosis, with the possibility of collecting histological fragments.[4-8]

Method

Retrospective cohort analysis of hospital records of patients undergoing ultrasound-guided percutaneous biopsy and/or CT scan based on positive or negative histological findings in patients undergoing the percutaneous technique as first alternative or after failure of an endoscopic technique. We used the same pathology laboratories for the analysis of our histological fragments.

Results

Fifty-five image-guided percutaneous biopsies were included, 11 of which had undergone prior endoscopic attempt with negative results. The average age was 62 years; 25 patients were male and 30 female. The mean size of the lesion was 4.75 cm, with 55% in the head and 45% in the body/tail of the pancreas. Positive results were possible in 85% of the cases, with 36 adenocarcinomas; three B-cell lymphomas and four metastases (two gastrointestinal tract, one renal, one pulmonary); one epithelial microcystic lesion; two neuroendocrine tumors; and one chronic pancreatitis. Of the 11 cases of prior negative biopsy by endoscopy, we were able to reach a diagnosis in 72%, with seven adenocarcinomas and one epithelial microcystic lesion. All results were obtained with only a minor complication characterized by a self-limited perihepatic hematoma. There was no tumor dissemination in the puncture needle path (Table 1).

Conclusion

In cases of negative endoscopic biopsies of pancreatic lesions, the ultrasound-guided percutaneous and/or CT method can be an effective and safe alternative for histological diagnosis.

Keywords: cancer, biopsy, CT-guided biopsy, pancreatic tumor.

TABLE 1 Positive results of image-guided percutaneous biopsies of pancreatic lesions.

Results	Number of patients
Adenocarcinoma	36
Lymphoma	3
Metastasis*	4
Epithelial microcystic lesion	1
Neuroendocrine	2
Chronic pancreatitis	1
Total	47

*Two gastrointestinal tract; one renal; and one small cell lung carcinoma.

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Metaplastic squamous cell carcinoma of the breast: A case report and literature review

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Summary

Metaplastic tumors are rare and represent a heterogeneous group of neoplasms showing dominant areas of non-glandular differentiation. Etiology and pathogenesis of this type of lesion in the breast is uncertain. The most common sources of metastatic squamous cell carcinoma of the breast are lung, esophagus, cervix, and urinary bladder. Squamous cell carcinomas may present clinically with inflammation and average size greater than breast adenocarcinoma. As for imaging studies, mammography shows no typical findings and ultrasound can show a complicated cyst or an inflammatory process, among the differential diagnoses. Therefore, knowing this pathological entity, its clinical course and imaging findings is important to safely treat such a rare and aggressive disease. We herein report a case of metaplastic carcinoma, squamous subtype, diagnosed by core needle biopsy.

Keywords: breast, breast neoplasms, needle biopsy, carcinoma.

Introduction

Breast cancer is a heterogeneous entity regarding clinical and imaging presentation and biological behavior. The ductal type is the most common, followed by lobular carcinoma. Together they account for over 70% of carcinomas. Metaplastic tumors, in turn, are rare and represent a heterogeneous group of neoplasms showing dominant areas of non-glandular (spindle cell, squamous, and/or mesenchymal) differentiation.

Etiology and pathogenesis of this type of lesion in the breast is uncertain.[1] It is believed that it arises directly from the epithelium of the mammary ducts, while another theory is that the tumor grows from foci of squamous metaplasia within a pre-existing breast adenocarcinoma.[2] Another theory defended by Stevenson et al. is that the lesion is a disease with varying degrees of squamous metaplasia, representing an extreme form of squamous metaplasia inside the adenocarcinoma.[3]

Squamous cell carcinoma of the breast is an extremely rare type, representing less than 1% of all invasive breast carcinomas with a mean age for onset among women of 54 years.[2] When found in the breast, other sites of extra mammary lesions should be sought, since there is a possibility that this is a metastatic tumor and not a primary lesion. The most common sources of metastatic squamous cell carcinoma of the breast are lung, esophagus, cervix, and urinary bladder. There are no specific clinical and radiological signs for squamous cell carcinoma. For this reason, the nature or origin of the lesion needs to be determined.[3]

The objective of our study is to report a case of metaplastic carcinoma, squamous subtype, diagnosed by core needle biopsy.

Case report

Female patient, 59 years old, with a palpable mass in the lateral quadrant of the left breast. She denies having any systemic diseases or any family history of breast or ovary cancer. Physical examination revealed large breasts, with a palpable lesion in the upper-outer quadrant of the left breast, mobile and hard.

Mammography (Figure 1) showed a oval mass without microcalcifications, and presenting circumscribed margins. The ultrasound (Figure 2) revealed a complex cystic and solid mass with internal vascularity on color Doppler.

We performed an ultrasound-guided core needle biopsy (Figure 3), which led to the diagnosis of invasive ductal carcinoma, not otherwise specified (NOS), subsequently treated with neoadjuvant chemotherapy. During treatment, due to reduction in size of the lesion, a new core needle biopsy was requested. The new biopsy revealed a metaplastic squamous cell carcinoma, which was confirmed after surgical resection.

Discussion

Squamous cell carcinomas may present clinically with inflammation and average size greater than breast adenocarcinoma.[4] As for imaging studies, mammography shows no typical findings and ultrasound can show a complicated cyst or an inflammatory process, among the differential diagnoses.[1]

At diagnosis, lesions are large (greater than 4 cm) and predominantly cystic in over 50% of cases.[5] They present lymphatic dissemination less frequently than adenocarcinomas, in which the range is from 40 to 60%. In 10 to 30% of cases there is infiltration of lymph nodes at surgery and about 30 to 33% of patients develop distant metastases.[1,3,5] Positron emission tomography (PET-scan) is an imaging method that can be used to search for distant metastases or a primary site of tumor cells.[1]

The pathological criteria for establishing a secure diagnosis of squamous cell carcinoma of the breast include: (a) origin of the tumor does not depend on the

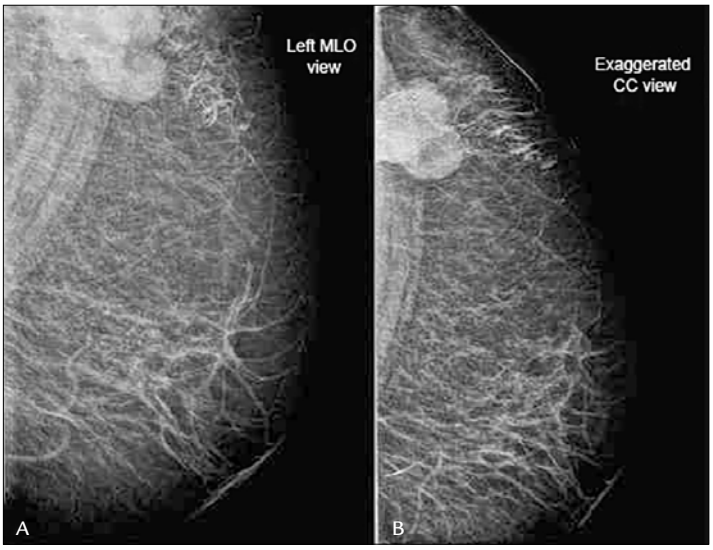

FIGURE 1 Left mammogram shows oval mass without microcalcifications and with circumscribed margins.

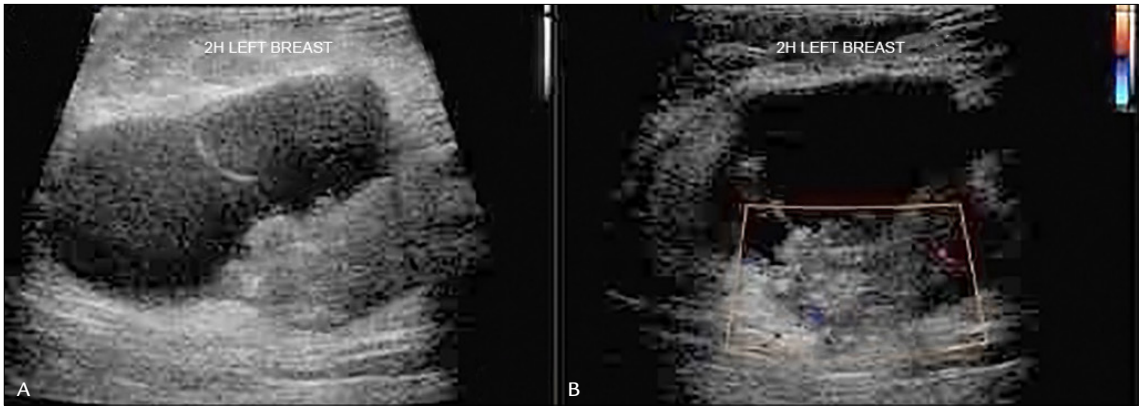

FIGURE 2 Ultrasound revealed a complex cystic and solid mass with internal vascularity on color Doppler, located in the upper-outer quadrant of the left breast.

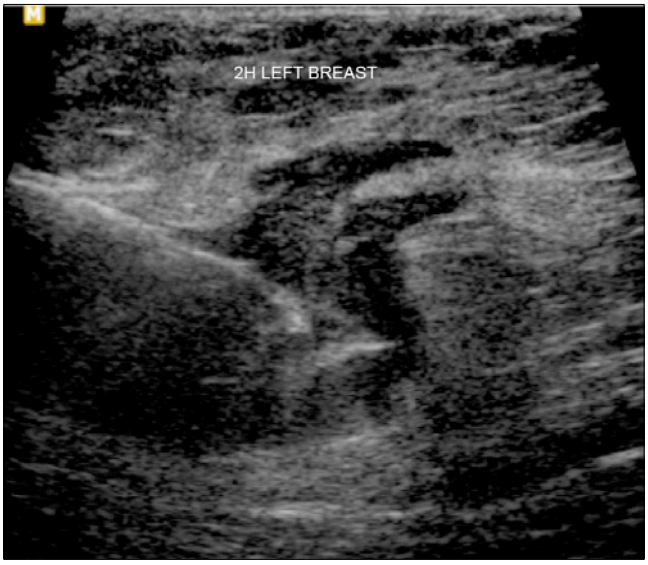

FIGURE 3 Ultrasound-guided core needle biopsy of the lesion.

skin, nipple or adnexal elements of the skin; (b) more than 90% of the tumor must be squamous; (c) there can be no other neoplastic invasive elements, ductal or mesenchymal, on the entire sample, and other sites of primary tumor must be ruled out.[6] To determine whether the tumor is a metaplastic carcinoma with squamous differentiation or a squamous cell carcinoma, a large sample of the lesion is required. However, it should be noted that the distinction between a primary tumor and a metastatic squamous cell carcinoma is unlikely to be solved by needle biopsy.[3]

In the case presented, the imaging findings were not classic invasive ductal carcinoma. The core needle biopsy represented only a small sample of the lesion and the representative elements of the first procedure indicated an invasive ductal tumor. However, keep in mind that the metaplastic elements can progress from one type to another after induction chemotherapy.[4]

Squamous cell carcinoma of the breast is usually a high-grade and hormone receptor-negative tumor. This means that the hormone-based therapy may not be efficacious in these tumors. Additionally, HER2 is usually not overexpressed or amplified in this disease. The high frequency of EGFR positivity is interesting and can be exploited in the development of future treatments.[5] Treatment of this type of tumor does not differ from other histologic types common in the breast and may involve surgery, chemotherapy, hormonal therapy, and radiotherapy. The therapeutic regimen most suitable for this rare disease is still unclear.[5]

Therefore, knowing this pathological entity, its clinical course and imaging findings is important to safely treat such a rare and aggressive disease.

Resumo

Carcinoma metaplásico espinocelular da mama: relato de caso e revisão da literatura

Os tumores metaplásicos são raros e representam um grupo heterogêneo de neoplasias que mostram áreas dominantes de diferenciação não glandular. A etiologia e patogenia desse tipo de lesão na mama é incerta. As causas mais comuns de carcinoma metastático de células escamosas na mama são o pulmão, o esôfago, o colo uterino e a bexiga urinária. Os carcinomas espinocelulares podem apresentar-se clinicamente com inflamação e tamanho médio maior do que o do adenocarcinoma da mama. A mamografia não apresenta achados típicos, e a ultrassonografia pode mostrar um cisto complicado ou um processo inflamatório, entre os diagnósticos diferenciais. Conhecer essa entidade patológica, seu curso clínico e os achados de imagem é importante para um manejo seguro, pois trata-se de entidade rara e agressiva. Este trabalho relata um caso de carcinoma metaplásico, subtipo espinocelular, diagnosticado por biópsia com agulha grossa.

Palavras-chave: mama, neoplasias da mama, biópsia por agulha, carcinoma.

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The diagnosis of acute appendicitis in pregnant *versus* non-pregnant women: A comparative study

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Summary

Objective: To investigate whether the diagnosis of acute appendicitis is affected by pregnancy or not.
Method: A retrospective study with the analysis of the medical records of all women suspected of having appendicitis who underwent appendectomy at our hospital between June 2010 and March 2015 were reviewed. The patients were divided into two groups according to whether they were pregnant or not during the surgery: group I, pregnant women, and group II, non-pregnant women.
Results: During the study period, 38 pregnant women and 169 non-pregnant women underwent appendectomy. The time from admission to the operation was not statistically different (2.17±1.47 days in group I *vs.* 1.98±1.66 day in group II; p=0.288). The pregnant group had longer hospital stay than the non-pregnant group (p=0.04). Ultrasonography (USG) was used as the first diagnostic modality in 36/38 patients in group I and 161/169 in group II. The non-visualized appendix on ultrasound was seen in 17 patients in group I and 51 patients in group II, which was not statistically different. Sensitivity and specificity of USG in diagnosis of acute appendicitis were 61.29 and 80.00% in group I, and 93.0 and 31.6% in group II, respectively.
Conclusion: Although the diagnosis of appendicitis in pregnant women is not delayed, careful assessment of these patients suspected of having appendicitis should be encouraged when USG examination is normal or nondiagnostic.

Keywords: appendicitis, pregnancy, ultrasonography, diagnosis.

Study conducted at the Department of General Surgery and at the Department of Obstetrics and Gynecology, School of Medicine, Yüzüncü Yıl University, Van, Turkey

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Introduction

Appendicitis is the most common non-obstetric surgical emergency during pregnancy, occurring in 1 in 1,000 births reported by a large cohort study including 7,114 pregnant women with appendicitis.[1] The diagnosis of appendicitis during pregnancy is challenging and it is reported that 25 to 50% of patients had incorrect preoperative diagnosis for several reasons.[2] Due to the symptoms and complaints such as nausea, loss of appetite, vomiting, and mild-lower abdominal pain are frequent during the normal pregnancy and also in acute appendicitis, it is reasonable to make efforts to increase and facilitate the early diagnosis and treatment of acute appendicitis.[3]

It has been reported that any delay or misdiagnosis of acute appendicitis will eventually result in perforated or complex appendicitis with peritonitis, which is associated with high rates of early delivery, miscarriage, and fetal loss.[4] Despite the tendency to late diagnosis of acute appendicitis during pregnancy, it is reported up to 23% of negative appendectomy rate.[5] However, a recent study reported that higher rates of adverse obstetric outcomes were observed amongst pregnant women with negative appendectomy.[6] Ultrasonography (USG) is a non-invasive and inexpensive test, which does not expose the patient to radiation, and is reported to have sensitivity and specificity of 86 and 81% for the diagnosis of acute appendicitis, respectively.[7] The major disadvantage of USG is its operator dependent character. There are also speculations that the physiological and anatomical changes due to the gravid uterus within the abdomen make the diagnosis of

acute appendicitis in pregnant women more difficult than in non-pregnant women.[2]

The purpose of the current study was to investigate whether the diagnosis of appendicitis is affected by pregnancy or not and to evaluate and compare the diagnostic accuracy of USG as an imaging modality in the diagnosis of appendicitis in pregnant and non-pregnant women matched for age and reproductive period.

Method

This study was conducted in our tertiary referral hospital of Yüzüncü Yıl University, School of Medicine, Department of General Surgery after obtaining the institutional ethics committee approval. We retrospectively reviewed and analyzed all the medical files of pregnant women whom underwent appendectomy, either open or laparoscopic, for suspected appendicitis during a 5-year period from June 2010 to March 2015. The data was obtained from our hospital's computer electronic database with the code of surgical operation of appendectomy. The patient demographics, time until hospital admission, applied imaging modalities, laboratory analysis, data regarding surgical interventions including the time from admission to the surgery and intraoperative findings, histological results, postoperative data such as hospital stay were documented. In order to compare the variables, non-pregnant women were used as controls for the pregnant group. The two groups were matched for age and reproductive period. The non-pregnant group comprised women aged between 18 to 45 years, to eliminate the age bias as a confounding variable. The retrospective chart review of non-pregnant women was retrieved from the medical records of women who underwent appendectomy and had a negative pregnancy test during the surgery. The exclusion criteria were women with < 18 or > 45 years of age, patients with chronic appendicitis and patients who underwent appendectomy during any intra-abdominal surgery being considered an incidental case.

As a diagnostic imaging modality, the USG was used with graded compression technique and all the results were interpreted by the experienced radiologists. The USG resulted as either diagnosis of appendicitis or normal/unvisualized (nondiagnostic). The final pathology results were grouped as normal appendix, acute appendicitis and complex appendicitis. Complex appendicitis was defined as any signs of gangrenous, phlegmonous or perforated appendicitis with or without generalized peritonitis. All the surgeries were performed by the senior registrar in the Department of General Surgery under the supervision of consultants. The final diagnosis was accepted as negative appendectomy in case of resected appendix without any histologically proven inflammation.

The main outcome variables were the time of diagnosis from first admission to the operation, negative appendectomy rate and the diagnostic accuracy of USG for appendicitis in pregnant and non-pregnant groups.

The data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) software version 13. Descriptive statistics for constant variables are reported as means ± standard deviations and range, and categorical variables are reported as numbers (n) and percentages (%). Mann-Whitney U test and Chi-square test were used for analysis of data between the two groups. The Pearson correlation coefficient was determined for each group to compare the associations between variables. P-value < 0.05 was considered significant for all statistical analyses.

Results

A total of 38 pregnant and 169 non-pregnant women who were eligible for the study underwent appendectomy for being suspected of having appendicitis during the 5-year investigation period in our hospital. During this time, there were 6,540 births in our center and yielding an overall incidence of appendicitis in pregnant women of 0.58%. The mean age of group I (pregnant women) and group II (non-pregnant women) was 27.29±7.63 and 28.09±7.47, respectively, which was not statistically different. The demographics of the two groups are shown in Table 1. The leukocyte count was statistically higher in the non-pregnant group (13.88±5.08) than in the pregnant group (12.94±4.02) (p=0.008). Of the 38 patients in group I, 32 (84.2%) women had histologically proven appendicitis, of whom 22 (57.9%) had acute suppurative appendicitis and 10 (26.3%) had complex appendicitis. The negative appendectomy rate in group I was 15.8% (n=6). In group II, 149 out of 169 non-pregnant women had histologically proven appendicitis with a negative appendectomy rate of 11.8% (n=20). A hundred and four (104) women in group II had acute appendicitis and 45 women had complex appendicitis. The negative appendectomy rate was not statistically different between the two groups (p=0.796). When comparing the histological results of cases with appendicitis within each group, no statistically significant difference was seen with regards to the rate of acute or complex appendicitis between the two groups as shown in Table 1 (p=0.805). The ultrasound examination was used as initial diagnostic modality for 36 (94.7%) patients in group I and 161 (95.3%) in group II. There was a statistically higher rate of non-visualized appendix vermiformis on USG in the pregnant group compared with the non-pregnant group (p=0.041). When

examining the USG findings, appendix size greater than 7 mm was seen in 11 (28.9%) patients in group I and 88 (52.1%) in group II, which was not statistically significantly different (p=0.059). Also, heterogeneity of mesoappendix detected on USG was seen in 21 (58.3%) women in group I and 109 (67.7%) in group II, which was also not statistically significantly different (p=0.059).

As shown in Table 2, the time from admission to the operation was not statistically different between the groups (p=0.288). There was a statistically lower rate of laparoscopic appendectomy in group I, with 10 (26.3%) in group I and 91 (55.2%) in group II (p=0.001). The majority of pregnant women underwent open (laparotomy) appendectomy (73.7%). The length of hospital stay was statistically longer in the pregnant group than in the non-pregnant patients (p=0.04).

The USG findings and histopathologic results of both pregnant and non-pregnant patients were examined and compared. In 20 patients, appendicitis was confirmed histologically, and 19 of those presented acute or complex forms. The sensitivity and specificity of USG in the diagnosis of appendicitis were found to be 61.29 and 80.00%, respectively, in group I. In group II, 145 patients were diagnosed on USG as appendicitis and the histopathology showed 142 out of these 145 patients having an appendix with confirmed inflammation either acute suppurative or complex form. The sensitivity and specificity of USG in group II were 93.0 and 31.6%, respectively. We found that the accuracy rate of USG for diagnosis of acute appendicitis was lower in the pregnant group compared with the non-pregnant group, at 63.86 and 85.7%, respectively (Table 3).

TABLE 1 Demographic and diagnostic variables of pregnant and non-pregnant women who underwent appendectomy.

	Group I, pregnant (N=38)	Group II, non-pregnant (N=169)	p-value
Age, year (mean±SD)	27.29±7.63	28.09±7.47	0.553
Leukocyte count, x 103 (mean±SD)	12.94±4.02	13.88±5.08	**0.008**
USG results			**0.01**
Non-visualized/normal, n (%)	16 (44.4%)	16 (9.9%)	
Acute appendicitis, n (%)	20 (55.5%)	145 (90.0%)	
USG findings			0.059
Heterogeneity of the mesoappendix, n (%)	21 (58.3%)	109 (67.7%)	
Non-visualized appendix, n (%)	17 (47.2%)	51 (31.6%)	
Appendix size < 7 mm, n (%)	6 (16.6%)	22 (13.6%)	
Appendix size > 7 mm, n (%)	11 (30.5%)	88 (54.6%)	
Pathology results			0.796
Normal, n (%)	6 (15.8%)	20 (11.8%)	
Acute appendicitis, n (%)	22 (57.9%)	104 (61.5%)	
Complex appendicitis, n (%)	10 (26.3%)	45 (26.6%)	

p<0.05 indicates statistical significance; USG: ultrasonography.

TABLE 2 Perioperative characteristics of the two groups.

	Group I, pregnant (N=38)	Group II, non-pregnant (N=169)	p-value
Time from admission to the operation, days (mean±SD)	2.13±1.47	1.98±1.66	0.288
Length of hospital stay, days (mean±SD)	3.94±2.92	2.59±1.99	**0.04**
Type of operation			**0.001**
Laparoscopy, n (%)	10 (26.3%)	91 (55.2%)	
Laparotomy, n (%)	28 (73.7%)	78 (46.1%)	
Conversion in operation, n (%)	0	0	

p<0.05 indicates statistically significant difference.

TABLE 3 Comparison of diagnostic accuracy of USG for appendicitis in pregnant and non-pregnant women undergoing appendectomy.

		Pregnant (USG)		Non-pregnant (USG)		
		Normal	Inflammation	Normal	Inflammation	p
Pathology	Normal	4	1	6	13	0.001
	Inflammation	12	19	10	132	
	Accuracy	63.89%		85.7%		
	Sensitivity	61.29%		".0		
	Specificity	80.00%		1.6		

USG: ultrasonography; 1 means appendicitis, 2 means pathologically confirmed appendicitis either acute or complex; p<0.05 indicates statistically significance.

Discussion

Appendectomy for suspected appendicitis is the most commonly performed non-obstetric operation during pregnancy.[1] It is a well-established data that appendicitis during pregnancy is associated with increasing maternal--fetal mortality and morbidity including fetal loss, abortion, and preterm birth.[4] The correct diagnosis of appendicitis is challenging and reported to be often inaccurate during pregnancy.[8] Also, in several recent reports, it was shown that fetal and maternal complications are particularly high in cases with complex appendicitis.[1,4,9] So any delay in the timely diagnosis of appendicitis will result in perforated appendicitis with peritonitis, and eventually raise the occurrence of complications. It was reported that pregnancy itself may cause delay in the diagnosis, since physiological and anatomical changes associated with pregnancy may obscure the diagnosis of appendicitis.[8] In order to explain this, we aimed to investigate pregnant and non-pregnant patients who underwent appendectomy for suspected appendicitis.

It is speculated and reported that the diagnosis of appendicitis during pregnancy is delayed due to several factors such as nausea, vomiting, and loss of appetite, which are common symptoms in both situations; the typical right lower quadrant pain seen with appendicitis, which is obscured during pregnancy due to the shift of the appendix upward and laterally as the uterus grows; and also leukocytosis, which is an important finding of appendicitis and a physiological laboratory finding during pregnancy.[10] Our findings were not consistent with the literature.[4,10] In our study, we found that no statistically significant difference in time from first admission to operation was observed between the two groups (p=0.288). However, in contrast to the literature, the leukocyte count was higher in the non-pregnant group than in the pregnant patients with appendicitis.

It has been reported that USG has a sensitivity and specificity of 86 and 81% for diagnosing acute appendicitis in the general population, respectively.[7] However, its accuracy in pregnant women suspected of having acute appendicitis remains unknown.[11] In our study, the majority of patients in the two groups underwent USG examination (36/38 in pregnant group and 161/169 in non--pregnant group) and the sensitivity and specificity of USG for detecting acute appendicitis in pregnant and non--pregnant group were 61.2 and 80%, 93 and 31.6%, respectively, which was statistically different. The accuracy of USG to diagnose the appendicitis confirmed by final pathology was 63.8% among pregnant and 85.7% among the non-pregnant patients, which was statistically different (p=0.001). So the accuracy of ultrasound is higher in non-pregnant women than pregnant women when diagnosing acute appendicitis. Our results show that when USG was positive for acute appendicitis, no need for further diagnostic test is required; however, if USG is normal or nondiagnostic, further clinical assessment and imaging should be performed. It is reported that USG has a high rate of non-visualization of the appendix during pregnancy.[12] Similarly, Aggenbach et al. reported, in a study that evaluated 21 pregnant patients who underwent appendectomy, 75% of non-visualized appendix on USG.[13] Our result was inconsistent with this study, since we found non-visualized appendix in only 45.7% of the pregnant patients, less than the previously reported data. However, when comparing the non-visualization of appendix on USG, we observed that it was higher in the pregnant group than in the non-pregnant group, which was statistically significant (p=0.01). This is possibly related to the altered anatomic location of the appendix, enlarged uterus with viable fetus, obesity, overlying bowel gas, and experience of the operator.[8]

Perforated appendicitis during pregnancy has been reported to increase the risk of maternal mortality and fetal loss. Besides, pregnant women tend to have more perforated appendicitis than non-pregnant ones.[14] McGory et al., in their study evaluating the impact of negative appen-

dectomy on the subsequent fetal loss, found that there was no delay in the diagnosis of appendicitis in pregnant women.[4] Consistent with this data, after excluding women with negative appendicitis, we observed that 26.3% of the pregnant women had complex appendicitis, compared with 26.6% of non-pregnant women, indicating that there is no meaningful impact of delay in the diagnosis of appendicitis in pregnant women.

Several studies in the literature have reported that the negative appendectomy rate is high in pregnant women and increases the risk of fetal loss and maternal mortality.[4,13] McGory et al. reported a negative appendectomy rate of 23% in pregnant women compared to 18% in non-pregnant women ($p<0.05$). In a study that included 968 women, of which 87 were pregnant, Ito et al. reported that the negative appendectomy rate in the pregnant group was significantly higher than in the non-pregnant group (36% *vs.* 14%; $p<0.001$).[15] They deduced from the study that negative appendectomy during pregnancy is not free of risk to the fetus. In our study, in contrast to the previous reports, we found a negative appendectomy rate of 15.8% in the pregnant group and 11.8% in the non-pregnant group, which was not statistically different ($p=0.796$). We think this may be due to the use of high rate of USG examinations before the operation, especially in the pregnant group. Likewise, Wallace et al. compared the negative appendectomy rates among pregnant patients suspected of having appendicitis who were clinically evaluated (54%), who underwent ultrasonographic evaluation (36%), and who underwent ultrasound/CT evaluation (8%). They reported a significant reduction in the negative appendectomy rate in the ultrasound/CT group compared to the clinical evaluation group (8% *vs.* 54%, $p<0.05$).[16]

Appendectomy can be performed through laparoscopy or open technique. During the past decades laparoscopic appendectomy has gained wide acceptance for the treatment of acute appendicitis. However, in pregnant women, the use of laparoscopy carries some doubts regarding its feasibility, safety and tolerability. So the choice for surgical approach is possibly dependant on whether the woman is pregnant and on the surgeon's preference.[17] Cheng et al. stated in a study that laparoscopic appendectomy can be performed safely in pregnant patients without bringing additional maternal complications compared to open appendectomy.[18] McGory et al., in a study that included a large number of pregnant women treated with appendectomy (n=3,133), reported laparoscopic appendectomy was performed in 454 (14%) pregnant patients. They also reported that the fetal loss rate was substantially higher in patients undergoing laparoscopic appendectomy (7%) than in patients undergoing open (3%) appendectomy.[4] In our study, laparoscopic appendectomy was performed in ten patients in the pregnant group (26.3%) and 91 patients in non-pregnant group (55.2%), showing that a majority of pregnant women underwent open appendectomy. Even though the maternal and fetal outcomes were not included in our study's design, unpublished data from our institution comparing the maternal and fetal outcomes of open *versus* laparoscopic appendectomy in pregnant women including 48 patients showed no differences in fetal loss and maternal complications. Not-surprisingly, the length of hospital stay among pregnant women who underwent appendectomy was statistically longer than among the non-pregnant women ($p=0.04$), which may be associated with the evaluation of pregnant women in the obstetric unit with additional medical treatments and, thus, lengthened the hospital stay.

The main limitation of our study is inherent to its retrospective character and the data being reviewed from medical records, which may have some missing points. Also, sample size may limit interpretation of some of the outcomes. Another limitation is that different radiologists evaluated the patients, even though they are all experienced, and multiple pathologists examined the obtained specimens. The strength of our study may be attributed to the fact that it was conducted in a single center, which is a tertiary hospital experienced on these case series.

Conclusion

In the present study, we found no delay in the diagnosis of appendicitis in pregnant women compared with non-pregnant women. The present study shows that ultrasound examination has a low diagnostic accuracy for acute appendicitis in pregnant women compared with non-pregnant women. In order to avoid any delay in the accurate and timely diagnosis of acute appendicitis in pregnant women, other imaging modalities and further clinical assessments should be kept in mind when USG examination is negative for appendicitis.

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Resumo

O diagnóstico de apendicite aguda em mulheres grávidas *versus* não grávidas: um estudo comparativo

Objetivo: investigar se o diagnóstico de apendicite aguda é afetado por gravidez ou não.
Método: estudo retrospectivo com análise dos prontuários médicos de todas as mulheres que tiveram suspeita de apendicite e foram submetidas à apendicectomia em nosso hospital entre junho de 2010 e março de 2015. As pacientes foram divididas em dois grupos, de acordo com a presença de gravidez durante a cirurgia: grupo I, mulheres grávidas; grupo II, mulheres não grávidas.
Resultados: durante o período do estudo, 38 mulheres grávidas e 169 mulheres não grávidas foram submetidas à apendicectomia. O tempo desde a internação até a cirurgia não foi estatisticamente diferente (2,17±1,47 dias no grupo I *vs.* 1,98±1,66 dia no grupo II, p=0,288). O grupo das grávidas apresentou uma estadia hospitalar mais longa que o grupo das não grávidas (p=0,04). A ultrassonografia foi usada como primeira modalidade de diagnóstico em 36/38 pacientes no grupo I e em 161/169 no grupo II. O apêndice não visualizado na ultrassonografia foi visto em 17 pacientes no grupo I e 51 pacientes no grupo II, e não foi estatisticamente diferente. A sensibilidade e especificidade da ultrassonografia no diagnóstico de apendicite aguda foram 61,29 e 80,00% no grupo I e 93,0 e 31,6% no grupo II, respectivamente.
Conclusão: embora o diagnóstico de apendicite em mulheres grávidas não seja protelado, recomenda-se uma avaliação cuidadosa quando o exame de ultrassonografia for normal ou não diagnóstico nessas pacientes.

Palavras-chave: apendicite, gravidez, ultrassonografia, diagnóstico.

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Wake-up stroke: Clinical characteristics, sedentary lifestyle, and daytime sleepiness

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Summary

Objective: Wake-up stroke (WUS) is defined when the exact time of the beginning of the symptoms cannot be determined, for the deficits are perceived upon awakening. Sleep alterations are important risk factors for stroke and cardiovascular diseases. This study evaluates the characteristics of patients with and without WUS, the presence of daytime sleepiness, and associated risk factors.
Method: Patients with ischemic stroke were investigated about the presence of WUS. Clinical and demographic characteristics were evaluated. Stroke severity was studied by the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (MRS), and daytime sleepiness severity was studied by the Epworth Sleepiness Scale (ESS).
Results: Seventy patients (57.1% men) aged from 32 to 80 years (58.5±13.3) were studied. WUS was observed in 24.3%. Arterial hypertension (67.1%), type 2 diabetes (27.1%), and hyperlipidemia (22.8%) were frequent. Type 2 diabetes and sedentary lifestyle were more common in patients with WUS ($p<0.05$). Overall, mild, moderate or very few symptoms of stroke (NIHSS<5) were predominant (62.3%). Among all cases, 20% had excessive daytime sleepiness (ESS>10). No differences were found between patients with and without WUS as regards stroke severity or excessive daytime sleepiness. Patients with excessive daytime sleepiness were younger and had more sedentary lifestyle ($p<0.05$). Individuals with previous history of heavy drinking had more daytime sleepiness ($p=0.03$).
Conclusion: Wake-up stroke occurs in approximately 25% of stroke cases. In this study, patients with WUS had more diabetes and sedentary lifestyle. Daytime sleepiness is frequent and is associated with sedentary lifestyle and heavy drinking.

Keywords: ischemic stroke, sedentary lifestyle, sleep, diabetes, heavy drinking.

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Introduction

Among patients affected by stroke, 20 to 25% cannot precise the exact time of symptoms onset, for the deficits are perceived upon awakening.[1-3] These types of stroke are denominated wake-up stroke (WUS). In such cases, the therapeutic time window which is one of the criteria for thrombolytic therapy is not available.[4-6]

Controversies about clinical differences, risk factors, and prognosis between WUS and "stroke while awake" remain. The majority of studies register similarities between clinical characteristics and risk factors; however, there are divergences mainly regarding the evolution and clinical presentation.[7]

A previous study involving 17,398 patients (International Stroke Trial) observed the clinical profile and evolution of WUS and found no significant differences regarding age, gender, and average blood pressure. It has been shown that patients with WUS present less atrial fibrillation, less total anterior circulation syndrome, less compromise of consciousness, and more lacunar syndrome. It was hypoth-

esized that WUS would be associated with a lower probability of development of functional dependence probably due to a milder clinical profile (predominance of lacunar syndrome). It has been said that despite their more benign presentations, the outcome of WUS is similar to other ischemic strokes.[8] Adding to the controversy, hypertension, smoking, and worse clinical severity have been associated with stroke during sleep; however, fatality was not different between groups with WUS and stroke while awake.[9]

A retrospective study involving 2,289 patients, in which the Modified Rankin Scale (MRS) and the National Institutes of Health Stroke Scale (NIHSS) were used, showed that WUS was associated with worse clinical outcome.[7] In opposition to these findings, another retrospective study with 1,854 patients showed a similar clinical outcome in WUS.[10]

It has been recognized that short sleep duration and daytime sleepiness are important risk factors for the manifestations of arterial hypertension, diabetes, and obesity.[11] Recent studies show that a reduction of sleep duration increases the mortality for any cause.[12] It is also shown that daytime sleepiness is an independent risk factor for the occurrence of stroke and other cardiovascular events.[13] Together, these findings indicate that sleep alterations are important risk factors for stroke. Moreover, sedentary lifestyle and excessive alcohol drinking have been recognized as potentially harmful to health.[14] Given that clinical characteristics of WUS are still conflicting, additional studies on this subject can provide insight into the pathological mechanisms of this condition and suggest new therapeutic approaches.

The objectives of this study were to evaluate clinical characteristics of patients with WUS as compared to general ischemic stroke, and to further examine the relationship with excessive daytime sleepiness, sedentary lifestyle, and heavy drinking.

Method

Study design

A cross-sectional study was performed on ischemic stroke patients admitted to a single academic stroke center from 2013 to 2014. Initially, 114 patients that filled the eligibility criteria and agreed to participate in the study were recruited. Forty-four patients were excluded due to clinical deterioration, waiver, exceeding the time limit inclusion, transfer to support hospitals and/or hospital discharge (Figure 1). The protocol was approved by the local Research Ethics Committee and written informed consent was obtained in all cases (UFC-CE 422.106).

Sample description

Patients of both gender aged 18 to 85 years, with time onset of symptoms less than 15 days, neuroimaging excluding non-ischemic lesion, stable clinical-neurological state, and capacity (patients or relatives) to provide a written consent were included. Subjects were excluded if NIHSS was above 25, comprehension deficit was severe enough to prevent evaluation tests, and severe comorbidities were present. Among all, patients who went to bed in their normal state of health and first noticed stroke symptoms upon awakening were classified as WUS.

Clinical evaluation

Clinical and demographic data included age, gender, and anthropometric measures. Arterial hypertension, diabetes, hyperlipidemia, heart disease, smoking, heavy drinking, sedentary lifestyle, and obesity were all evaluated. Arterial hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or current use of antihypertensive medications.[15] Diabetes was defined as the presence of a fastening ≥ 126 mg/dL, postprandial glucose concentration ≥ 200 mg/dL, or diabetes symptoms and a plasmatic glucose concentration (last meal time independent) ≥ 200 mg/dL.[16] Hyperlipidemia was defined as an alteration in lipid profile, with low density cholesterol ≥ 100 mg/dL, high density cholesterol < 40 mg/dL, and/or triglycerides > 150 mg/dL.[17] Previous history of heart disease was informed by patients and/or caregivers. All data were confirmed by chart review. Patients were classified as physically active when involved in moderated to intense physical activity for, at least, 150 minutes/week. Heavy drinking was defined as the ingestion of five or more drinks per day at least once per month or more than 30 drinks per month. Smoking was defined as the use of tobacco for the last 12 months.[18]

The following anthropometric parameters related to cardiovascular risks were evaluated: body mass index (BMI),[19] neck circumference,[20] waist circumference, and waist-hip index (WHI).[21] Neck circumference was considered abnormal if > 43 cm in men and > 38 cm in women; waist circumference was abnormal if > 102 cm in both genders; waist-hip index was considered abnormal if > 0.91 in men and > 0.84 in women. Daytime sleepiness was evaluated by the Epworth Sleepiness Scale (ESS);[22] the ischemic lesion gravity, through the NIHSS;[23] the individual's functional capacity, through the MRS;[24] and the clinical location of the lesion, through the Oxfordshire Community Stroke Project (OCSP).[25]

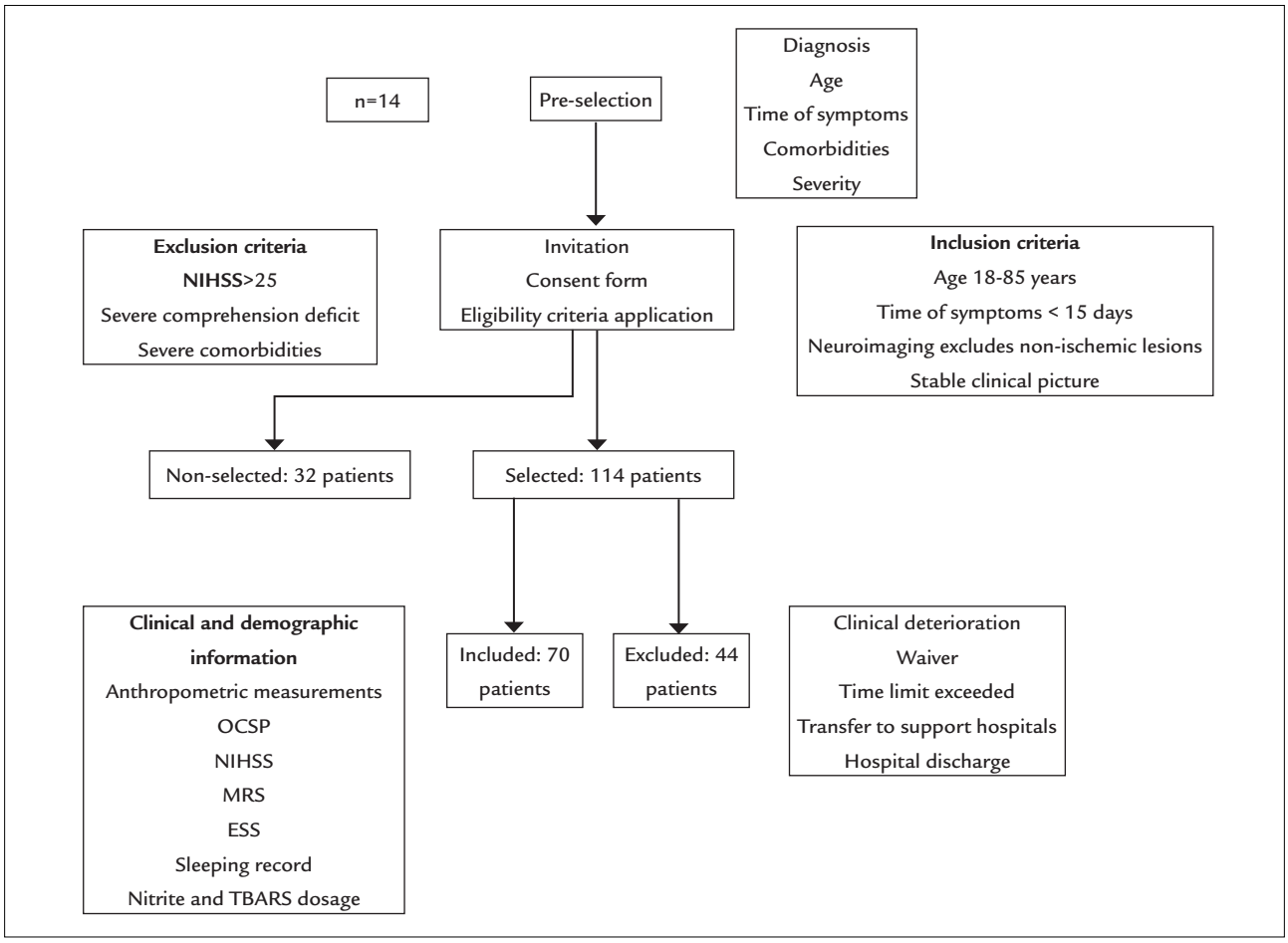

FIGURE 1 Flowchart of patient selection and evaluation.
NIHSS: National Institutes of Health Stroke Scale; OCSP: Oxfordshire Community Stroke Project; MRS: Modified Rankin Scale; ESS: Epworth Sleepiness Scale; TBARS: thiobarbituric acid reactive substances.

Statistical analysis

Data were examined for normality using the Shapiro-Wilk and for homogeneity of variances the Levene test. The descriptive analysis was presented as absolute numbers, frequency, variation, average, and standard deviation. The Fisher's test or Chi-square test was performed for between group comparisons. The Mann-Whitney's U test for continuous variables and the Student's t test for the variables with normal distribution and homogeneity of variance were performed when adequate. Statistical analysis was performed with the Statistic Package for Social Sciences (SPSS, Norusis, 1993) software for Windows. The level of significance was set at $p<0.05$. Data are quoted as mean±SD.

Results

Patients (N=70) aged from 32 to 83 were studied (mean = 58.5±13.3). Overall, a non-significant male gender (n=40; 57.1%) predominance over female gender (n=30; 42.9%) was observed. Wake-up stroke was diagnosed in 17 patients (24.3%); 53 patients (75.7%) were identified as having had stroke while awake. Arterial hypertension was confirmed within the majority of the cases (n=47; 67.1%). Diabetes was found in approximately a quarter of the studied population (n=19; 27.1%). Disturb of lipid metabolism was confirmed in 16 patients (22.8%). Forty-six patients (65.7%) were identified as physically inactive and 24 (34.3%) confirmed a history of regular physical activity. Smoking was informed by 22 patients (31.4%). Heavy drinking was found in 17 patients (26.1%).

Among all, waist measure was revealed as abnormal (> 102 cm) in 17 patients (24%). Women presented more WHI cases (WHI>0.8, 89%) than men (WHI>1.0, 55.0%) (exact Fisher test, p=0.002). In the entire group, it was noticed that 40% of the patients (n=28) had normal BMI and 40% were overweight (n=28). Only 20% (n=14) showed obesity and no differences were found in men (37% normal BMI; 49% overweight; and 14% obesity) as compared to women (40% normal BMI; 40% overweight; and 20% obe-

sity) (exact Fisher test, p=0.56). Two men presented severe obesity (BMI>35).

Patients with WUS as compared to stroke while awake did not differ in regard to gender and age. Similarly, there was no difference in arterial hypertension, previous smoking habits or heavy drinking between the two groups. In this study, diabetes was more frequent in WUS (exact Fisher test, p=0.03). Also, reports of sedentary habits were more common among WUS patients (exact Fisher test, p=0.04) (Table 1).

In the overall sample, 62.3% presented mild, moderated, or few symptoms as evaluated by the NIHSS scale

TABLE 1 Clinical and demographic characteristics and results of behavioral scales of patients with wake-up stroke *versus* non wake-up stroke.

Clinical and demographic characteristics	All patients (N=70)	Non wake-up (n=53)	Wake-up (n=17)	p-value
Male/female, n	40/30	30/23	10/7	[a]0.87
%	57.1/42.9	56.5/43.4	58.8/41.2	
Age, range	32-83	32-82	40-83	[b]0.95
Mean (SD)	58.5 (13.3)	58.6 (13.9)	58.4 (11.6)	
Hypertension (yes/no)	47/23	33/20	14/3	[a]0.15
%	67.1/32.9	62.7/ 37.3	82.4/17.6	
Diabetes (yes/no)	19/51	11/42	8/9	[a]0.03
%	27.1/72.9	20.8/79.2	47.1/52.9	
Hyperlipidemia (yes/no)	16/49	12/41	5/12	[a]0.47
%	22.8/77.2	22.6/77.4	29.4/70.6	
Smoking (yes/no)	22/48	16/37	6/11	[a]0.69
%	31.4/68.6	30.2/69.8	35.3/64.7	
Heavy drinking (yes/no)	17/53	10/43	5/12	[a]0.47
%	26.1/73.9	18.86/81.14	29.4/70.6	
Heart disease (yes/no)	6/61	6/47	1/16	[a]0.68
%	8.5/91.5	11.3/88.7	5.9/94.1	
Sedentary lifestyle (yes/no)	47/23	32/21	14/2	[a]0.04
%	67.1/32.9	60.4/39.6	82.4/17.6	
Neck circumference, range	30.0-54.0	32-52	30-54	[b]0.92
Mean (SD)	39.8 (5.1)	39.7 (4.6)	39.9 (6.6)	
BMI, range	21.4-38.6	21.4-38.6		[b]0.74
Mean (SD)	27.0 (3.8)	27.1 (3.7)		
Waist (cm), range	65-134	65-134	76-128	0.83
Mean (SD)	95.5 (12.4)	95.3 (12.3)	96.12 (9.9)	
Hip (cm), range	62-124	67-124	62-122	0.90
Mean (SD)	97.8 (11.0)	97.9 (9.9)	97.5 (14.3)	
Waist-hip ratio, range	0.75-1.12	0.80-1.12	0.75-1.04	[b]0.51
Mean (SD)	0.96 (0.07)	0.97 (0.07)	0.95 (0.07)	
Behavioral questionnaires				
NIH Stroke Scale, range		0-14	0-18	0.58
Mean (SD)		4.8 (4.1)	6.2 (6.1)	
Modified Rankin Scale, range		0-5	1-5	0.18
Mean (SD)		2.0	2.5	
OCSP, range		1-4	1-4	0.10
Mean (SD)		2	3	
Epworth Sleepiness Scale, range		0-16	0-12	0.46
Mean (SD)		6.3 (3.7)	7.0 (4.1)	

NIH: National Institutes of Health; OCSP: Oxfordshire Community Stroke Project; BMI: body mass index; SD: standard deviation. [a]Fisher exact test; [b]Student t test, p<0.05.

(NIHSS<5). Similarly, as evaluated by the MRS scale, 62.3% showed indicative signs of a mild stroke (MR≤2). The indication of vascular territories involved as evaluated by the OCSP scale revealed a great variability. The symptoms of daytime sleepiness in the last 30 days (ESS>10) were identified in 20% of the patients. Stroke severity (NIHSS), functional performance (MRS), classification of infarct (OCSP), and daytime sleepiness were not different between groups with WUS as compared to stroke while awake (Table 1).

Patients with excessive daytime sleepiness were younger (p=0.02), had more reports of heavy drinking (p=0.03), and more records of previous physical inactivity (p=0.03). Among patients with excessive daytime sleepiness, a trend for a higher number of cases with WUS and arterial hypertension was observed. Regarding stroke severity as evaluated by the NIHSS and MRS scales, and the vascular territory according to the OCSP scale, no differences were found between patients with and without excessive daytime sleepiness (Table 2).

Discussion

In this study it is shown that WUS represents approximately a quarter of the ischemic stroke patients. Previous reports indicate a prevalence that varies from 5 to 30%. The thrombolytic therapy for ischemic stroke can only

TABLE 2 Demographic and clinical characteristics of stroke patients with and without daytime sleepiness.

	Without daytime sleepiness n=56	With daytime sleepiness n=14	p-value
Gender (M/F)	31/25	10/4	[a]0.33
%	55.4/44.6	71.42/28.58	
Age, range	32-83	32-78	[b]0.02
Mean (SD)	60.5 (12.9)	50.3 (13.2)	
Wake-up stroke (yes/no)	9/45	6/8	[a]0.11
%	16.1/83.9	42.9/57.1	
Hypertension (yes/no)	39/15	7/7	[a]0.17
%	69.6/30.4	50/50	
Diabetes (yes/no)	14/40	2/10	[a]0.71
%	25/75	14.3/85.7	
Hyperlipidemia (yes/no)	14/42	5/9	[a]0.71
%	25/75	35.7/64.3	
Smoking (yes/no)	17/39	6/8	[a]0.49
%	30.4/69.6	42.9/57.1	
Heavy drinking (yes/no)	11/45	6/8	[a]0.03
%	19.6/80.4	42.9/57.1	
Heart disease (yes/no)	8/48	2/12	[a]0.36
%	14.3/85.7	14.3/85.7	
Sedentary lifestyle (yes/no)	33/23	12/2	[a]0.03
%	58.9/41.1	85.7/14.3	
Waist (cm), range	65-134	77-114	[b]0.42
Mean (SD)	96.7 (12.3)	93.4 (12.9)	
Hip (cm), range	62-124	85-115	[b]0.54
Mean (SD)	98.54	96.27	
Neck circumference (cm), range	30-54	33.5-50	[b]0.25
Mean (SD)	39.6 (5.4)	41.5 (4.1)	
BMI, range	21.4-38.6	23.0-37.6	[b]0.98
Mean (SD)	27.1 (3.6)	27.1 (4.9)	
Waist-hip ratio, range	0.75-1.09	0.84-1.12	[a]0.96
Mean (SD)	0.97 (0.7)	0.97 (0.8)	

SD: standard deviation; BMI: body mass index; [a]Fisher exact test; [b]Student t test, p<0.05.

be administrated in a narrow time window. Therefore, considering that patients with WUS may comprise up to 30% of the ischemic strokes, a significant number of cases may have this alternative of treatment compromised.

It has been reported that the patients with WUS present worse clinical presentation, and, as opposed to it, there are reports showing no difference between WUS and stroke while awake. Our study revealed the latter pattern in the overall sample. In an interesting way, however, the patients with WUS presented more diabetes and a sedentary lifestyle. To the best of our knowledge, similar reports have not been described. A previous study showed a relationship between WUS and smoking.[9]

Daytime sleepiness has been associated with an increase in mortality by any cause and with major occurrence of cerebrovascular diseases.[26,27] Daytime sleepiness is also a clinical sign of obstructive sleep apnea which by its turn is an independent factor to greater mortality in stroke.[28] In the current study, 20% of the patients had excessive daytime sleepiness and this was higher among the younger, in those with history of sedentary lifestyle and heavy drinking. It must be considered that daytime sleepiness is a complex symptom and of probable multifactorial cause. The occurrence of heavy drinking in association with daytime sleepiness suggests an additional cause for neuronal lesions.

Regarding the conundrum of therapy for WUS patients, recently, it has been shown that the characterization of the penumbra zone is a decisive factor for the use of reperfusion therapies.[29] The perfusion-diffusion mismatch has been the most used method to access the penumbra zone: the diffusion weighted image (DWI) sequence shows the irreversible ischemia area and the perfusion sequence detects the hypoperfusion area. It is important to remember that the hypoperfused lesions without hyperintensity area in the DWI represent the penumbra zone. Therefore, due to its excellent sensibility and specificity in diagnosing stroke in its acute phase, the magnetic resonance imaging can be essential for the patient with stroke.[30,31] The exam lasts less than 10 minutes, confirms the ischemia, excludes the stroke mimics and identifies the penumbra (perfusion-diffusion mismatch), promoting additional information for the decision taking regarding the thrombolytic therapy. Such procedures would be particularly useful in WUS cases.

Limitations to this study must be acknowledged. Presently, a small sample of patients was involved. However, our results are in agreement with previous reports. Moreover, the frequency of excessive daytime sleepiness, sedentary lifestyle and heavy drinking are noteworthy.

Conclusion

The current study shows that WUS occurs in approximately 25% of patients with ischemic stroke. Stroke severity and daytime sleepiness were similar in patients with WUS as compared to stroke while awake. In this study, diabetes and sedentary lifestyle were more frequent in WUS patients. Overall, excessive daytime sleepiness was present in 20% and was more frequent in patients of younger age, in those with sedentary lifestyle or with heavy drinking.

Resumo

Wake-up stroke: achados clínicos, sedentarismo e sonolência diurna

Objetivo: *wake-up stroke* (WUS) define o acidente vascular cerebral (AVC) que ocorre sem horário preciso de início, pois os sintomas manifestam-se ao despertar. Alterações do sono associam-se a maior risco de AVC e doenças cardíacas. Este estudo avalia as características dos pacientes com e sem WUS, a presença de sonolência diurna e os fatores de risco associados.
Método: pacientes com AVC isquêmico foram identificados quanto à presença de WUS. Foram avaliadas as características clínico-demográficas, a gravidade do AVC pela National Institutes of Health Stroke Scale (NIHSS) e pela Modified Rankin Scale (MRS) e o grau de sonolência pela Epworth Sleepiness Scale (ESS).
Resultados: setenta pacientes (57,1% homens) com idade entre 32 e 80 anos (58,5±13,3) foram estudados. *Wake-up stroke* foi observado em 24,3% dos casos. Hipertensão arterial sistêmica (67,1%), diabetes (27,1%) e distúrbio do metabolismo lipídico (22,8%) foram frequentes. Diabetes e hábitos sedentários foram mais comuns nos casos com WUS (p<0,05). Na amostra total, 62,3% dos casos apresentavam AVC leve, moderado ou com poucos sintomas (NIHSS<5). Sonolência excessiva diurna (SED) (ESS>10) foi identificada em 20% dos pacientes. Não houve diferença entre os grupos com e sem WUS quanto à gravidade do AVC e o grau de sonolência. Pacientes com SED eram mais jovens e mais sedentários (p<0,05). Os indivíduos com etilismo tinham maior grau de sonolência (p=0,03).
Conclusão: *wake-up stroke* manifesta-se em 25% dos casos de AVC isquêmico. Neste estudo, os pacientes com WUS apresentaram mais diabetes e sedentarismo. Sonolência diurna é frequente e associa-se a hábitos sedentários e etilismo.

Palavras-chave: acidente vascular cerebral isquêmico, sedentarismo, sono, diabetes, alcoolismo.

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Correlation between maximum voluntary contraction and endurance measured by digital palpation and manometry: An observational study

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Summary

Introduction: Digital palpation and manometry are methods that can provide information regarding maximum voluntary contraction (MVC) and endurance of the pelvic floor muscles (PFM), and a strong correlation between these variables can be expected.
Objective: To investigate the correlation between MVC and endurance, measured by digital palpation and manometry.
Method: Forty-two women, with mean age of 58.1 years (±10.2), and predominant symptoms of stress urinary incontinence (SUI), were included. Examination was firstly conducted by digital palpation and subsequently using a Peritron manometer. MVC was measured using a 0-5 score, based on the Oxford Grading Scale. Endurance was assessed based on the PERFECT scheme.
Results: We found a significant positive correlation between the MVC measured by digital palpation and the peak manometric pressure ($r=0.579$, $p<0.001$), and between the measurements of the endurance by Peritron manometer and the PERFECT assessment scheme ($r=0.559$, $p<0.001$).
Conclusion: Our results revealed a positive and significant correlation between the capacity and maintenance of PFM contraction using digital and manometer evaluations in women with predominant symptoms of SUI.

Keywords: pelvic floor, stress urinary incontinence, palpation/methods, vaginal squeeze pressure, manometry.

Introduction

According to the International Continence Society (ICS), pelvic floor muscle (PFM) function is defined by the ability to perform a normal or strong voluntary contraction, with the presence of an involuntary contraction, resulting in a "circular closing of the vagina, the urethra, and the anus" and in a "cranioventral movement of the perineum and upward movement of the pelvic organs."[1]

PFM training should be recommended as a first-line conservative management in the treatment of urinary incontinence,[2,3] as demonstrated by numerous randomized controlled trials.[4-7] The success of treatment with exercises is dependent on the achievement of strength and endurance, which consequently leads to improvement of the PFM function. Evaluation of PFM function is a difficult task, as there is no consensus regarding the best method to evaluate or control the effects of PFM training. There are various methods to verify and quantify PFM function supported by the ICS, which include visual inspection, intravaginal palpation, electromyography, pressure measurements, and imaging methods, such as ultrasound, magnetic resonance imaging (MRI), and video urodynamics. Visual inspection and digital palpation are the most common methods used by physiotherapists.[1,8]

The vaginal palpation was first described by Kegel,[9] who performed it to teach patients how to contract the

muscles, classifying muscle contraction subjectively as correct or incorrect. Currently, digital palpation is still considered an essential part of the PFM examination, and has become widespread due to its low cost, and also because it is well accepted by the patients. The evaluation of muscle strength and endurance provides information about the severity of muscle weakness and forms the basis for patient-specific exercise programs.[10]

In recent years, different methods have been developed to evaluate PFM function quantitatively.[11,12] The measurement of vaginal pressure has been considered a reproducible method.[13,14] However, practitioners should be aware that increased intra-abdominal pressure might occur during the evaluation and influence the results. Thus, this method should not be used alone.[13]

Considering that both digital and manometric methods are able to provide information with respect to maximal voluntary contraction (MVC) and endurance, a strong correlation between these variables can be expected. Thus, the aim of this study was to investigate this correlation, as measured by digital palpation and manometry.

Method

Study design

We present an observational and correlational study assessing the correlation between MVC and endurance measured by digital palpation and manometry.

Women admitted with untreated mixed stress urinary incontinence (SUI) and more than 2 g of leakage, as proven by a pad test with a standardized bladder volume,[15] were enrolled in this trial at the Division of Urogynecology and Reconstructive Pelvic Surgery of the Universidade Federal de São Paulo (Unifesp), Brazil. This study was approved by the Review Board Committee of this institution (CEP 1981/10). Each participant provided a written informed consent.

Patients with less than 2 g of urinary leakage (by pad test) and/or inability to contract the PFM were not included. Potential subjects were excluded if they had chronic degenerative diseases affecting the muscular and nerve tissues, diabetes, cerebrovascular diseases or overt neurological conditions, or autoimmune connective tissue disorders; if they were pregnant; or if they had previously undergone pelvic floor re-education programs and/or pelvic floor surgery.

To ascertain adequate PFM contraction, each volunteer was assessed by inspection and digital vaginal palpation to observe a lift of the pelvic floor in a superior, anterior direction and a constriction around the urethra, vagina, and rectum while in supine position.[16] The patients were requested to "lift and squeeze the PFM as hard as possible." The co-contraction of the gluteal, hip adductor and rectus abdominal muscles was discouraged.

Once enrolled by a physiotherapist investigator, each subject completed a questionnaire designed to collect demographic characteristics such as age, body mass index (BMI), parity, and hormonal status.

Procedure

The assessments of the MVC and muscle endurance by digital palpation and vaginal squeeze pressure measurement were conducted by a physiotherapist specialized in PFM rehabilitation. Digital and vaginal pressure evaluations were carried out randomly, on the same day, with a 1-hour interval between measurements. The sequence of measurements was MVC followed by endurance. Three consecutive muscle contractions were recorded, with a 10-second interval between efforts,[17] and the best of three was registered.[18]

One researcher (T.F.) was responsible for evaluating all patients and did not have knowledge about the analysis of correlation between the measurements. This researcher was instructed to use the same verbal command in all measurements. These results are part of a larger study involving pre- and post-physical therapy treatment. Subsequently, the main investigator (F.F.) performed the analysis of data. Both researchers are physiotherapists specialized in pelvic floor dysfunctions.

Digital palpation

Digital palpation was used to assess PFM strength and endurance. To quantify muscle strength, a score from 0-5 was given based on the previously validated Oxford Grading Scale (Table 1).[19] Endurance was recorded via the PERFECT assessment scheme.[20] Endurance was expressed as the length of time, up to 10 seconds, that an MVC could be sustained. Thus, the contraction was registered until the muscle began to fatigue.

TABLE 1 Assessment of PFM activity according to the Oxford Grading Scale modified by Laycock.

Oxford Grading Scale by Laycock	
0	No muscle activity
1	Minor muscle "flicker"
2	Weak muscle activity without a circular contraction
3	Moderate muscle contraction
4	Good muscle contraction
5	Strong muscle contraction

Vaginal squeeze pressure measurement

The vaginal squeeze pressure measurement was performed using a Peritron manometer (Cardio Design™, Victoria, Australia). This equipment has a conical vaginal catheter, with diameter and length of 26 mm and 108 mm, respectively. The vaginal catheter was connected to a handheld microprocessor with latex tubing, allowing the transmission of pressure (cmH_2O) when the insert is compressed by external pressure. The catheter was covered with a sterile latex sleeve for each patient. The vaginal catheter was inserted into the vaginal canal until the full extent of the compressible portion of the device was above the level of the hymenal ring. The baseline pressure reading was recorded after the catheter was inflated to 100 cmH_2O, and then the device was reset.

Statistical analysis

SPSS (Statistical Package for Social Sciences, IBM Company, Chicago, USA) version 21.0 was chosen for the statistical analyses. Spearman's correlation test was used to correlate the values obtained using Peritron manometer, the modified Oxford Grading Scale and the PERFECT assessment scheme. P-values were set to <0.05 to indicate statistical significance. The power of the relationship between the variables was classified as high reliability (0.80 to 1.00), moderate reliability (0.60 to 0.80), and questionable reliability (<0.59), according to Richman et al.[21]

Results

Recruitment, retention, and compliance

Forty-six (46) women diagnosed with mixed and SUI in the period from March 2011 to October 2013 were included in the study. Four women were excluded from the study because they were unable to perform a proper PFM contraction. The remaining 42 participants underwent digital assessment and vaginal pressure measurement. None of the women declined to participate in this study.

Baseline characteristics

The mean age was 58.1 years (±10.2 years), BMI was 29.3 kg/m^2 (±5.8 kg/m^2), and the mean parity was 3.3 (±2.6). Thirty-one (73.8%) women were menopaused. The mean of urinary leakage registered in pad test was 18.1 g (±24.8 g).

Digital and vaginal pressure measurements

MVC was classified based on the Oxford Grading Scale system as flicker (n=2), weak (n=20), moderate (n=13), good (n=3), and strong (n=4). The vaginal pressure measurements revealed an average score of 22.0 cmH_2O (±15.0 cmH_2O), and the Oxford Grading Scale revealed an average score of 2.6 (±1.0). There was a significant positive correlation between MVC according to the Oxford Grading Scale score and the peak pressure of manometry ($r=0.579$, $p<0.001$) (Figure 1).

Measurements of endurance by Peritron manometer and the PERFECT assessment scheme yielded an average score of 3.8 seconds (±1.6 seconds) and 3.0 seconds (±1.4 seconds), respectively. There was a significant positive correlation between these variables ($r=0.559$, $p<0.001$) (Figure 2).

Discussion

Ability to contract the PFM has been addressed by many studies. Instruction is mandatory and should be performed by verbal commands, followed by digital palpation and/or manometry.[5,6,22] Digital palpation is not considered a reproducible or valid method for measuring the PFM strength,[17] and peak pressure of manometry should not be used alone.[16] Therefore, it is noteworthy for clinical practice that the combined use of both methods has a good correlation.

A recent prospective cohort study was conducted to verify the correlation between PFM function as determined by the Oxford Grading Scale and perineometry in pregnant and postpartum women. The authors found a positive correlation, indicating that both vaginal palpation and perineometry are valid and reliable methods for measure the PFM function.[12] Accordingly, Ferreira et al. reported good inter-observer reliability for the modified Oxford Grading Scale and moderate reliability for manometry.[23]

Frawley et al. investigated the intra-observer reliability of bidigital evaluation and vaginal manometry, as well as resistance in different positions. The authors stated that both methods are reliable for quantifying MVC in standing and supine positions. Additionally, manometry is more reliable than vaginal palpation.[24]

Two studies investigated the inter-rater reliability of other palpation scoring systems, with squeeze pressures ranging from moderate to high ($r=0.60$ to $r=0.90$).[25,26] Our findings suggest that the correlation coefficient is questionable with respect to MVC ($r=0.57$) and muscle endurance ($r=0.55$). Likewise, previous studies have shown weak inter-rater reliability for the Oxford Grading Scale using Cohen's Kappa (0.37)[17] and moderate inter-rater reliability for the Peritron manometer.[23] Da Roza et al. have also found a moderate correlation between digital evaluation and manometry ($r=0.65$) in nulliparous athlete students.[27]

Ultrasound imaging is considered a responsive and reliable method to assess the PFM movement during contraction.[28] Dietz et al. correlated the cranioventral displacement on ultrasound with vaginal palpation and

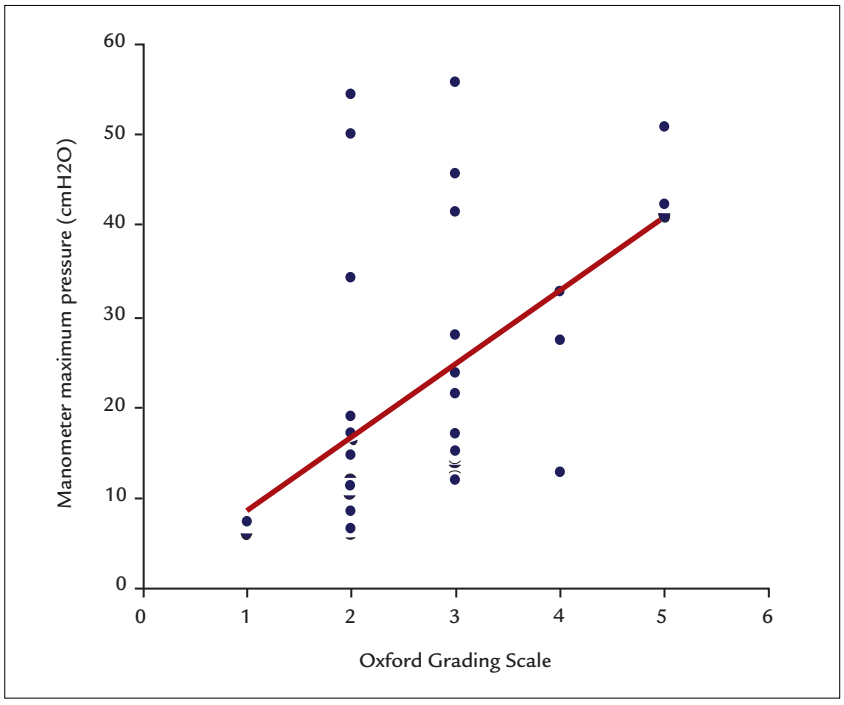

FIGURE 1 Maximum voluntary contraction measured by the Oxford Grading Scale.

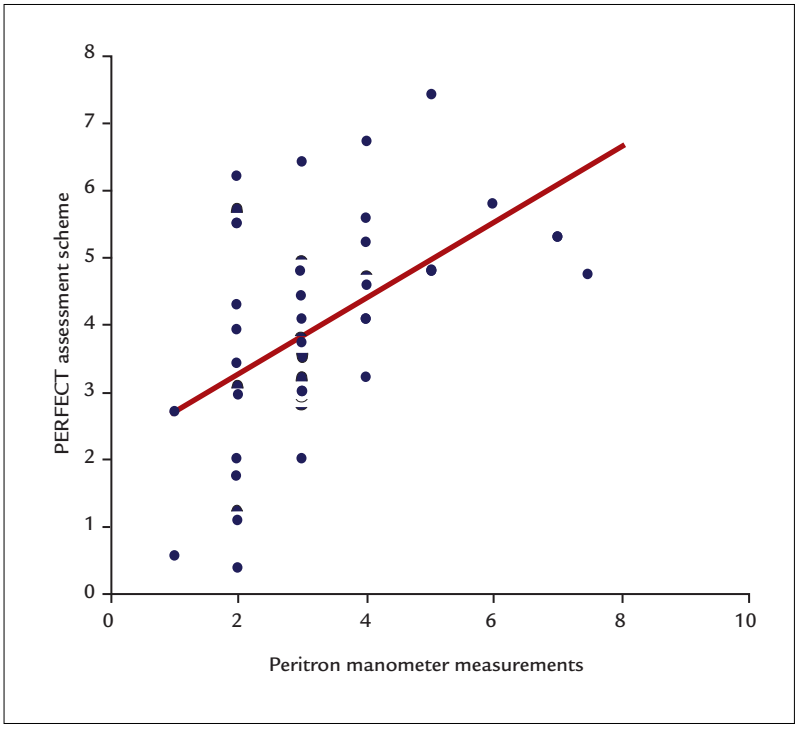

FIGURE 2 PERFECT assessment scheme *vs*. Peritron manometer – endurance measurements.

perineometry and found a highly significant correlation (r=0.62 and r=0.52, respectively).[29] Another study found a moderate association between ultrasound and perineometry in women with pelvic organ prolapse.[30] However, the perineal ultrasound does not offer the possibility of quantifying PFM contraction.[31]

Dietz et al. performed a comparative study of bidigital palpation and 4D ultrasound to evaluate trauma in the levator ani muscle. The authors found poor agreement between the two methods and concluded that imaging has a higher reliability than vaginal palpation, even when performed by a trained and experienced physiotherapist.[32]

Further studies using perineometry to evaluate the PFM are required to avoid capturing the action of the other muscle groups that form the wall of the abdominopelvic cavity,[33] because an increase in abdominal pressure will affect the urethral, vaginal and rectal pressures.[34] However, Perschers et al. assessed the effect of contraction of the abdominal muscles concomitant with the pelvic floor and reported no significant increase in readings during digital palpation, perineometry, electromyography or ultrasound.[31] In the present study, all women who were able to contract the PFM correctly were included, and only contractions with a simultaneous inward movement of the catheter or perineum were considered valid.[13]

Measurements of vaginal squeeze pressure depend on the vaginal probe that is used. Differences may arise due to the length and diameter of the probes, straining, a learning effect or different placement of the devices inside the vagina.[17] Bo et al. found mean values of maximum squeeze pressure of 19.7 cmH_2O and 36.5 cmH_2O after evaluating with different types of manometers ($p<0.01$).[35] Some factors, such as age, BMI, size of genital hiatus and parity, must be taken into consideration to assess the reliability of the evaluation of PFM by manometry.[36] Nevertheless, Hundley et al. reported that none of these variables influence the examination.[33] Brækken et al. reported that thicker muscles and a smaller levator hiatus were associated with greater strength and muscular endurance; additionally, a smaller levator hiatus was associated with higher vaginal resting pressure.[30]

The strength of the present study was the evaluation of muscle endurance, which is recognized but not commonly reported in the literature. Endurance reveals the severity of muscle weakness and is recommended to be included in all PFM training prescriptions.[36] The weakness of this study was the limited sample size.

In our study, the correlation found could be considered questionable because these methods are grounded on different principles. Vaginal pressure detects the compression of the PFM, while the Oxford Scale analyzes the compression and elevation of these muscles. In our opinion, the evaluation of compression and elevation performed separately should be considered and investigated.

We have demonstrated the importance of pelvic floor bidigital evaluation and manometry in providing various data that can enrich existing clinical and scientific knowledge. These methods have limitations, and their reliability in the academic field is still questioned. The training and experience of the evaluator are of extreme importance, as these metrics determine how reliable and realistic the results are. Our findings suggest there is still a gap in the existing information regarding the relationships among these variables, particularly pelvic muscle endurance. We recommend further studies with strong methodological design should be performed.

Conclusion

Our results revealed a positive and significant correlation between the capacity and maintenance of PFM contraction using digital and manometer evaluations in women with predominant symptoms of SUI. However, this correlation was classified as questionable.

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Resumo

Correlação entre contração voluntária máxima e *endurance* avaliados por palpação digital e manometria: um estudo observacional

Introdução: a palpação digital e a manometria são métodos capazes de fornecer informações sobre contração voluntária máxima (CVM) e *endurance* da musculatura do assoalho pélvico (MAP), e pode-se esperar uma forte correlação entre essas variáveis.
Objetivo: investigar a correlação entre CVM e *endurance*, avaliados por palpação digital e manometria.
Método: incluíram-se 42 mulheres, com idade média de 58,1 anos (±10,2) e sintomas predominantes de incontinência urinária de esforço (IUE). Realizou-se primeiramente o exame digital, seguido pela manometria (Peritron®). Mensuraram-se a CVM de acordo com a escala de Oxford (0-5 pontos) e o *endurance* pelo esquema PERFECT.
Resultados: encontrou-se correlação positiva entre CVM mensurada por palpação digital e pressão mano-

métrica de pico (r=0,579; p<0,001), e entre as medições do *endurance* avaliado pelo Peritron e o esquema PERFECT (r=0,559; p<0,001).

Conclusão: os resultados revelaram correlação positiva e significativa entre a capacidade e a manutenção de contração dos MAP por meio das avaliações digital e manométrica em mulheres com IUE.

Palavras-chave: assoalho pélvico, incontinência urinária de esforço, palpação/métodos, pressão de contração vaginal, manometria.

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Outcomes of allogeneic stem cell transplantation among patients with acute myeloid leukemia presenting active disease: Experience of a single European Comprehensive Cancer Center

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Summary

Introduction: Allogeneic hematopoietic stem cell transplantation (ASCT) represents a potentially curative approach for patients with relapsed or refractory acute myeloid leukemia (AML). We report the outcome of relapsed/refractory AML patients treated with ASCT.
Method: A retrospective cohort from 1994 to 2013 that included 61 patients with diagnosis of relapsed/refractory AML. Outcomes of interest were transplant-related mortality (TRM), incidence of acute and chronic graft-versus-host disease (GVHD), relapse incidence, progression-free survival (PFS) and overall survival (OS). Statistical significance was set at $p<0.05$.
Results: The median age was 61 years (range 1 to 65). The cumulative incidence of 90 days, 1 year, and 3 years TRM were 60%, 26.7%, and 13.3%, respectively ($p<0.001$). The incidence of relapse was 21.7% at 1 year, 13% at 3 years, and 8.7% at 5 years. Median OS was estimated to be 8 months (95CI 3.266-12.734) and median PFS, 3 months (95CI 1.835-4.165).
Conclusion: In our cohort, TRM in first years after ASCT remains considerable, but ASCT in this setting seems to be a good choice for AML patients with active disease. However, novel approaches are needed to reduce TRM and relapse in this set of patients.

Keywords: acute myeloid leukemia, heterologous transplantation, bone marrow neoplasms.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells which lose their ability to differentiate normally and to respond to normal regulators of proliferation.[1,2] Intensified treatment and improvement in supportive care have resulted in an enhanced outcome for patients with AML. At diagnosis, AML patients are evaluated by clinical risk factors and are considered for allogeneic stem cell transplantation (ASCT) based on the risk factors.[3] Cytogenetic abnormalities are among the most widely recognized risk factors in AML patients.[4] AML with karyotype t(8;21), inv(16), t(16;16), and t(15;17) are expected to be controlled with chemotherapy alone, and patients with these forms of AML are thus categorized into a favorable cytogenetic risk group.[4,5] Therefore, indication of ASCT for patients in this group is considered not at the first complete remission but at the state of relapse, after the second remission or just in case of failure to achieve remission.[3,5,6] Recent results from clinical trials indicate a 1-year overall survival (OS) rate of 60 to 70%.[7-9] In children with AML who relapsed post-ASCT and after a second ASCT, it was reported at approximately 30 to 40% by Lee et al.[9] In 2013, survival outcomes were reported to be similar between

adolescents and children with AML following ASCT.[10] Myeloablative preparative regimen used for ASCT induces profound neutropenia and platelet decrease.[11] Prolonged time of recovery from neutropenia is associated with high risk of infections and severe sepsis. Although granulocyte colony-stimulate factors can be used to help in neutrophil recovery, it delays platelet engraftment as well as immune recovery and may increase the incidence of graft-versus-host disease (GVHD), transplant-related mortality (TRM) and death.[2,12] Nevertheless, ASCT represents a potentially curative approach for patients with relapsed or refractory AML in spite of significant TRM and comorbidity, such as veno-occlusive disease and sepsis.[11] Several regimens with different dose intensities have been studied as conditioning therapies before ASCT in patients with AML.[13] In addition, the choice between myeloablative conditioning, non-myeloablative regimens and reduced intensity conditioning regimens depends on the disease behavior as well as patient overall condition and tolerated toxicities, even though outcomes can be questioned.[14] Thus, ASCT for patients with relapsed/refractory disease could represent an important therapeutic option in order to improve survival in an attempt to control a novel relapse.

Herein, we report the results of a retrospective cohort with the primary endpoint of assessing outcomes in a southern European comprehensive cancer center. We analyzed OS, progression-free survival (PFS), and incidence of relapse after the second ASCT post-high dose induction chemotherapy in patients with relapse/refractory disease. The secondary endpoints of this study were the assessment of TRM and GVHD rate.

Method

Design

Our retrospective cohort includes data from January 1994 to January 2013 collected at the Central Comprehensive Cancer Hospital in northern Portugal: the Portuguese Oncology Institute (IPO-Porto), Porto, Portugal. The study was conducted according to the Declaration of Helsinki. Signed written-informed consent form was obtained from all patients involved in this study.

Patients

The patient inclusion criteria were the following: confirmed diagnosis of relapsed/refractory AML (based on morphological findings of the bone marrow aspirates and immune-phenotype analysis of leukemic cells by flow cytometry or immune histochemical analysis) and adequate hematologic, renal, and hepatic function. Patients who did not meet the inclusion criteria were excluded from this study. Data were collected from clinical records at the participant institution. All patients involved in this study were Portuguese Caucasians.

Treatment regimen

ASCT was performed on 61 patients in active disease (relapsed/refractory). The preparative regimens and stem cell sources differed between the participants.

Endpoints

The primary endpoint of our study was OS, which was defined as the period between the date of first recurrence diagnosis and death due to the disease/last medical visit. Progression-free survival was defined as the period between the date of first recurrence diagnosis and the date of second recurrence diagnosis. Complete response (CR) was considered normocellular bone marrow (≤ 5% blast), peripheral blood with neutrophils ≥ 1500/μL, absence of any AML sign. Partial response (PR) referred to normocellular bone marrow (6 to 25% blasts) or organic sign of AML. Failure/no response (NR) included patients with clinical disease or bone marrow with ≥ 5% blasts post-transplant. The secondary endpoints were TRM and incidence of acute and chronic GVHD.

Statistical analysis

Chi-squared and Wilcoxon-Mann-Whitney tests were used to compare the frequency distributions of variables such as age, sex, TRM, acute and chronic GVHD rates. We analyzed OS and PFS using a Kaplan-Meier curve. All statistical tests were two-sided, and $p<0.05$ was considered the threshold of statistical significance. All data analyses were performed using IBM® SPSS Statistics, version 22.0 (Chicago, USA).

Results

Patients' characteristics

Table 1 and Table 2 summarize the characteristics of the 61 patients involved in our study. Median age was 61 years (1 to 65) and the majority of patients were older than 18 years. Female gender corresponded to 55.7% of all patients. With respect to French-American-British (FAB) classification, the majority of patients corresponded to M1 (10.3%), M2 (34.5%), M4 (10.3%), and M7 (10.3%). The mainstay of our cohort was to evaluate outcome of AML patients with active disease. Patients with first relapse were 23 out of 59 (39%); second resistance relapse, 7 out of 59 (11.9%); disease not treated, 2 out of 59 (3.4%); primary resistance relapse, 11 out of 59 (18.6%); graft

failure, 11 out of 59 (18.6%); third relapse, 2 out of 59 (3.4%). Approximately half of patients were treated with non-myeloablative regimens (55.7%) and the majority had HLA-related disease (83.9%). Also, 54 out of 61 patients (88.5%) were treated with stem cells from peripheral blood source.

TABLE 1 Characteristics of the patients.

Characteristics	Patients, n	Rate %
Patients analyzed	61	100
Age, years	61 (1-65)	
< 2 years	1/61	1.6
2 – 9 years	8/61	13.1
10 – 17 years	5/61	8.2
18 – 45 years	24/61	39.3
> 45 years	23/61	37.7
Sex		
Male	27/61	44.3
Female	34/61	55.7
FAB type		
M0	2/58	3.4
M1	6/58	10.3
M2	20/58	34.5
M3	1/58	1.7
M4	6/58	10.3
M5	5/58	8.6
M6	1/58	1.7
M7	6/58	10.3
Not classified	11/58	18.9
Missing data	3	

FAB: French-American-British classification.

TABLE 2 Characteristics of disease status, preparative regimens, and transplant-related issues.

Characteristic	Patients, n	%
Disease status		
First no treated relapse	23/59	39
Second resistance relapse	7/59	11.9
Disease not treated	2/59	3.4
Primary resistant disease	11/59	18.6
Progressive disease	1/59	1.7
Graft failure	11/59	18.6
Third relapse	2/59	3.4
First relapse – responsive disease	1/59	1.7
Second relapse – responsive disease	1/59	1.7
Missing data	2	3.3

(Continue)

TABLE 2 (Cont.) Characteristics of disease status, preparative regimens, and transplant-related issues.

Characteristic	Patients, n	%
Conditioning regimen		
Myeloablative	27	44.3
Non-myeloablative	34	55.7
Donor status		
Parents	3	4.9
Siblings	48	78.7
Matched unrelated	10	16.4
HLA		
Related	47/56	83.9
Mismatched	9/56	16.1
Missing data	5	
Stem cell source		
Umbilical cord	1/61	1.6
Bone marrow	6/61	9.8
Peripheral blood	54/61	88.5
Best response		
Complete response	2/23	8.7
Partial response	3/23	13
Failure or no response	18/23	78.3
Not possible to assess*	38	
Censor		
Overall mortality	42/61	68.85
Disease-related mortality	27/61	44.26
Transplant-related mortality	15/61	24.59

HLA: anti-human leukocyte antigen; *these data were not possible to assess due to transplant-related mortality or early disease-related mortality prior to response assessment.

Outcomes: Clinical response, overall survival, and progression--free survival

In terms of clinical response, 2 out of 23 patients (8.7%) presented completed response and 3 out of 23 patients (9.8%) presented partial response. The incidence of relapse was 13 out of 23 patients (56.5%) in the first 90 days post--ASCT; 5 out of 23 (21.7%) in the first year; 3 out of 23 (13%) in the third year; and 2 out of 23 (8.7%) in the fifth year post-ASCT (Table 3). The overall mortality post-ASCT in our set of patients with active disease (relapse or refractory AML) was 42 out of 61 (68.85%): 15 out of 44 patients due to TRM and 27 out of 44 patients due to AML (Table 2). In addition, mortality was higher in the first 90 days post-ASCT, 20 out of 42 (47.6%), than in the first year, 18 out of 44 (42.8%); in the third year, 2 out of 44 (4.7%); and in the fifth year, 4 out of 44 (9.5%) post-ASCT, $p<0.001$. Moreover, median PFS was 3 months (95CI 1.835-4.165) and median OS was 8 months (95CI 3.266-12.734).

Transplant-related mortality, disease mortality, and graft-versus--host disease

Table 3 summarizes data regarding TRM: 9 out of 15 patients (60%) in the 90 days post-ASCT, 4 out of 15 (26.7%) in the first year, 2 out of 15 patients (13.3%) in the third year post-ASCT (p=0.136). Table 3 also shows mortality due to AML: 11 out of 27 patients (40.7%) in the first 90 days post-ASCT; 14 out of 27 (51.83%) in the first year; and 4 out of 27 patients (14.8%) in the fifth year post-ASCT (p=0.005). In spite of the high amount of missing data regarding GVHD status throughout our clinical records, we could verify that 20 out of 47 patients (42.6%) presented with acute grade II–IV GVHD and 11 out of 17 patients (64.7%) presented with chronic grade II–IV GVHD.

Discussion

AML with active disease (relapsed/refractory) remains a challenge for clinicians worldwide, especially in patients previously treated with ASCT.[15] In this setting of patients, prognosis is still poor and this group may benefit from new drug developments and alternative approaches for disease control and delay of a novel relapse.[16,17] In patients with relapsed AML, depending on cytogenetic profile, age and time of first remission, cytarabine-based salvage chemotherapy is sometimes satisfactory.[15,18,19] However, only a few randomized studies address this issue, which thus remains a gray area.[20,21] In second line setting, favorable, intermediate or high intermediate group are suitable to SWOG 9126 protocol (high dose cytarabine, daunorubicin and cyclosporine).[22,23] Our cohort did not provide the cytogenetic profile of the studied population due to the presence of active disease and therefore its irrelevance in this framework. In addition, we included patients since 1994, and, by then, data such as these were not available. ASCT should only be proposed to patients with second remission in case of HLA-matched donor or HLA-mismatched donor depending on age.[24] Patients in the high-risk group and with time of remission less than 6 months should be referred to clinical trials or better supportive care.[25-27] In our cohort, 59 out of 61 patients presented active disease, i.e., patients who had failure in previous treatments, including previous ASCT. Despite that, our population was relatively heterogeneous; the present manuscript reports the experience of a large reference Comprehensive Cancer Center in southern Europe that serves a 3 million habitant area in the North of Portugal. Most of our patients were female and with M1, M2, M4, and M7 FAB classification (Table 1). In addition, the donor sample was mostly family-related and HLA-related, which favored our results (Table 2). In terms of response, we observed 2 out of 23 (8.7%) complete response patients in our cohort and an overall mortality of 68.85% (42 out of 61 patients). This data reflects the disease aggressiveness of our set of patients. However, it also represents relatively good results compared to best supportive care and others approaches previously published in the literature.[26,28] Interestingly, in 2013, Ivanoff et al. reported a cohort of 47 patients with acute/refractory AML, after at least one course of intensive chemotherapy, treated with 5-azacytidine in three different French institutions. The overall response rate was higher (38%) than in our cohort (21.7%) and the median OS (9 months) was also slightly higher than in our study (8 months).[29] However, despite the relatively inferior results compared to the French cohort using 5-azacytidine, our

TABLE 3 Outcomes at 90 days, 1 year, 3 years and 5 years.

Outcomes	90 days	1 year (n, %)	3 years (n, %)	5 years (n, %)	Total (n)	p-value*
Relapse or progression						
Relapse	13/23 (56.5%)	5/23 (21.7%)	3/23 (13%)	2/23 (8.7%)	23	NR
Missing data	-	-	-	-	38	
Overall survival						
Mortality	20/42 (47.6)	18/42 (42.8%)	2/42 (4.7%)	4/42 (9.5%)	42	<0.001
Missing data					0	
TRM						
Mortality – TRM	9/15 (60%)	4/15 (26.7%)	2/15 (13.3%)	0	15	0.136
Missing data	-	-	-	-	0	
Disease mortality						
Mortality – AML	11/27 (40.7%)	14/27 (51.8%)	0	4/27 (14.8%)	27	0.005
Missing data	-	-	-	-	0	

n: number of patients; *Chi-square test; NR: not reported; TRM: transplant-related mortality; AML: acute myeloid leukemia.

cohort provided a high number of patients (61 *versus* 47) and a similar OS to the 5-azacytidine study. Of note, randomized clinical trials are warranted in order to compare the real effectiveness of both approaches in relapsed/refractory AML patients. In our cohort, conditioning regimen data are reported in Table 2 and Table 3. Myeloablative and non-myeloablative regimen were well balanced and applied at the physician's discretion and according to institutional protocol indications.[26] In 2012, Bornhäuser et al.[30] published an interesting phase III trial with 99 patients randomly assigned to receive reduced-intensity regimen and 96 patients to receive standard conditioning regimen. The incidence of non-relapse mortality, relapse incidence at 3 years, PFS at 3 years, and OS at 3 years did not differ significantly between groups.[30] However, grade III-IV toxicities were less common in the reduced intensity group. This trial was stopped early due to a slow inclusion of patients. The authors concluded that reduced intensity conditioning had similar survival outcomes compared to standard regimens with few side effects and thus should be offered to AML patients aged less than 60 years in first complete remission.[30] Therefore, we believe that the conditioning regimen used in our study did not affect the outcomes of our set of patients as a confounding factor. However, for those patients who relapse after ASCT, prognosis is particularly poor with limited reported literature addressing this issue. In our study, the majority of patients relapsed in the first 90 days post-ASCT (56.5%) and a minority relapsed 5 years after ASCT (8.7%) (Table 3). Likewise, mortality in the first 90 days (47.6%) and after 1 year (42.8%) were higher than the mortality at 3 (4.7%) and 5 years (9.5%) ($p<0.001$). This fact could be due to the extreme agressiveness of the disease, high toxicity grades, and difficult clinical management. In addition, TRM tended to occur in the first 90 days post-ASCT (60%) compared to the first (26.7%) and third years (13.3%) post-ASCT ($p=0.136$). In 2013, Lee et al.[9] published a retrospective study in which they reviewed 49 patients with AML who received ASCT and who had subsequently relapsed. The 5-year OS was 31.6% and all three recipients of second ASCT died. Thus, Lee et al. concluded that treatment with curative intent was able to save a minor but important subset of patients with AML who relapsed after ASCT.[9] Notably, even though our patients have been treated with prophylaxis to GVHD with cyclosporine and mycophenolate mofetil, grade II-IV acute GVHD occurred in a considerable number of patients. In 2012, another South Korean study reported a set of 142 consecutive AML patients treated with ASCT who also presented high acute (37.6-53.7%) and chronic (8.9-19.5%) GVHD incidence.[31] In addition, another study[32] by Baron et al. reported that grade III-IV and extensive GVHD had influence in OS of AML patients treated with ASCT. Thus, improvement in prevention and treatment of severe GVHD could have influence in prognosis of those patients, even though it is a difficult issue to overcome.[32]

Conclusion

In conclusion, relapsed/refractory AML post-ASCT remains a very aggressive disease.[26] Many efforts throughout the clinical and scientific communities are underway in order to develop novel strategies for best treatment care.[21,25,27] Nevertheless, there is still a gray area where the highlights in patient's clinical managements with respect to a best therapeutic choice and side-effects control are the mainstay of this field. In our cohort, TRM remains considerable, but ASCT in this setting seems to be a good choice for AML patients with active disease. However, new approaches are needed in order to reduce TRM, GVHD incidence and relapse in this set of patients.

Resumo

Resultados do transplante alogênico de células-tronco em doentes com leucemia mieloide aguda com doença ativa: experiência de um único Centro Oncológico Europeu

Introdução: o transplante alogênico de células-tronco hematopoiéticas (TCTH-alo) representa uma abordagem potencialmente curativa para pacientes com leucemia mieloide aguda (LMA) recorrente ou refratária. Nosso trabalho apresenta o resultado de pacientes com recaída ou doença refratária tratados com TCTH-alo.

Método: coorte retrospectiva incluindo 61 pacientes de 1994 a 2013 com diagnóstico de recidiva/LMA refratária. Os desfechos de interesse foram mortalidade relacionada ao transplante (MRT), incidência da doença aguda e crônica do enxerto contra hospedeiro (DECH), incidência de recaídas, sobrevida livre de progressão (PFS – *progression-free survival*) e sobrevida global (SG). A significância estatística foi considerada para $p<0,05$.

Resultados: a média de idade foi de 61 anos (variação de 1 a 65). A incidência cumulativa de 90 dias, 1 ano e 3 anos de MRT foram de 60%, 26,7% e 13,3%, respectivamente ($p<0,001$). A incidência de recaída foi de 21,7% em 1 ano, 13% em 3 anos e 8,7% em 5 anos. A SG mediana foi estimada em 8 meses (IC 95% 3,266-12,734) e a mediana de PFS, em 3 meses (IC 95% 1,835-4,165).

Conclusão: em nossa coorte, MRT no primeiro ano após o transplante permanece considerável, mas TCTH-alo

nesse cenário parece ser uma boa opção para pacientes com LMA ativa. No entanto, novas abordagens são necessárias para reduzir MRT e recaída nesse conjunto de pacientes.

Palavras-chave: leucemia mieloide aguda, transplante heterólogo, neoplasias da medula óssea.

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Application of prognostic score IPSET-thrombosis in patients with essential thrombocythemia of a Brazilian public service

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Summary

Introduction: In patients with essential thrombocythemia (ET), the vascular complications contribute to morbidity and mortality. To better predict the occurrence of thrombotic events, an International Prognostic Score for Thrombosis in Essential Thrombocythemia (IPSET-thrombosis) has recently been proposed. We present the application of this score and compare its results with the usual classification system.

Method: We retrospectively evaluated the characteristics and risk factors for thrombosis of 46 patients with a diagnosis of ET seen in the last 6 years at Faculdade de Medicina do ABC (FMABC).

Results: Thrombosis in the arterial territory was more prevalent than in venous sites. We observed that cardiovascular risk factors (hypertension, hypercholesterolemia, *diabetes mellitus*, and smoking) were also risk factors for thrombosis ($p<0.001$). Age over 60 years and presence of JAK2 V617F mutation were not associated with the occurrence of thrombotic events. No patient classified by IPSET-thrombosis as low risk had a thrombotic event. Furthermore, using the IPSET-thrombosis scale, we identified two patients who had thrombotic events during follow-up and were otherwise classified in the low-risk group of the traditional classification. Leukocytosis at diagnosis was significantly associated with arterial thrombosis ($p=0.02$), while splenomegaly was associated with venous thrombotic events ($p=0.01$).

Conclusion: Cardiovascular risk factors and leukocytosis were directly associated with arterial thrombosis. IPSET-thrombosis appears to be better than the traditional classification at identifying lower risk patients who do not need specific therapy.

Keywords: essential thrombocythemia, thrombosis, prognosis.

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Introduction

Essential thrombocythemia (ET) is a clonal disorder of the hematopoietic stem cells that is part of the chronic myeloproliferative neoplasms (cMPN).[1] ET diagnosis requires a sustained increase in platelet count (≥ 450 x 103/mm^3) and megakaryocytic hyperplasia. Furthermore, to diagnose ET, there should not be any clinical, pathological or molecular evidence to support the diagnosis of polycythemia vera, myelofibrosis, chronic myelogenous leukemia, myelodysplastic syndrome or reactive thrombocytosis.[2] Among the cMPN, ET is the most common and also has the most favorable clinical course. Survival is about 20 years in patients diagnosed with ET after 60 years of age, and approximately 33 years for younger individuals.[3,4]

Several authors identified molecular alterations in ET such as Janus Kinase 2 (JAK2) V617F mutation in 60% of patients, mutations in the thrombopoietin receptor gene in 4%, and mutations in the calreticulin gene in 15 to 32% of them.[5-7] These findings relate to the pathogenesis of ET and are important to differentiate it from reactive throm-

bocytosis. The absence of these molecular changes, however, does not exclude ET, since 15 to 20% of the patients can be triple negative.[3,8] There is no relationship between mutational status and reduced survival in ET.[3]

The natural history of ET is characterized by the increase in vascular complications and potential risk of progression to acute myeloid leukemia in about 5%, while transformation into myelofibrosis is a little more frequent.[8] Since thrombotic events constitute the main complication of ET and because of its impact on survival, risk stratification for thrombosis is an essential part of the initial clinical evaluation of ET patients. In fact, being over the age of 60 years and having a history of previous thrombosis are two well-established risk factors for thrombosis in these patients. These two factors allowed to stratify ET subjects into a low- (without any of these two risk factors) or a high-risk category (presence of one or both factors).[8-10] Based on this classification, clinical guidelines advise prescribing cytoreductive therapy for high-risk patients in order to avoid thrombotic complications.[9,10]

Recently, the International Prognostic Score for Thrombosis in Essential Thrombocythemia (IPSET--thrombosis) study[10] examined the impact of new risk factors for ET risk-stratification. In fact, IPSET-thrombosis includes, in addition to age and previous history of thrombosis, the presence of JAK2 mutation and cardiovascular risk factors (hypercholesterolemia, hypertension, *diabetes mellitus*, and smoking).

In our study, we applied the IPSET-thrombosis and compared it with the risk stratification system traditionally used in patients with ET based on age and previous history of thrombotic events. Additionally, we sought to identify which risk factors were associated with thrombosis in this population.

Method

This study included 46 patients with a diagnosis of ET established according to the revised criteria of World Health Organization in 2008. We obtained patient information from electronic health records, which include all the clinical data from April 2008 onwards. Data was collected retrospectively, at a single public university institution, Hospital Estadual Mário Covas (HEMC), Faculdade de Medicina do ABC (FMABC).

We analyzed the following data: demographic characteristics (sex, age), clinical and laboratory data (complete blood count at diagnosis and JAK2 mutation), history of previous thrombosis, bleeding or thrombotic events during follow-up. In addition, we analyzed the presence of cardiovascular risk factors such as hypertension, diabetes, current or recent smoking habit, and dyslipidemia. In this study, we considered as thrombotic events: acute myocardial infarction, ischemic stroke, deep vein thrombosis and arterial thrombosis if documented by imaging studies.

We stratified patients according to the traditional classification strata in two groups: low risk and high risk for thrombosis. In this classification, the presence of any one of the two criteria (age ≥ 60 years or previous thrombosis) already defines the risk as high. We also classified patients according to the recent IPSET-thrombosis score that identifies three risk groups: low (0-1 points), intermediate (2 points), and high risk (3-4 points). IPSET-thrombosis considers the following variables: age (1 point), presence of cardiovascular risk factors (1 point), presence of JAK2 V617F mutation (2 points), and a history of thrombosis (2 points).

For statistical analysis, we evaluated associations between categorical variables using Chi-square or Fisher exact tests. In order to assess the presence of significant associations between qualitative and quantitative variables, we used t-Student test. All analyses were carried out with the aid of the SPSS® software version 17.0 (SPSS ® Inc.; Illinois, USA). We considered significant p-values less than 0.05 ($p<0.05$).

Results

Between April 2008 and January 2015, we included 46 consecutive patients with a diagnosis of ET seen at HEMC. The median age at diagnosis was 61 years, with a female predominance. Microcirculatory symptoms were reported by approximately one-third of the patients, headache being the most frequent complaint. Fifteen (32.6%) patients had splenomegaly at diagnosis; 24 (52.2%) had hypertension; 5 (10.9%) had diabetes; 17 (37%) had dyslipidemia; and 8 (17.4%) were smokers. The median white blood cells (WBC) and platelet counts were 9,375/mm^3 and 753,000/mm^3, respectively. Twenty patients (43.5%) had WBC greater than 11,000/mm^3 and 12 (26%) had a platelet count greater than 1 million/mm^3. We tested 42 patients (91.3%) for JAK2 V617F mutation, of which 24 (57.1%) were positive for this abnormality. Table 1 summarizes the clinical and laboratory data of the patients included at diagnosis.

According to the current risk classification, we classified 16 patients (34.8%) as low risk and 30 as high risk for thrombosis at diagnosis (Table 2). Of the 19 patients who had thrombotic events, two had these events before the diagnosis of thrombosis, while 11 presented these events concomitant to the diagnosis of ET, and six had thrombotic events during follow-up.

TABLE 1 Clinical and laboratory characteristics.

Variables	n (%)
Female	31 (67.4)
Age at diagnosis – years, median (range)	61 (16-85)
≥ 60 years	23 (50)
JAK2, n=42	24 (57.1)
Hemoglobin at diagnosis – g/dL, median (range)	14.0 (7.2-18.4)
White blood cells count at diagnosis – x 103/mm^3, median (range)	9.375 (2.04-27.36)
Platelets at diagnosis – x 103/mm^3, median (range)	753 (327-1800)
White blood cells count ≥ 11 x 103/mm^3	20 (43.5)
Platelets ≥ 1,000 x 103/mm^3	12 (26)
Splenomegaly	15 (32.6)
Thrombosis	19 (41.3)
Venous thrombosis, n=19	6 (31.6)
Arterial thrombosis, n=19	13 (68.4)
Bleeding	10 (21.7)

n: number of patients.

TABLE 2 Risk stratification at diagnosis.

Variables	n (%)
Risk stratification – usual classification system, N=46	
Low risk	16 (34.8)
High risk	30 (65.2)
Risk stratification – IPSET-thrombosis, n=44#	
Low risk	12 (27.3)
Intermediate risk	8 (18.2)
High risk	24 (54.5)

n: number of patients; #absence of JAK2 mutation data.

Thirteen patients (68.4%) presented arterial thrombosis and six (31.6%) had venous thrombosis. Of the patients who experienced thrombotic events, two belonged to the low-risk category and 17 to the high-risk, by the classical risk classification (Table 3). Of the 17 patients classified as high risk for thrombosis, 14 (82.3%) were using cytoreductive therapy with hydroxyurea. Applying IPSET-thrombosis, we observed that the low-risk category consisted of only 12 patients; the high-risk group had 24 patients, while eight patients had intermediate risk (Table 2). Two patients, however, could not be classified by IPSET-thrombosis because of the absence of data regarding JAK2 mutations, and both belonged to the high-risk group by the previous classification due to age above 60 years. Of the four patients who were no longer considered low risk, when we applied the IPSET-thrombosis score, two were allocated to the IPSET-thrombosis high-risk category and two to the intermediate-risk category. Interestingly, the two patients reclassified as high-risk by IPSET-thrombosis developed thrombosis during follow-up. Furthermore, considering the parameters of IPSET-thrombosis, no low-risk patient had any thrombotic event during the follow-up period. We observed only one patient categorized as intermediate risk with a thrombotic event detected prior to ET diagnosis, while 18 (75%) of the high-risk category patients had thrombotic complication during follow-up (Table 3).

TABLE 3 Association between risk stratification and thrombosis.

Variables	Thrombosis (n=19)	No thrombosis (n=27)	p
Risk stratification – usual classification system			
Low risk	2 (10.5%)	14 (51.9%)	0.04
High risk	17 (89.5%)	13 (48.1%)	
Risk stratification – IPSET-thrombosis, n=44#			
Low risk	0	12 (48%)	<0.001
Intermediate risk	1 (5.3%)	7 (28%)	
High risk	18 (94.7%)	6 (24%)	

n: number of patients; #absence of JAK2 mutation data.

While evaluating in our population the risk factors that could correlate with thrombosis, we observed that patients with a thrombotic event in the venous territory had significantly more instances of splenomegaly (p=0.01). In relation to arterial thrombosis, risk factors identified were the presence of a cardiovascular risk factor (p<0.001) and high WBC at diagnosis (p=0.02).

Age over 60 years and the presence of JAK2 mutation were not significantly associated with arterial or venous thrombotic phenomena in our study sample (Table 4).

Discussion

Indication of therapy in patients with ET depends on their thrombotic risk.[11-13] Therefore, prognostic systems to classify patients into risk categories are critical because they should receive myelosuppressive therapy if classified as high risk. However, if patients are deemed as having low risk for thrombosis, myelosuppressive therapy can be avoided. Therefore, attempts to improve current risk estimation algorithms include additional variables with potential prognostic impact such as the presence of JAK2 mutation and cardiovascular risk factors.[1,10] As a result, a new model was recently proposed and called IPSET-thrombosis score.[10]

TABLE 4 Association between thrombosis and clinical and laboratory parameters.

Variables	Thrombosis (n=19)	p	Venous thrombosis (n=6)	p	Arterial thrombosis (n=13)	p
≥ 60 years	11 (57.9%)	0.2	4 (66.7%)	0.5	7 (53.8%)	0.9
JAK2, n=42	11 (64.7%)	0.4	4 (66.7%)	0.6	7 (63.3%)	0.3
WBC at diagnosis/mm^3, median	12,325	0.04	9,165	0.4	13,300	0.02
Splenomegaly	9 (47.4%)	0.07	5 (83.3%)	0.004	4 (30.7%)	0.8
Cardiovascular risk factors[#]	17 (89.5%)	0.01	5 (83.3%)	0.4	12 (92.3%)	0.03

n: number of patients; WBC: white blood cells; [#]tobacco use, arterial hypertension, diabetes and hypercholesterolemia (at least one).

In our population, according to the current risk stratifying protocol based solely on age and previous history of thrombosis, 16 patients belonged to the low-risk and 30 to the high-risk group. Applying the IPSET-thrombosis score, we observed a decrease in size of the low-risk group, since two patients were allocated to the intermediate and two to the high-risk group. The two patients who were categorized as high risk by IPSET-thrombosis were not receiving cytoreductive therapy and developed thrombosis during follow-up. Possibly, if we had employed IPSET-thrombosis classification initially, these two patients would have received cytoreductive therapy and perhaps would not have had thrombotic manifestations. It is important to stress that none of the patients considered low-risk based on the IPSET-thrombosis classification had any thrombotic event during our study.

In relation to the high-risk group of the traditional classification containing 30 patients, in only 28 we were able to apply the IPSET-thrombosis score. Twenty-four patients remained in the high-risk category of the IPSET-thrombosis criteria. Of the four patients who were removed from the high-risk group, three were allocated into the low-risk category and one into the intermediate-risk according to IPSET-thrombosis criteria. All these patients were receiving cytoreductive therapy, and none of them presented clinical thrombosis during follow-up. Therefore, we could have spared perhaps two patients from cytoreductive therapy. Furthermore, in our study, the application of IPSET-thrombosis would have changed the risk classification in six (13.6%) and the management of at least four (9.5%) patients. Our results agree with those of Barbui et al.,[10] who also showed that IPSET-thrombosis outperform the traditional risk stratification system.

So far, the indication of treatment for ET is guided by the guidelines of the LeukemiaNet,[14] which is based on the traditional risk stratification.[15] In the future, however, some authors already believe that the IPSET-thrombosis classification will be incorporated to stratify patients with ET.[8,9,16]

The demographic characteristics, clinical and laboratory parameters of our sample of patients are similar to those described in the literature.[3] Hemorrhagic events were less prevalent than the thrombotic ones also in agreement with previous studies.[17-19] Additionally, in agreement with other authors, we found a significant association between splenomegaly and venous thrombosis, and cardiovascular risk factors and a high WBC with arterial thrombosis.[1,7,8,10,16]

Interestingly, age ≥ 60 years in our cohort of patients was not a significant risk factor for thrombosis. The lack of correlation between older age and thrombosis was also seen in other recent studies such as those of Lekovic et al.[1] and Montanaro et al.[20] The presence of JAK2 mutation was not significantly associated with thrombosis in our study, contrary to information well-established in the literature.[14,16,20-22] We believe that our small sample size may explain why we found no correlation between thrombosis risk and the presence of JAK2 mutation.

Our study has limitations. It is retrospective and included a small sample of ET patients who had a relatively short follow-up. However, even considering the shortcomings mentioned above, we could clearly see that the risk classification afforded by IPSET-thrombosis could improve the therapeutic management of ET in about 10% of patients.

Resumo

Aplicação do escore prognóstico IPSET-trombose nos pacientes com trombocitemia essencial em um hospital público brasileiro

Introdução: em pacientes com trombocitemia essencial (TE), complicações vasculares contribuem para morbidade e mortalidade. Para melhor predizer a ocorrência de eventos trombóticos, um escore prognóstico internacional de trombose para TE (IPSET-trombose) foi recentemente desenvolvido. Apresentamos aqui a aplicação des-

se escore e comparamos seus resultados com o sistema de classificação usual.

Método: avaliamos retrospectivamente as características e os fatores de risco para trombose em 46 pacientes com diagnóstico de TE que foram atendidos nos últimos 6 anos na Faculdade de Medicina do ABC.

Resultados: trombose em território arterial é mais prevalente que em sítio venoso. Observamos que fatores de risco cardiovascular (hipertensão, hipercolesterolemia, *diabetes mellitus* e tabagismo) foram considerados fatores de risco para trombose (p<0,001). Idade > 60 anos e presença de mutação JAK2 V617F não se associaram à ocorrência de eventos trombóticos. Nenhum paciente classificado como baixo risco pelo IPSET-trombose apresentou evento trombótico. Quando comparado à classificação de risco tradicional, IPSET-trombose foi capaz de identificar dois pacientes que evoluíram com trombose no seguimento e estavam categorizados no grupo de baixo risco. Leucocitose ao diagnóstico foi mais prevalente em pacientes que apresentaram trombose arterial (p=0,02), e esplenomegalia, entre aqueles com evento trombótico venoso (p=0,01).

Conclusão: fatores de risco cardiovascular e leucocitose se associaram de forma direta com trombose arterial. IPSET-trombose parece ser melhor que a classificação tradicional na identificação de pacientes de baixo risco que não precisam de terapia específica.

Palavras-chave: trombocitemia essencial, trombose, prognóstico.

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Interest in research among medical students: Challenges for the undergraduate education

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Summary

Introduction: In recent decades, there has been a reduction in the number of graduates from medical schools who choose to pursue a career in scientific research. That has an impact on the profile of graduates, since medical education depends on understanding the formation of scientific evidence. The construction of new knowledge is also hampered by the reduction of medical scientists, whose clinical experience with patients provides an essential step towards medical science evolution.
Objective: The present cross-sectional study sought to identify the interest in research among medical students from a federal university in southern Brazil.
Method: Medical students from a federal university were asked to respond to a self-administered questionnaire that sought to identify the level of knowledge about the importance of scientific research in medical training, and the interest of this population in this element of their training.
Results: 278 medical students from the first to the sixth year responded to the questionnaire, and 81.7% stated their interest in medical research. However, only 4.7% of respondents considered research as first in degree of importance to their medical training. The variable "interest in research" showed no statistically significant association with age, gender, presence of physicians in the family, or other prior college courses.
Conclusion: Although interest in research is clearly present among the students, this is still an underexplored element among the population studied. The incorporation of research in the learning process depends on stimulus and guidance until it becomes culturally consolidated as an essential element of the medical training.

Keywords: medical schools, biomedical research, medical education, motivation, learning, career choice.

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Introduction

Continued progress in medicine is fundamentally dependent on the training and performance of scientists dedicated to research in the health sciences. Although not limited to such, the participation of medical scientists in research in the medical field represents a valuable contribution, given the clinical orientation of the training given to such professionals. The problem is that even in countries with a renowned calling for science, such as the USA, it is increasingly less common for doctors to decide to focus their careers on scientific activity.[1] A formula that appears to contribute to solving this problem is the early inclusion of these future professionals in the world of scientific research during their academic training. Fur-

thermore, the intersection between studying for medical practice and academic scientific activity allows the future professional to be placed on a path of cooperative participation in the process of constructing their own medical training, contributing to the development of both their clinical and their scientific skills.

The importance of scientific research for the physician goes beyond their direct involvement with this activity. Modern medicine is based on the search for evidence leading to a specific diagnosis and, for this reason, all physicians should know about research in order to understand the process for the formation of evidence.[2] This close relationship is the basis for certain ideas stating that research fundamentals should be presented during the medical student's undergraduate period, and not just as another career option for those who have obtained their MD.

As most students entering medical school are unaware of how scientific research functions and its importance, interest in scientific activity tends to emerge during the course. The factors leading to the emergence of this interest are unknown. However, the influence of a scientific methodology course[3] and the opportunity to participate in scientific research during the entire degree tend to produce more researchers than limited participation during part of the higher education course.[4]

Based on these considerations, this study has the purpose of describing the interest in research among medical students at a federal university in Brazil, aimed at enhancing the educational planning of scientific methodology as subject and discussing its importance to medical training.

Method

This is a cross-sectional study in which a questionnaire was applied to medical students at the Federal University of Health Sciences of Porto Alegre. All students from the first to the sixth year of the course were considered eligible to participate. Participation was voluntary, after an explanation about the research and signing the informed consent form. The project was approved by the institution's Ethics Committee (project number 10-646).

To calculate the sample size, interest in research among freshmen was estimated at approximately 20%, while among graduates this figure might possibly be higher, at 60%. For this difference, considering an alpha of 0.05 and a beta of 0.20, it would be necessary to study 28 students from each course year. A safety margin of 20% was added to compensate for possible losses.

The questionnaire contained questions about: the respondent's stage of the course; what would be the most important item for medical training in the respondent's opinion: practice, theory or research; if they had been in a different undergraduate program previously; if they had had contact with scientific research while in the other course; if there were physicians in their family; if any relative had postgraduate academic titles; if the respondent worked or intended to work with scientific research during the undergraduate program; if they intended to work with scientific research after graduation; if they intended to pursue an academic career; if they had any published scientific studies. Collection of data was held during the academic months of May to September 2011, by supervisors in the scientific methodology course trained specifically for this purpose.

The data was analyzed using a specific statistics program (SPSS for Windows). Tables were made of the absolute frequencies and percentages for characterization of the sample. The continuous variables were described using means and standard deviations, or medians and interquartile ranges. The comparisons between groups were undertaken using chi-squared test, Fisher's exact test, linear correlation, or t-test according to the variables compared. The values considered significant were those with $p<0.05$.

Results

The research population consisted of 278 medical students from the Federal University of Health Sciences of Porto Alegre. The average age of the population was 22.26 years, with a standard deviation of 2.898. One hundred and fifteen (115) participants were male and 163 were female. Students from all six years of the medical course participated, distributed according to the figures shown in Table 1. Most of the participants originate from the state of Rio Grande do Sul. The distribution of origins can be seen in Table 1.

As observed in the data presented in Table 2, 81.7% of the respondents declared they had an interest in research during their training. A percentage of 60.8% stated they had an interest in continuing research activities after graduation, 58.6% stated they had a desire to pursue an academic career and 10.4% declared that they already had a scientific publication.

When asked to rank the importance of the items "research", "theory", and "practice" for the medical training, 4.7% of respondents put research in first place. 77.7% of the sample chose practice as the pillar of greatest importance to their training.

TABLE 1 Demographic characteristics of the population.

Characteristic	Value
Age (years)	22.26±2.898
Gender	
Male	115 (41.4%)
Female	163 (58.6%)
Year	
1st	43 (15.5%)
2nd	45 (16.2%)
3rd	72 (25.9%)
4th	57 (20.5%)
5th	32 (11.5%)
6th	29 (10.4%)
Have you already taken a different undergraduate course?	
Yes	68 (24.5%)
No	210 (75.5%)
Do you have relatives who are physicians?	
Yes	58 (20.9%)
No	196 (70.5%)
Did not respond	24 (8.6%)
Student's state of origin	
Rio Grande do Sul (RS)	191 (68.71%)
São Paulo (SP)	31 (11.15%)
Santa Catarina (SC)	18 (6.47%)
Paraná (PR)	10 (3.6%)
Minas Gerais (MG)	8 (2.88%)
Goiás (GO)	7 (2.52%)
Distrito Federal (DF)	3 (1.08%)
Alagoas (AL)	1 (0.36%)
Espírito Santo (ES)	1 (0.36%)
Mato Grosso do Sul (MS)	1 (0.36%)
Mato Grosso (MT)	1 (0.36%)
Piauí (PI)	1 (0.36%)
Rondônia (RO)	1 (0.36%)
Did not respond	4 (1.44%)
Total	278 (100%)

TABLE 2 Interest in research.

Question	N
Do you work or plan to work with research during your undergraduate program?	
Yes	227 (81.7%)
No	50 (18%)
Did not respond	1 (0.4%)
Do you plan to continue working with research after graduation?	
Yes	169 (60.8%)
No	71 (25.5%)
Did not respond	38 (13.7%)
Do you intend to pursue an academic career?	
Yes	163 (58.6%)
No	110 (39.6%)
Did not respond	5 (1.8%)
In your opinion, which is the most important for medical training: "research", "theory" or "practice"?	
Research	13 (4.7%)
Theory	49 (17.6%)
Practice	216 (77.7%)
Do you have any studies published in a scientific journal?	
Yes	29 (10.4%)
No	247 (88.8%)
Did not respond	2 (0.7%)

The data presented in Figure 1 indicate the variation between the 6 years of the medical course in terms of interest in research during and after the course, respectively.

Considering the variables "research during the undergraduate program" and "interest in research after the course", it was noted that people with an interest during the course also reported that they intend to maintain this interest after they graduate ($p<0.001$). The interest during the undergraduate program variable did not present a statistically significant association with age ($p=0.755$), gender ($p=0.118$), presence of physicians in the family ($p=0.387$) or other prior higher education course ($p=0.314$). Similarly, the variable interest in research after graduation also showed no significant associations with the variables age ($p=0.972$), gender ($p=0.744$), presence of physicians in the family ($p=1.00$) or other prior higher education course ($p=0.115$).

Discussion

In this cross-sectional study with students from all years of the medicine course at the Federal University of Health Sciences of Porto Alegre, it was noted that a large proportion of students is interested in conducting research activities during their training and continuing these activities after the conclusion of the course. More than half of the students want to pursue an academic career. Some of the respondents are already effectively involved in the scientific process, and a significant proportion of undergraduates (around 10%) declared that they already had a scientific publication.

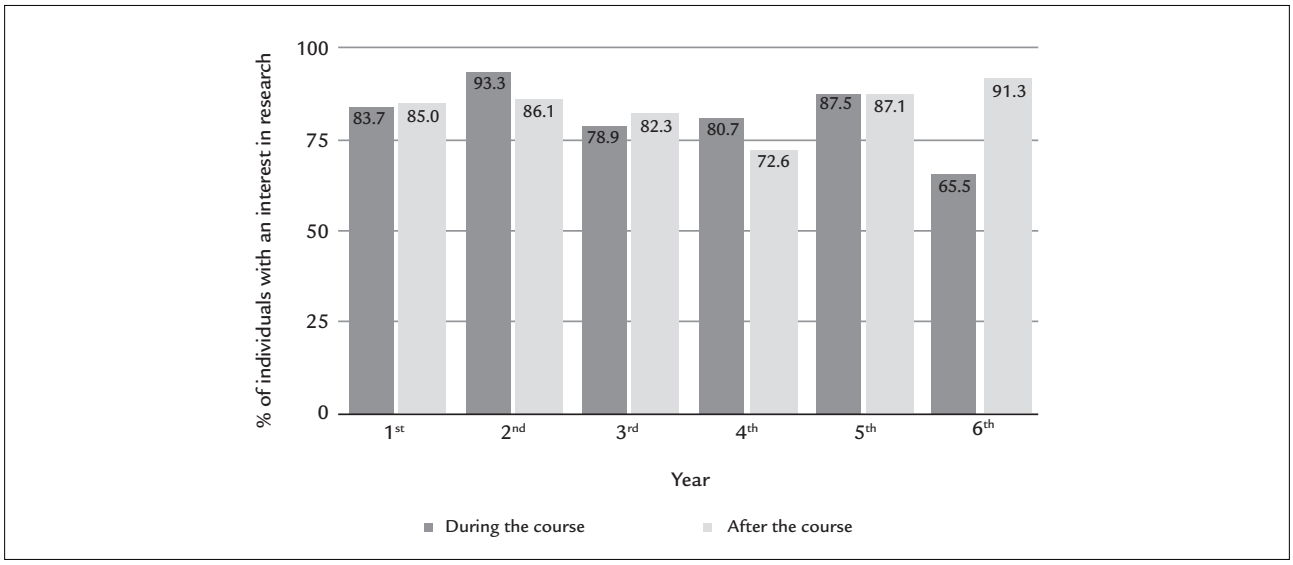

FIGURE 1 Proportion of respondents with an interest in research.

The advancement of scientific studies in the biomedical areas has increased the need to recruit more and more health professionals to the area of research.[5] Preliminary studies demonstrate high levels of interest in research among medical students, with the intention of integrating scientific activity with their curricular activity. However, many of them do not understand the benefits of research during their training period.[6] Despite growing interest over time during the medical course,[3] a decreasing number of new medical researchers have effectively been verified in recent years.[7]

This verification contrasts with the research's findings, which indicate a high level of interest in an academic career among students. This apparent discrepancy may be explained by specific characteristics of the university where the research was conducted. Since the beginning of the process that culminated in the transformation of the Federal University Foundation of Medical Sciences of Port Alegre into the Federal University of Health Sciences of Porto Alegre, in 2008, several other courses in the health area were added to the institution. With the addition of these new biomedical science courses, such as pharmacy, physiotherapy, and nursing, there was a boom in the field of research within the university, with the opening of new, modern research laboratories, in addition to the possibility of dialog and partnerships between various academic courses. This event has probably changed the profile of our medical school graduates, traditionally a professional more inclined to medical practice than research activity, as shown in the studies referenced above.

In the present study, we noted that most of the medical students of the Federal University of Health Sciences of Porto Alegre who responded to the survey stated they had an interest in research activities. The initial hypothesis that estimated interest to the order of 20% among freshmen and interest in 60% of graduating students was not confirmed. Instead, a more equitable and homogeneous distribution was found throughout the course, without significant fluctuations.

We also noted that a portion of the respondents to the survey already had published scientific studies. Depending on the characteristics of certain studies in the health area, some of which were undertaken over a long period of time and therefore sometimes involving a rotating team of researchers, we should also consider that other students who were possibly participating in research projects at the time the questionnaire was applied could have their work published by the end of their undergraduate program, or even afterwards.

Most of the students who participate in scientific studies choose research in clinical areas.[5] Previous studies have already shown that medical students in the first years, who are studying basic sciences, are more eager to participate in clinical trials than students carrying out medical rotations.[8] Payment is also an important motivational factor for research.[5,8]

For Ley and Rosenberg, there are three obstacles for medical students pursuing an academic career: accumulated debts (with student loans); the long training period; and uncertainty of success.[9] From the first factor, we can

derive the urgency of financial independence, in contrast to the second factor, namely the long path required for building a solid academic career. Considering this, clinical practice seems to be justified as a first-choice option, to the detriment of an academic career, which thereby lacks new aspirants. Thus, there is a need for governments and institutions to develop or improve incentive and benefit programs in order to elicit more physicians as candidates for an academic career.

Some medical students consider scientific research crucial for their future medical activity,[6] with 80% of them stating their interest in putting into practice what they learned in their respective study has increased. Better guidance for medical students to conduct scientific studies is also considered crucial, so that they can publish their work and maintain their interest in science.[10] Even those who do not wish to pursue an academic career can benefit from the experience of scientific research in their professional practice given that nowadays professionals who know how to search scientific information and to critically evaluate it are essential.

Analyzing the interest in research seen in the different stages of the medical course, there is a relatively homogeneous and high distribution across all years. This information seems relevant to us, considering that academic research is traditionally an optional and voluntary element in medical training in Brazil, and that the compulsory curricular demands include a high amount of theoretical subjects in the early years, corresponding to the basic and clinical cycles and to mandatory internships, during the internship cycle, during the last years of medical training.

However, the positive data showing the interest in research contrast with the widely known fact that there is a shortage of medical professionals that effectively end up pursuing an academic career. Compared to curricular academic activity, research activity requires proactive effort from the student, as well as greater independence. However, although this independence is a desirable attribute for a researcher, it should be included in a scenario that takes into consideration that the student is still an apprentice and, as such, requires constant direction, especially during their freshman year and while being introduced to research. Therefore, stimulating the emergence of new researchers requires the implementation of affirmative and comprehensive action in order to direct the student at early stages.

Targeted actions have been tested worldwide in order to deal with the declining interest in scientific careers within the medical world. At a faculty of Queen's University in Canada, a study has shown that the inclusion of a compulsory elective subject called Critical Investigation in the students' medical curriculum led to positive results in the motivation of such students in relation to research activities.[7] The results of a similar study at Zagreb University of Medicine in Croatia are in accord, showing that the experience of a compulsory subject, The Principles of Scientific Research in Medicine, led to a positive impact on students' perception in relation to science and scientific research.[11]

In Brazil, similar initiatives have been implemented with the aim of encouraging national scientific production. Examples of this are the Science without Borders and Young Talents for Science programs, both implemented by the Brazilian federal government through its research funding agencies, with the purpose of investing in the creation of future researchers, also in the medical field.

Analyzing the results of our research involving this specific population, the importance given to research for medical training draws our attention, as it has been put in last place on a scale of priorities that also include theory and practice as instruments for training. Only 4.7% of respondents put research in the first place in level of importance to their training. It seems to us that this is in accordance with a technicist trend within medical education,[12-14] in which the incorporation of technology and the ability of the future doctor to understand it have replaced more intuitive medicine focused on medical history, whose investigative process depends more on method than technology. This impression is corroborated by the fact that the vast majority chose practice as the pillar of greatest importance to their training.

An interest in research does not necessarily imply a choice for a future academic career. When considered well, an interest in research means understanding its importance to medical training, which, in addition to technique, is also questioning and investigative. Furthermore, it means considering a commitment to active participation in educational training itself.

Technicist medicine seems to want to dispense with training based on individual discoveries through research in favor of training that enables understanding of ultramodern tests and technicized diagnostics. Here, concern is not for the advent of technology, which is always welcome in order to assist health professionals, but for gradual abandonment in the training of future doctors dedicated to scientific research, which is important not only to universities but also to medical outpatient clinics and individual practices.

During the analysis of the data collected for the research, the data were cross-referenced in order to find

variables that could elucidate the reasons that lead to an interest in research. Among these potential variables, the data relating to an interest in research were cross-referenced with: the gender of the respondent; any previous university degree; the existence of physicians among relatives; and the existence of researchers among relatives. No statistically valid relationship was found in the cross-referencing of the data collected from participating medical students.

The absence of a specific determinant of interest in research reinforces the importance of the issue, given that it implies that occasional factors must be multiple and scattered. It can also be implied that such factors are probably of an essentially individual nature. Thus, a project for encouraging research would also possibly have to operate in a manner that is more personalized to the individual characteristics and demands of the students.

Furthermore, it seems to us that in the diversion away from the career of researcher there is an underlying sociocultural element that identifies the physician mostly as the operator of medicine and less as its developer or instigator. This divergence between clinical practice and investigative practice becomes more and more relevant to the extent in which the benefits of modern medicine, such as genetic and molecular approaches to diseases, require an investigative capacity from the physician within the clinical assessment of such,[15] meaning that advances made by research may cut across the distance between the laboratory and the doctor's office.

Although playing a fundamental role for the initial guidance of those students already inclined toward scientific research, introductory courses specifically aimed at encouraging and focusing on research, such as scientific methodology, do not appear to adequately fulfill the role of stimulating the vocation for research by itself. It seems to us that a change to the content of the subjects in the medical degree, that is, including greater focus on the development of investigative skills, could contribute much to the awakening new scientific vocations among the students.

Limitations of the study

The data were collected using a non-validated, self-applied questionnaire. The sample was comprised of respondents who volunteered to the survey, which in itself may have selected individuals already predisposed to the field of research. However, as the objective of this work was to provide an overview about interest in research, and given that we achieved a number of respondents according to that specified initially in the methodology, these possible limitations do not negate the value of the study's findings.

Conclusion

The study conducted showed that medical students at the Federal University of Health Sciences of Porto Alegre are inclined toward research activity. However, it was not possible to identify which factors hold an influence on this inclination. This circumstance poses a challenge for planning actions focused at stimulating research, and suggests that whenever working on specific aspects is impossible, the approach should perhaps begin with an educational plan directed to research, in which the student is monitored in a serial manner throughout their training, with permanent incentives and the establishment of goals, ranging from an understanding of the importance of the subject up to effective publication of a scientific work.

Resumo

Interesse em pesquisa entre estudantes de medicina: desafios para a graduação

Introdução: nas últimas décadas, diminuiu o número de egressos de escolas médicas que optam por se dedicar à pesquisa científica. Isso tem impacto sobre o perfil dos profissionais formados, já que o aprendizado médico é indissociável da compreensão da formação da evidência científica. A formação de novo conhecimento é prejudicada com a redução de pesquisadores médicos, cujo contato clínico com os pacientes fornece etapa essencial na evolução da ciência médica.
Objetivo: o presente estudo transversal buscou identificar o interesse em pesquisa entre estudantes de medicina de uma universidade federal do Sul do Brasil.
Método: estudantes de medicina de uma universidade federal foram convidados a responder um questionário autoaplicável que buscou identificar o nível de conhecimento sobre a importância da pesquisa científica na formação do médico, bem como o interesse dessa população por esse elemento da formação.
Resultados: 278 estudantes de todas as séries do curso de medicina responderam ao questionário, e 81,7% declararam interesse pela pesquisa científica. Contudo, apenas 4,7% dos entrevistados consideraram a pesquisa em primeiro lugar em grau de importância para a sua formação. A variável "interesse em pesquisa" não apresentou associação estatisticamente significativa com idade, gênero, presença de médicos na família ou outro curso superior prévio.

Conclusão: embora o interesse em pesquisa esteja claramente presente entre os estudantes, este é um elemento da formação ainda pouco explorado pela população estudada. A incorporação da pesquisa na rotina do aprendizado depende de estímulo e orientação até que esteja culturalmente consolidada como matriz essencial da formação.

Palavras-chave: escolas médicas, pesquisa biomédica, educação médica, motivação, aprendizagem, escolha da profissão.

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Longitudinal assessment of nutritional risk in patients under chemo or radiotherapy

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Summary

Objective: To compare nutritional risk in adult patients undergoing chemotherapy and radiotherapy in the beginning, middle, and end of oncologic treatment.
Method: This prospective, comparative study included 83 adult patients, 44 undergoing chemotherapy (CT group) and 39 undergoing radiotherapy (RT group) at an oncology treatment center. Nutritional risk was determined by NRS-2002 in the beginning, middle, and end of therapy. Statistical analysis was performed using Statistica 8.0 software.
Results: No differences in food intake or body mass index were observed between the CT (24.6±4.8 kg/m²) and RT groups (25.0±5.9 kg/m², p=0.75). Weight loss in the preceding 3 months was detected in 56.8% of CT group and 38.5% of RT group (p=0.09). The weight loss percentage compared with the usual weight within 3 months was greater (p<0.001) in the CT (11.4±6.5%) than in the RT group (3.9±6.8%). In the beginning of treatment, we observed high percentages of patients at moderate (18.2 *vs.* 15.4%, p=0.73) and high nutritional risk (61.4 *vs.* 48.7%, p=0.25), with no statistical difference between the CT and RT groups, respectively. During therapy, the nutritional risk remained unaltered in both groups. In the end of therapy, the majority of patients were at moderate (18.2 *vs.* 12.8%, p=0.50) or severe nutritional risk (50.0 *vs.* 51.3%, p=0.91), in the CT and RT groups, respectively, regardless of the type of oncologic treatment.
Conclusion: The high prevalence of patients at moderate or high nutritional risk in the beginning of treatment indicates the need for an early and continuous follow-up of the nutritional status of patients undergoing oncologic treatment.

Keywords: chemotherapy, radiotherapy, nutritional assessment, neoplasms, malnutrition, nutritional status.

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Introduction

The prevalence of malnutrition in cancer patients ranges from 30 to 80%[1] depending on the criteria used to define malnutrition, the site, type, and staging of the tumor, as well as the treatment's modality.[2] Malnutrition increases morbidity, mortality, costs to health and may cause intolerance and inadequate response to anti-cancer therapy.[3] Identifying and addressing the nutritional problems are essential for an early and proper treatment of patients undergoing cancer therapy. However, nutritional assessment is not a priority in cancer services so that malnutrition is often undiagnosed.[4,5]

Routine nutritional assessment is recommended to identify patients at nutritional risk, and uses validated tools for cancer patients.[5] The nutritional screening tools were created to identify quickly and easily individuals

in various stages of nutritional deficiency. One of these tools is the Nutritional Risk Screening-2002 (NRS-2002), recommended by the European Society for Parenteral and Enteral Nutrition (ESPEN).[6] The NRS-2002 can be applied to patients with various morbid conditions,[7] including cancer.

Worsening of nutritional status during the oncological therapy has been described[8] as a result of a combination of factors related to the tumor and toxicity of the treatment itself.[9] In this context, the objective of this study was to compare the nutritional risk in adult patients undergoing chemo and radiotherapy at the beginning, middle, and at the time of completion of cancer treatment.

Method

This prospective, descriptive study was approved by the Research Ethics Committee (Process 15822/2011) and conducted in the cancer treatment unit of a Brazilian public university hospital. Data collection was done by two trained evaluators from a convenience sample consisting of adult patients who started cancer treatment, excluding those under simultaneous chemo and radiotherapy. All subjects who agreed to voluntary participate in the study were included, even those with physical, cognitive or emotional disabilities, which could hinder the communication between patient and evaluator.

The sample included 83 patients with cancer in the upper gastrointestinal tract (n=14), lower gastrointestinal tract (n=12), head and neck (n=12), bronchi or lungs (n=11), breast (n=11), urological (n=10), and other tumor sites (n=13). The subjects were grouped according to oncological treatment modality, with 44 patients undergoing chemotherapy (CT group) and 39, radiotherapy (RT group). There was no statistical difference in age (59.8±15.7 *vs.* 59.8±12.7 years, p=0.98) or percentage of male gender (54.6 *vs.* 69.2%, p=0.17) between the CT and RT groups, respectively. The distribution of individuals according to tumor site, habits, and living conditions was similar between groups, except for the largest number of people with alcohol abuse history among those treated with radiotherapy (22.7 *vs.* 46.1%, p=0.02).

The volunteers were evaluated based on the NRS-2002 protocol, which analyzed body mass index (BMI), recent weight loss history, changes in food intake and severity of the underlying disease.[6] Body weight was measured on an electronic scale for adults (Welmy® W200), with an accuracy of 100 g and a maximum capacity of 200 kg. Patients were weighed standing up straight, barefoot and with minimal clothing. Height was obtained from records in the patient's chart or measured using a graded metal rod with a maximum length of 2.0 m and accuracy of 0.5 cm. The BMI was calculated based on the formula: weight in kilograms divided by height in meters squared (kg/m^2). The patient and/or his guardian were asked about any unintentional weight loss in the prior 3 months and changes in food intake in the week before the evaluation.

Normal nutritional status was defined as the absence of weight loss < 5% and changes in food consumption. We considered low nutritional risk when the patient had one of the following criteria: a) weight loss > 5% in 3 months; b) food intake below the range 50 to 75% of normal needs in the previous week. Moderate nutritional risk was if the patient had two of the following criteria: a) weight loss > 5% in 2 months; b) BMI between 18.5 and 20.5 kg/m^2 in the presence of impairment of general condition; c) food consumption from 25 to 50% of normal needs in the previous week. And severe nutritional risk was if the patient had three of the following criteria: a) weight loss > 5% in 1 month (or > 15% in 3 months); b) BMI < 18.5 kg/m^2 associated with overall poor health; c) food intake below 25% of normal needs in the previous week. The final score was obtained by adding an additional point, considering that all patients had a diagnosis of cancer. According to the NRS-2002 questionnaire guidelines, we added a point to the previous items for patients older than 70 years.

The nutritional screening protocol was applied by two trained evaluators on three occasions, namely the first day, the middle, and the end of the oncologic treatment. Given that the average duration of chemotherapy was 90 days, the patients in the CT group were reevaluated in the 45th and 90th day. The radiation scheme included five weekly sessions for 6 weeks, so that patients in the RT group were reevaluated in the 15th and 30th day after the start of cancer treatment. In addition, at the beginning of treatment, the patients were asked about the number of daily meals, the consistency of the preferred food preparations, and changes in the pattern of consumption of food groups.

Statistical analysis was performed using Statistica software (version 8.0; StatSoft Inc, Tulsa, OK, USA). The comparative analysis was made by Student's t test. Numerical data are presented as mean and standard deviation; categorical data are presented as frequency. In all analyzes, the significance level was 5%.

Results

The initial assessment showed that both the anthropometric data and changes in food intake were similar between groups (Table 1). Compared to the RT group, a larger number of patients in the CT group showed weight loss in the first and second months before the start of

cancer treatment. Considering the individuals who lost weight, only, the percentage of weight loss was higher in the CT group in the first, second and third months before treatment. Analyzing the two groups together, 48.2% of patients had weight loss greater or equal to 5% over 3 months prior to evaluation.

TABLE 1 Criteria evaluated at the beginning of the study, according to oncological treatment modality, based on the questionnaire NRS-2002.

	CT group (n=44)	RT group (n=39)	p-value
Anthropometric data			
Usual weight (kg)	72.3±14.3	71.2±15.6	0.72
Current weight (kg)	66.8±15	68.5±16.8	0.61
Height (m)	1.64±0.09	1.65±0.08	0.52
BMI (kg/m²)	24.6±4.8	25±5.9	0.75
History of weight loss in 3 months			
Cases [n (%)]	25 (56.8)	15 (38.5)	0.09
Weight lost (kg)	7.9±4.6	2.6±4.3	<0.001
Loss percentage (%)	11.4±6.5	3.9±6.8	<0.001
History of weight loss in 2 months			
Cases [n (%)]	12 (27.3)	5 (12.8)	<0.001
Weight lost (kg)	5.8±5.3	0.5±1.4	<0.001
Loss percentage (%)	6.2±3.8	0.8±2.3	<0.001
History of weight loss in 1 month			
Cases [n (%)]	20 (45.4)	7 (17.9)	0.008
Weight lost (kg)	2.5±2.1	0.7±1.9	0.002
Loss percentage (%)	3.4±2.3	0.9±2.5	<0.001
Food intake compared to the usual			
> 75% [n (%)]	22 (50)	22 (56.4)	0.56
51 to 75% [n (%)]	10 (22.7)	3 (7.7)	0.06
26 to 50% [n (%)]	8 (18.2)	11 (28.2)	0.28
0 to 25% [n (%)]	4 (9.1)	3 (7.7)	0.82

BMI: body mass index; CT: chemotherapy; RT: radiotherapy.

TABLE 2 Nutritional risk in patients undergoing chemo or radiotherapy, according to the period of cancer treatment.

	CT group (n=44)	RT group (n=39)	p-value
Beginning of treatment			
Low risk	9 (20.4%)	14 (35.9%)	0.12
Moderate risk	8 (18.2%)	6 (15.4%)	0.73
Severe risk	27 (61.4%)	19 (48.7%)	0.25
Middle of therapy			
Low risk	15 (34.1%)	14 (35.9%)	0.86
Moderate risk	7 (15.9%)	8 (20.5%)	0.59
Severe risk	22 (50%)	17 (43.6%)	0.56
End of therapy			
Low risk	14 (31.8%)	14 (35.9%)	0.69
Moderate risk	8 (18.2%)	5 (12.8%)	0.50
Severe risk	22 (50%)	20 (51.3%)	0.91

CT: chemotherapy; RT: radiotherapy.

TABLE 3 Features of food intake in patients undergoing chemo or radiotherapy.

	CT group (n=44)	RT group (n=39)	p-value
Number of meals	4.0±1.0	4.2±1.1	0.42
Food consistency			
Solid [n, (%)]	40 (91.0)	32 (82)	0.91
Pasty [n, (%)]	2 (4.5)	2 (5)	0.57
Liquid [n, (%)]	2 (4.5)	5 (13)	0.37
Reduced intake of food groups			
Green leafy vegetables [n, (%)]	11 (25.0)	3 (7.7)	0.03
Other vegetables [n, (%)]	5 (11.4)	4 (10.3)	0.87
Cereals [n, (%)]	9 (20.4)	6 (15.4)	0.55
Meat [n, (%)]	11 (25.0)	11 (28.2)	0.74
Dairy [n, (%)]	4 (9.1)	2 (5.1)	0.48

CT: chemotherapy; RT: radiotherapy.

In the longitudinal comparison within each group (beginning, middle and end), there was no difference in the occurrence of mild, moderate or severe nutritional risks among the patients in the two study groups (Table 2). The NRS-2002 reveals a high prevalence of moderate or high nutritional risk in the first (79.6 *vs.* 64.1%), second (65.9 *vs.* 64.1%), and third (68.2 *vs.* 64.1%) assessments among the patients in the CT and RT groups, respectively.

There was no statistical difference in the number of daily meals and food consistency among the groups (Table 3). Patients undergoing chemotherapy reported a reduction in the consumption of vegetables. When asked about a reason for this change, patients reported having received guidance from their treating physician, aimed at preventing infections related to microbiological contamination of raw foods. In both groups, about 25% of patients reported a reduction in meat intake, justified by the difficulty in chewing, nausea and vomiting, and changes in taste and smell.

Discussion

Although BMI and history of reduction in food intake were similar at baseline, this study documented the highest percentage of weight loss in patients undergoing chemotherapy compared to those under radiotherapy. At

baseline, moderate or severe nutritional risk scores were similar and high in both groups, remaining relatively constant until the end of treatment. The patients consumed four meals daily, preferably eating solid foods and reducing meat consumption. The patients undergoing chemotherapy showed greater reduction in consumption of vegetables compared to those treated with radiotherapy.

In this study, a large number of patients experienced moderate or severe nutritional risk at the start of chemotherapy (79.6%) and radiotherapy (64.1%). In the sequential evaluation, the patients maintained this nutritional risk until the end of treatment, so that severe risk occurred in 50% of cases under chemotherapy and 51.3% of those undergoing radiotherapy. The prevalence of compromised nutritional status in our study is consistent with results of studies by other researchers.[10-13] Based on the NRS-2002, severe nutritional risk was documented in 50% of patients before the start of cancer treatment[13] and in 76% of individuals with various types of cancers.[11] Among patients recently hospitalized with various types of cancer, the use of Patient-Generated Subjective Global Assessment protocol showed varying degrees of malnutrition in about 70% of cases.[10,12] In Australia, the risk of malnutrition was documented in 64% of patients admitted to a public hospital specializing in cancer treatment,[14] but only in 17% of cases treated in an outpatient oncology unit.[5]

Female gender and age were associated with nutritional risk.[13] Patients hospitalized with cancer have higher nutritional risk rates[10,12] than those seen in the oncologic treatment center.[5,8] There is a difference in the prevalence of severe malnutrition, ranging 17 to 43% of the cases evaluated. Such differences may be attributed to different tumor sites, as seen in the study by Fernández-López (2013),[12] which included patients with tumors in the head and neck, pancreas, lung, and lower and upper gastrointestinal tract, while Bauer et al. (2002)[10] assessed patients with lymphoma, myeloma, sarcoma, breast cancer, prostate cancer, esophageal, and lung cancer.

In this study, weight loss greater or equal to 5% in the previous 3 months was documented in 48.2% of cases, regardless of the mode of cancer treatment. These results are similar to those documented in patients recently admitted to the oncology department of a general hospital in Mexico, where weight loss greater than 5% occurred in 40.3% of cases, stratified as mild loss (8.8%), moderate (9.7%) or severe (21.8%).[13] Nevertheless, Fernández-López et al. (2013)[12] documented that 69% of cancer patients in their sample lost more than 5% of their usual weight over the 3 months prior to treatment with the highest frequency among those with tumors of the digestive tract. Weight loss, anorexia,[15] and dysphagia[16] occur commonly in cancer, particularly in advanced stages and tumors in locations that compromise food intake.

In our study, food intake less than 50% from the usual consumption occurred in 27.3 and 35.9% of patients undergoing chemotherapy and radiotherapy, respectively. Similar results have been documented in newly hospitalized cancer patients with moderate to severe food intake impairment in 56% of cases.[13] In patients at cancer centers, limited food consumption varied between 10 and 80%,[8] attributed to complaints of nausea and vomiting,[8,12] as well as early satiety.[12]

A limitation of our study is that the patients had various types of cancer, which hampers a comprehensive analysis of the results, considering that patients with cancer in the upper and lower digestive system and tumors of the head and neck are at greater nutritional risk.[17,18] On the other hand, the strength of our study was the application of three sequential evaluations during treatment, which allowed us to identify high nutritional risk at the beginning of cancer therapy. Our results suggest that dietary/nutritional measures should be implemented from the start of cancer treatment, aiming to improve the nutritional status or even prevent its deterioration. In developed countries, most malnourished patients in cancer centers do not receive nutritional guidance.[8] The inclusion of nutrition professionals in oncology services will allow early nutritional guidance, including nutritional therapy, if necessary.[11] The diet's nutritional value, feeding frequency, and consistency of the food can affect the severity of gastrointestinal symptoms and cause negative impact on food intake, nutritional status, and quality of life.[16] For example, patients can be instructed to drink pasty or liquid foods, eating fractionated meals and in small volumes,[16] or to fortify their diet and use nutritional supplements orally.[19]

The fact that the nutritional risk of the patients in our study was maintained without deterioration can be seen as a positive aspect of the service, as there are reports of worsened nutritional status during cancer treatment.[8] Our results can be attributed to individual dietary guidance given by the researchers, including delivery of written material containing basic information and general dietary behaviors to minimize food complaints during the oncological treatment. In addition, where necessary, the patients were referred to outpatient care specialized in enteral nutrition. Still, we believe that nutritional risk could have been further reduced if specialized dietary guidance and early enteral nutrition therapy were deployed.

We found a high prevalence of moderate or severe nutritional risk at the start of chemotherapy and radio-

therapy and this scenario was maintained during and after treatment. It is well documented that inadequate nutritional intake is involved in maintaining the nutritional risk during cancer treatment. In the last decade, it has been postulated that inflammation plays a central role in the cachexia of cancer, based on studies showing the effects of inflammatory mediators such as TNF-alpha, IFN-gamma, IL-1, IL-6.[19-21] In this context, in addition to nutritional counseling with the purpose of reducing the nutritional risk, a major scientific challenge in this area is to develop studies evaluating the effect of specific nutrients to reduce inflammatory cytokines involved in the etiology of neoplastic cachexia.

Resumo

Avaliação longitudinal do risco nutricional em pacientes sob quimio ou radioterapia

Objetivo: comparar o risco nutricional de pacientes adultos submetidos a quimio e radioterapia no início, no meio e ao término do tratamento oncológico.
Método: estudo prospectivo e comparativo conduzido com 83 pacientes adultos de um centro de tratamento oncológico, sendo 44 sujeitos sob quimioterapia (grupo QTx) e 39 sob radioterapia (grupo RTx). O risco nutricional foi determinado pelo questionário NRS-2002 no início, ao meio e ao término da terapia. A análise estatística foi feita com o software Statistica 8.0.
Resultados: não houve diferença no padrão de ingestão alimentar e no IMC (24,6±4,8 *vs.* 25±5,9 kg/m²; p=0,75) nos grupos QTx e RTx, respectivamente. Perda de peso nos 3 meses precedentes ocorreu em 56,8% dos pacientes sob quimioterapia e em 38,5% daqueles sob radioterapia (p=0,09). Os pacientes do grupo QTx apresentaram maior porcentagem de perda de peso em relação ao habitual em 3 meses (11,4±6,5 *vs.* 3,9±6,8%; p<0,001). No início do tratamento, houve alta taxa de risco nutricional moderado (18,2 *vs.* 15,4%; p=0,73) e grave (61,4 *vs.* 48,7%; p=0,25), sem diferença estatística entre os grupos QTx e RTx, respectivamente. No meio do tratamento, o risco nutricional foi mantido em ambos os grupos. Ao término da terapia, mais da metade dos pacientes apresentava risco nutricional moderado (18,2 *vs.* 12,8%; p=0,50) ou grave (50 *vs.* 51,3%; p=0,91), independentemente da modalidade de tratamento oncológico.
Conclusão: a alta prevalência de risco nutricional moderado ou grave no início do tratamento aponta para a necessidade de abordagem nutricional precoce e permanente durante a terapia oncológica.

Palavras-chave: quimioterapia, radioterapia, avaliação nutricional, neoplasias, desnutrição, estado nutricional.

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A pioneering healthcare model applying large-scale production concepts: Principles and performance after more than 11,000 transplants at Hospital do Rim

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Summary

The kidney transplant program at Hospital do Rim (hrim) is a unique healthcare model that applies the same principles of repetition of processes used in industrial production. This model, devised by Frederick Taylor, is founded on principles of scientific management that involve planning, rational execution of work, and distribution of responsibilities. The expected result is increased efficiency, improvement of results and optimization of resources. This model, almost completely subsidized by the Unified Health System (SUS, in the Portuguese acronym), has been used at the hrim in more than 11,000 transplants over the last 18 years. The hrim model consists of eight interconnected modules: organ procurement organization, preparation for the transplant, admission for transplant, surgical procedure, post-operative period, outpatient clinic, support units, and coordination and quality control. The flow of medical activities enables organized and systematic care of all patients. The improvement of the activities in each module is constant, with full monitoring of various administrative, health care, and performance indicators. The continuous improvement in clinical results confirms the efficiency of the program. Between 1998 and 2015, an increase was noted in graft survival (77.4 *vs*. 90.4%, p<0.001) and patient survival (90.5 *vs*. 95.1%, p=0.001). The high productivity, efficiency, and progressive improvement of the results obtained with this model suggest that it could be applied to other therapeutic areas that require large-scale care, preserving the humanistic characteristic of providing health care activity.

Keywords: kidney transplantation, tissue and organ procurement, renal insufficiency, Unified Health System.

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Introduction

Brazil, one of the few countries with universal health coverage established in its Federal Constitution and provided by the Unified Health System (SUS),[1] has developed health care models that exceed the expectations of a developing country. Health programs that include nationwide vaccination, treatment of patients infected with the HIV virus, and organ transplants are examples of international significance.[2]

Brazil has the second largest national transplant program, second only to the United States. Every year around 8,000 solid organ transplants are performed, 5,556 of which are kidney transplants,[3] with more than 90% under the SUS system, making it the world's largest public program in this therapeutic area. The regulation of the program and coordination of the procurement and distribution of organs are carried out by the National Transplant System (SNT), a public service created in 1997, and put into operation by the Notification, Procurement and Organ Distribution Centers (CNCDO) and Organ Procurement Organizations (OPO) established in the 27 State Departments of Health.

Hospital do Rim (hrim), one of the main players in this system, began a unique medical care model in 1998, aimed at conducting at least one kidney transplant per day.[4] As such, it has been perfecting this model using concepts from the systematic repetition of processes, as applied in industrial production and published in 1911 by Frederick Taylor in his book *The principles of scientific management*, which is still poorly applied in healthcare. These principles

involve scientific planning, rational and broken-down execution of the work, and the distribution of roles and responsibilities based on each personal development. The goal of this process is greater production, quality and systematic attainment of established goals. In this model the patient passes through specialized health care modules until the post-transplant period, when they are preferably treated by a single physician. As a consequence of this model, the annual number of transplants has gradually grown over this 18-year period, with over 850 kidney transplants conducted annually since 2009 (Figure 1).[5] These results have made the hrim the largest international kidney transplant center, treating patients from all regions of Brazil and, similar to what is done in the national transplant program, more than 90% of these activities are performed through the SUS.[6] In this article, we describe this medical model in detail and the results obtained over the last 18 years, aware that it could be applied in other clinical situations of health assistance, as well as in other regions.

Program structure

The hrim, administered by the Oswaldo Ramos Foundation, has 151 hospital beds, with 16 in the intensive care unit, six in the immediate post-operative unit and nine in a day hospital unit. The surgical center offers four rooms and six beds for post-anesthetic recovery. All of the physicians employed by the hospital completed a medical residency in their respective specialty, and most of them are involved in graduate programs. The application of the large-scale production concepts is monitored weekly through analysis of the main clinical and administrative indicators, enabling early correction of deviations or distortions.[7]

Module A: Organ Procurement Organization (OPO)

In the regions of Greater São Paulo and Baixada Santista, with 21,000,000 inhabitants, the entire organ donation process is coordinated by four OPOs. The OPO at Escola Paulista de Medicina (OPO-EPM), administered by the Oswaldo Ramos Foundation, operates in a region of 6,000,000 inhabitants, with 75 hospitals in the Greater São Paulo and Baixada Santista. The team is made up of two coordinators, that is, a nephrologist and a nurse, alongside ten nurses divided into daily shifts and a team of surgeons dedicated to kidney extraction. This team carries out extensive supplementary activity to spread and consolidate the culture of organ donation in society, including the promotion of educational and training courses for physicians and hospital coordinators, in addition to routine visits to hospitals in the region.[8]

Module B: Preparation for the transplant

Registration, clinical assessments, and preparation of candidates for kidney transplants with living or deceased donors are carried out in this module, including simultaneous pancreas and kidney transplant candidates. After a first contact, which may be by telephone or e-mail, the first evaluation is scheduled within a maximum of 2 weeks. The service is carried out daily and conducted by a multidisciplinary team that includes nephrologists, surgeons, cardiologists, and a social worker. The risks and benefits of the transplant are discussed with potential donors and recipients.

Registration and preparation for the transplant with a living kidney donor includes the identification of the donor based on clinical criteria and blood and genetic compatibility, according to SNT regulations. All of the tests required for assessment of donor and recipient as well as evaluations with specialists are scheduled and carried out at the hrim, thereby avoiding difficulties and inefficiencies in the scheduling of laboratory tests and medical evaluations at several clinics. The steps involved in preparing the patient for the transplant are controlled using algorithms, preventing unnecessary delays, until the date of the transplant is scheduled.

The registration of transplant candidates with a deceased donor involves a clinical and laboratory assessment, including serologic tests for communicable diseases. Registration on the waiting list is based on blood type (ABO). During this evaluation, genetic typing of the candidate's HLA system is scheduled at the immunogenetics laboratory, which advises them to store a serum sample every 3 months for the completion of crossmatching (antibodies against the donor's HLA system in the serum of the recipient). Clinical reassessment and reorientation of the candidates are conducted annually, with complementary tests repeated according to clinical recommendations.

Module C: Admission for transplant

For transplants with kidney from a living donor, both the recipient and the donor are admitted on the eve of surgery, with clinical reassessment and a detailed review of all laboratory and genetic compatibility tests. Routine preoperative tests for surgery of medium complexity are carried out. The risks and benefits of organ transplantation are discussed with the donor and the recipient again, followed by the signing of a consent form for donation and transplantation. The surgery is elective, and normally carried out early in the morning on the following day.

For kidney transplants from deceased donor, the identification of potential recipient is conducted by the State Department of Health and is based primarily on the ABO blood type identity and higher compatibility with the donor's HLA genetic system from among all active candidates on the waiting list. Candidates identified and registered at our transplant center are then contacted by phone using a structured interview to assess their current medical conditions. Based on this interview, the potential candidate is invited to immediately undergo preoperative tests and clinical examinations. Once the recipient is defined, the risks and benefits of organ transplantation are once again discussed before signing a consent form to perform the transplant. The average time between the identification of the candidate and admission to the operating room is around 20 hours.

Module D: Surgical procedure

The surgical team is composed of eight urologists and two urology residents per year, divided into set teams from Monday to Friday and on-call shifts on weekends. The duration of the kidney transplant surgery varies from 90 to 120 minutes, while nephrectomy of a living donor varies between 60 to 90 minutes. General anesthesia is applied to both the donor and the recipient. Donor nephrectomy is performed through an anterior lumbotomy incision, and on the recipient is performed using a modified Gibson incision with vascular anastomosis to the iliac vessels and the ureter on the bladder according to the Gregoir or Politano-Leadbetter technique. The implantation of ureteral catheters and drainage of the renal area are not performed routinely.[9] For deceased donors, both kidneys are removed en bloc, most often associated with the removal of the abdominal or thoracic organs, with participation of multiple teams.

Module E: Post-operative period

After surgery, the donors and recipients are maintained in the immediate post-operative unit, where they remain for the first 18 to 24 hours. During this period, they are under the care of a specialized team that monitors clinical and surgical complications in addition to initiating treatment with immunosuppressants according to predetermined protocols.

Patients are conducted, from admission to discharge, at one of the four units with 30 beds, each of which managed by two of the hospital's physicians, divided into 6-hour shifts, in addition to night and on-call physicians. All clinical and surgical activity is coordinated by one nephrologist and one urologist, with the routine clinical support of three infectious disease doctors, two cardiologists, and two pathologists. Daily visits and hospital discharge are multidisciplinary with subsequent automatic scheduling of the first evaluation at the outpatient unit.

Module F: Outpatient clinic

The outpatient department includes ten consulting rooms, three nursing stations, and an emergency room, while management is coordinated by a senior nephrologist. Coordination of clinical care is performed by two experienced nephrologists, one in the morning and another in the afternoon. The health care flow is linear, starting with a nursing evaluation and followed by medical, pharmaceutical, psychological, and social work services, and ending with the scheduling of the following evaluation and obtainment of the necessary documentation for the dispense of medication at public pharmacies.

The evaluations follow a predetermined schedule, the frequency of which is higher in the first months and then quarterly a year after the first year of transplant. Laboratory tests can be performed in the morning, with results available on the same day. Daily attendance is performed by a specialized medical team, with an average of 16 patients per 5-hour shift per physician. The coordinators guide the majority of evaluations, especially when they involve changes in conduct or immunosuppression regimen. Patients who have health insurance can follow a similar flow, or can be forward for monitoring with their referring physician. Few patients are monitored solely by their referring nephrologists, even when they live in other states. Elective hospital readmissions are coordinated directly by the outpatient department. Emergency care is provided at the hospital emergency unit.

Module G: Support units

The model has complete care provided by independent support units: (1) dialysis treatment unit; (2) day hospital unit; (3) immunogenetics laboratory; (4) clinical pathology laboratory; (5) hospital infection control committee (CCIH); (6) diagnostic imaging unit; (7) urological investigation and intervention unit; (8) interventional cardiology unit; (9) renal pathology unit.

The immunogenetics laboratory (IGEN) performs all of the genetic tests on patients registered for transplantation at the hrim. The clinical laboratory, diagnostic imaging, and renal pathology units provide diagnostic support 24 hours a day. In addition to the determination of the blood concentration of various immunosuppressive drugs, the clinical laboratory con-

ducts all of the routine tests, and releases the final results on the same day as collection. Biological samples are taken by two groups of technicians, with capacity to attend up to ten patients simultaneously. The day hospital has nine beds for less complex procedures, such as kidney biopsies, and 16 stations for outpatient intravenous drug administration. Units for dialysis treatment, urological investigation and intervention, and cardiology provide diagnostic and therapeutic support both before and after the transplant. Lastly, in addition to promoting and monitoring hospital infection control measures, with special attention to multiresistant bacteria, the hospital infection control committee also works on advising patients, family members and employees about the behavior and prevention of epidemics such as dengue fever and influenza, which are a greater risk for transplant patients.

Module H: Coordination and quality control

Consists of a systematic meeting designed to be the first morning activity on the first day of the week (Monday, at 7:30 am to 8:30 am) involving the leaders of the modules described above and members of the senior management, with the aim of monitoring the performance of each module, benchmarking, and improvement of processes. This activity is aimed at the most thorough, close and personal cooperation between participants, with equitable division of the work and responsibilities among the leaders for maximum performance, applying the concepts of scientific management through the presentation of indicators. Leading and management activities are directed towards coordinated work with their groups of collaborators, disseminating the indicators of results, and seeking maximum individual and collective prosperity, considering that even tasks with systematic repetition must be reviewed for permanent improvement.

Program outcomes

Increase in the number of deceased donors

The number of brain death notifications by hospitals in the region of the OPO-EPM increased from 196 in 1999 to 684 in 2015. The number of effective donors (potential donors whose organs were actually donated and transplanted) increased from 43 to 202 in the same period. The efficiency of the process is characterized by the reduction in the percentage of family refusal of donation, falling from 78 to 43%, and the increase in the donation effectiveness in the same period, from 22 to 29% (Table 1).

TABLE 1 Comparison of productivity indicators in 1999 and 2015.

Productivity indicators	1999	2015
Effective deceased donors	43	202
Patients on the waiting list for transplant with kidneys from deceased donors	3,050	5,303
Total transplants	394	886
Adult with kidney from a living donor	271	205
Adult with kidney from a deceased donor	96	617
Pediatric with kidney from a living donor	22	4
Pediatric with kidney from a deceased donor	5	44
Simultaneous pancreas-kidney transplants	0	16
Cumulative number of transplants	503	12,724
Cumulative number of transplant recipients under monitoring	439	7,751
Number of evaluations at the outpatient department	7,295	59,781

Increase in the number of transplants

Between August 18, 1998 and December 31, 2015, 11,707 transplants were conducted at hrim, with 10,580 kidney transplants in adults, 856 pediatric kidney transplants and 271 simultaneous pancreas and kidney transplants. Over this 18-year period, the annual number of transplants has increased more than twice, from 394 in 1999 to 886 in 2015 (Figure 1). Linear growth was observed between 1999 and 2008, a period in which kidney transplants from living donors predominated. Between 2009 and 2015 the number of transplants has remained relatively stable at 856 to 919, but with a predominance of kidney transplants from deceased donors (76%). The same phenomenon was observed with pediatric transplants, with an increase of 27 to 74 transplants between 1999 and 2009, and subsequent stabilization and predominance of kidney transplants from deceased donors (Figure 1). Finally, the number of simultaneous kidney and pancreas transplants remains relatively stable at around 30 per year, with a decrease last year following an international trend, possibly justified by advances in pharmacological and glycemic control, as well as improved methods for the administration of insulin.

Currently, the hrim has 5,303 candidates registered on the kidney transplant waiting list and 338 for the combined pancreas and kidney transplant, which corresponds to 50% of the total number of candidates from the city of São Paulo registered on the single list (11,149) of the Health Secretariat (Table 1). The number of evaluations held for registration or annual reassessment of transplant candidates using a kidney from a deceased donor was 5,926 in 2015. In 2015, the number of registrations for performing kidney

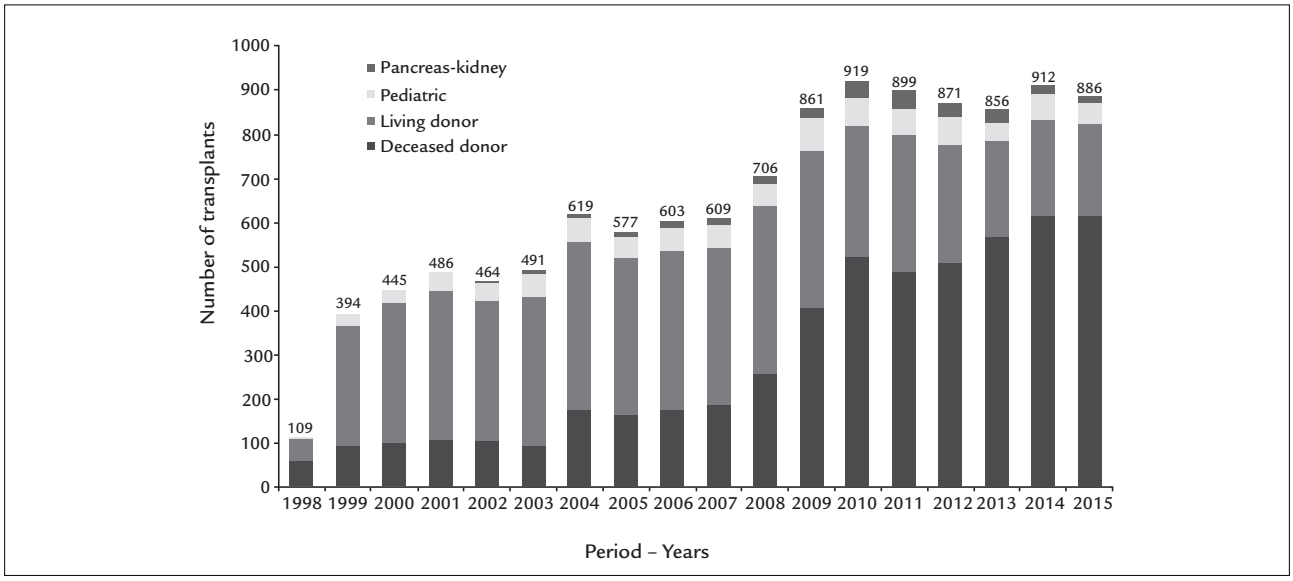

FIGURE 1 Annual number of transplants carried out at Hospital do Rim from August 18, 1998 to December 31, 2015, stratified by type of transplant: deceased, living, pediatric, and pancreas-kidney.

transplants from a living donor was 436, and the average time of the donor and recipient until the transplant was scheduled was 12 days. In 2015, 886 transplants were carried out at the hrim, including 617 from deceased donors, 205 from living donors, 48 pediatric transplants, and 16 kidney and pancreas transplants.

Quality control

Healthcare quality indicators are analyzed weekly. The global surgical complication rate directly related to the transplant procedure remains stable at around 6.5%, most of which are restricted to the surgical wound, and responsible for graft loss in 1.1% of transplants. The surgical technique currently used reduces or even eliminates any objective advantage of laparoscopic nephrectomy of the donor, the cost of which is significantly higher.

The average hospital stay is 8.2 days for recipients of a kidney from living donors and 12.5 days with kidneys from deceased donors. The early hospital readmission rate (less than 30 days after hospital discharge after the transplant), an indicator increasingly used by health insurers, is 26.6%.

Between 2005 and 2015, reductions were noted in the infection rates of the surgical site (6.3 *vs.* 2.5%), urinary tract infection (18.1 *vs.* 4.4%) and ventilation-associated pneumonia (25 *vs.* 0.4 per 1,000 cases of mechanical ventilation/day). On the other hand, there was a fluctuation in the rate of bloodstream infections, with 5.5 cases per 1,000 central venous catheters per day in 2005, 13.4 in 2007, and 2.6 in 2009. In 2015, the rate was 8.3 cases per 1,000/day, similar to other institutions, and probably associated with the increased incidence of infections caused by multiresistant bacteria (Figure 2).

Performance of the support units

In the period between 2003 and 2015, the immunogenetics laboratory increased the number of HLA system typing (4,203 to 4,374), sensitization tests for detection of anti-HLA antibodies in the serum (8,720 to 13,216), and cross-matching (5,670 to 14,577). The number of laboratory tests conducted by the laboratory increased 4.8 times between 1999 and 2015. In 2015, the number of tests conducted was 1,097,329, including determinations of the plasma and blood concentrations of immunosuppressive drugs. At the day hospital unit, an average of six biopsies of transplanted kidneys were conducted per day to investigate specific causes of dysfunction, as well as treating an average of five patients per day for outpatient treatment of infections, anemia and episodes of rejection of the transplanted kidney. The pathology lab processed and issued reports for 551 kidney biopsies on deceased donors and 2,500 on transplanted kidneys. The hemodynamic service, which also serves the general population, conducted 2,033 diagnostic coronary angiograms, 524 angioplasties with and without implantation of stents, as well as 49 angioplasties for treating stenosis of the artery of the transplanted kidney.

Efficiency in monitoring after the transplant

At the end of 2015, the number of patients being monitored at the post-transplant unit was 7,751 (Table 1). In

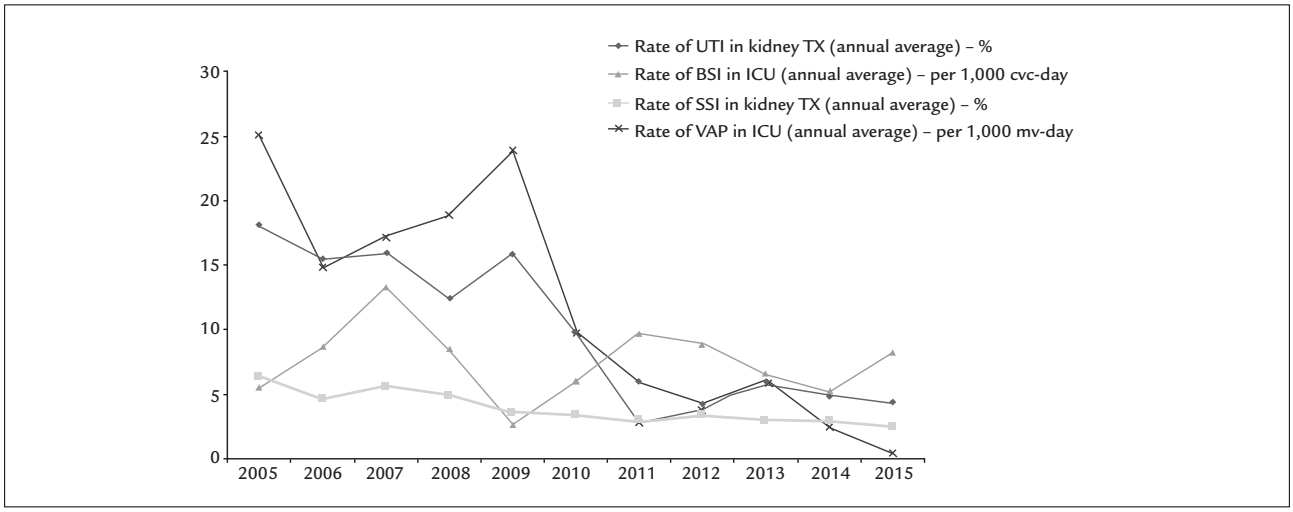

FIGURE 2 Indicators from the Hospital Infection Control Committee during the period from 2005 to 2015 for urinary tract infection, bloodstream infection, surgical site infection, and pneumonia associated with ventilation.

UTI: urinary tract infection; TX: transplant; BSI: bloodstream infection; ICU: intensive care unit; SSI: surgical site infection; VAP: ventilation-associated pneumonia; cvc: central venous catheter; mv: mechanical ventilation.

the same year, 59,781 medical evaluations were conducted, meaning an average of 237 daily evaluations.

Improvement of the survival results

The performance of a kidney transplant center is classically evaluated by graft survival, calculated as the percentage of transplant patients who complete the first year with the functioning kidney, stratified by the type of donor, living or deceased. It has been noted that cumulative graft survival in the first year for transplants from 1998 to 2002 was 89.2%, while for transplants from 2011–2014, graft survival was 92.5%. Graft survival in transplants with living donors increased from 93.9% in 1998–2002 to 97.2% in 2011–2014, and from 77.4 to 90.4% with deceased donors (Figure 3). Similarly, the survival of patients in transplants from a living donor increased from 97.8% in 1998–2002 to 98.7% in 2011–2014, and from 90.5 to 95.1% with deceased donors. Sixty percent (60%) of the 5,189 patients undergoing kidney transplants from deceased donors between 1998 and 2014 completed one year after transplant with graft function considered as excellent (creatinine less than 1.5 mg/dL). This proportion was 66% for the 5,377 recipients of kidney transplants from living donors conducted in the same period.

In relation to the 11,436 kidney transplants carried out between 1998 and 2015, 68% of patients are under monitoring, 12% lost graft function and returned to dialysis treatment, 12% died and 8% were transferred or no longer monitored at our unit. The most frequent cause of death was infection (53%), followed by cardiovascular complications (16%).

Education and Research Program

The large number of transplants conducted annually has enabled participation in national and international multicenter clinical studies, which are also important for identifying the best immunosuppressive regime in different types of patients, taking into account that the demographic characteristics of the Brazilian population differ from American and European populations. Between 1998 and 2015, over 3,000 patients were included in more than 60 phase I to IV clinical studies, contributing significantly to the adoption of new forms of immunosuppression by the regulatory agencies in the United States, Europe, and Brazil. Treatment strategies being investigated and validated at the hrim are subsequently adopted by various transplant centers in Brazil and abroad. In parallel, a training and education program in clinical research for pharmacists has been developed, involving 83 students that subsequently entered the labor market, whether in pharmaceutical industries, private companies or academic clinical research centers.

The growth of research and education activities led to the creation of the Education and Research Center (NEP, in the Portuguese acronym) in 2014. Between 1998 and 2015, 1,276 physicians, including 1,176 from Brazil and 100 from other countries, mainly in Latin America, participated in medical education activities at the hrim. In 2015, 364 undergraduate students, 49 residents (nephrol-

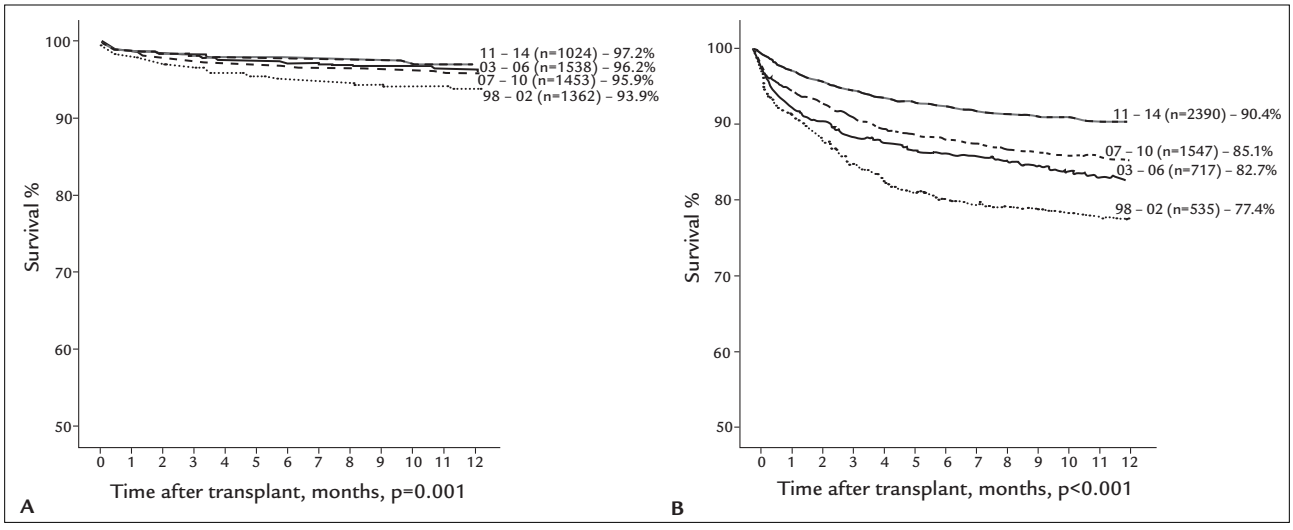

FIGURE 3 A. 12-month graft survival in recipients of kidney transplants from living donors in the period from 1998 to 2014. B. 12-month graft survival in recipients of kidney transplants from deceased donors in the period from 1998 to 2014.

ogy, urology, cardiology, infectious diseases, multidisciplinary, and pharmacy) and 136 interns were trained. In the same year, 17 scientific studies were conducted, including four doctoral dissertations and 13 master's degree theses, as well as 15 articles published in indexed journals and 75 papers presented at national and international conferences. At the national level, this model of continuing education has led to the creation of new transplant centers in several states and increased activity at existing centers.

Discussion

The hrim's transplant model is based on maximum specialization, systematic repetition, and improvement of processes by all of the professionals involved in each of its modules. This model, which has enabled a significant increase in the number of transplants performed, has also provided academic and healthcare training for professionals dedicated to this therapeutic area throughout the national territory, also including the country in the international context of clinical research in the area.[10] On two occasions, it has received approval by the Food and Drug Administration (FDA) as well as several hospital quality certifications, including national accreditation with excellence (Level 3) from the National Accreditation Organization (ONA), teaching hospital certification from the Ministry of Education and Culture and the Ministry of Health.

The efficiency and interconnection of the modules has influenced all of the performance metrics. In 1998, 75% of transplants were performed with kidneys from live donors, while from 2009 on the number of transplants with kidneys from deceased donors increased, reaching 76% of transplants performed in 2015.[11,12] The growth in the number of deceased donors, as well as the marked progress in dialysis assistance, has enabled us to apply more stringent criteria for kidney transplants from living donors. These restrictions are based on surgical risk (mortality rate after kidney donation at 3 per 10,000), and uncertainty about the risks of developing chronic kidney disease in the long-term, considering the progressive increase in the life expectancy of the general population.

The largest share of revenues is the result of remuneration for healthcare production by the SUS (62%) as well as supplementary health providers. A small fraction comes from clinical research activities or the obtainment of additional public funds. The remuneration of the medical team is variable depending on the intensity of their participation in the program. The production, administrative, and financial indicators are subject to monthly external audits and presented semiannually to the board of trustees and the Public Ministry through its trustee of foundations. This hierarchy of controls demands permanent administrative rigor, but the budget balance of the service to the SUS depends on surplus revenue from the service to patients treated under supplementary medicine and, to a lesser extent, from additional public funds.

Perspectives

The transplant model performed at the hrim results in increased productivity, efficiency, and progressive improvement of outcomes. This model can be applied in other medical intervention methods whose prevalence requires a large-scale care, such as the treatment of benign pros-

tatic hypertrophy, nephrolithiasis, ophthalmologic disorders, several types of cancer, implantation of orthopedic prostheses, and myocardial revascularization.

In our view, the greatest benefit of using this model could occur in developing countries, with limited availability of high complexity treatments for highly prevalent diseases. In these regions, the implementation of this model, even when restricted to a single institution, could offer effective treatments on a large scale for the majority of the population. Whatever the scenario, the application of this model for increased efficiency requires the principles of scientific management, introduced by Frederick Taylor and universally refined, to be incorporated and continuously enhanced by all the members of the institution.

Resumo

Um modelo pioneiro de aplicação dos conceitos da produção em larga escala na assistência à saúde: princípios e desempenho em mais de 11 mil transplantes no Hospital do Rim

O programa de transplante renal do Hospital do Rim (hrim) é um modelo único de assistência médica que aplica os princípios da repetição de processos utilizados na produção industrial. Esse modelo, idealizado por Frederick Taylor, é fundamentado em princípios da administração científica, que envolvem planejamento, execução racional do trabalho e distribuição de responsabilidades. O resultado esperado é o aumento da eficiência, melhoria dos resultados e otimização de recursos. Esse modelo, quase todo subsidiado pelo Sistema Único de Saúde (SUS), foi utilizado no hrim para a realização de mais de 11 mil transplantes nos últimos 18 anos. O modelo do hrim consiste em oito módulos interconectados: organização de procura de órgãos, preparo para o transplante, admissão para transplante, procedimento cirúrgico, pós-operatório, seguimento pós-transplante, unidades de apoio, e coordenação e controle de qualidade. O fluxo das atividades médicas permite o atendimento organizado e sistemático de todos os pacientes. O aperfeiçoamento das atividades de cada módulo é constante, com monitoramento integral de diversos indicadores administrativos, assistenciais e de desempenho. A melhora contínua dos resultados clínicos confirma a eficiência do programa. Entre 1998 e 2015, foi observado um aumento nas sobrevidas do enxerto (77,4 *vs.* 90,4%; p<0,001) e do paciente (90,5% *vs.* 95,1%; p=0,001), respectivamente. A elevada produtividade, a eficiência e a melhoria progressiva dos resultados obtidos sugerem que esse modelo pode ser aplicado em outras áreas terapêuticas que necessitam de assistência em larga escala, sem comprometer os conceitos humanísticos de nossa atividade assistencial.

Palavras-chave: transplante renal, organização de procura de órgãos e tecidos, insuficiência renal, Sistema Único de Saúde.

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Resting energy expenditure in critically ill patients: Evaluation methods and clinical applications

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Summary

Patients on intensive care present systemic, metabolic, and hormonal alterations that may adversely affect their nutritional condition and lead to fast and important depletion of lean mass and malnutrition. Several factors and medical conditions can influence the energy expenditure (EE) of critically ill patients, such as age, gender, surgery, serious infections, medications, ventilation modality, and organ dysfunction. Clinical conditions that can present with EE change include acute kidney injury, a complex disorder commonly seen in critically ill patients with manifestations that can range from minimum elevations in serum creatinine to renal failure requiring dialysis. The nutritional needs of this population are therefore complex, and determining the resting energy expenditure is essential to adjust the nutritional supply and to plan a proper diet, ensuring that energy requirements are met and avoiding complications associated with overfeeding and underfeeding. Several evaluation methods of EE in this population have been described, but all of them have limitations. Such methods include direct calorimetry, doubly labeled water, indirect calorimetry (IC), various predictive equations, and, more recently, the rule of thumb (kcal/kg of body weight). Currently, IC is considered the gold standard.

Keywords: energy expenditure, critically ill patient, energy requirement, indirect calorimetry.

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Importance of determining energy expenditure in critically ill patients

Adequate supply of nutrients is an essential part of the overall treatment of critically ill patients and adjustment of nutritional requirements to the individual needs of patients is a matter crucial to their clinical evolution, because both situations, overfeeding and underfeeding, may contribute to high morbidity and mortality in this population.[1,2] In such a context, an adequate assessment of energy expenditure (EE) is the basis of effective nutritional planning.[3]

Total energy expenditure (TEE) is defined as the energy required by the body daily, determined by adding the following components: basal energy expenditure (BEE), diet-induced thermogenesis (DIT) and physical activity (PA).[4]

BEE reflects the energy requirements to maintain the intracellular environment and mechanical processes such as respiration and cardiac function, as well as thermoregulatory mechanisms responsible for regulating the body temperature.[5,6] It is considered the main component in TEE, contributing 60 to 75% of the daily energy requirement for most sedentary individuals and approximately 50% for the physically active. BEE must be measured in thermoneutral conditions (20°C) in the absence of recent nutrient administration (12 to 14 hours of fasting), recent physical activity (at least 8 hours of sleep), and psychological stress, while the subject is fully awake, lying in silence, completely relaxed and breathing normally.

The energy corresponding to the thermal effect of food refers to the expenditure caused by digestion, absorption, transport, processing, assimilation and/or storage of nutrients, which varies according to substrate consumed and represents 5 to 15% of the TEE.[4] It is considered that in a usual mixed diet (with lipids, carbohydrates, and proteins), the thermal effect of food is approximately 5 to 7% of its energy content.

Finally, the EE for the completion of the external mechanical work is defined as the effect of physical activity, representing 15 to 30% of the daily TEE. The variation takes into account intensity and duration of exertion.[6]

As described, the measurement of BEE requires the individual to remain in specific conditions, which often makes it difficult to obtain a baseline. Thus, usually, the resting energy expenditure (REE), which is very close to the BEE, is measured with the subject at rest. REE may be 3 to 10% greater than BEE due to DIT and the influence of the latest PA.[4,7]

Factors such as age, gender, body composition, hormones, and genetics can exert influence on the REE in both healthy individuals and those who are ill. Body composition is believed to be one of the major determinants of metabolic rate, so that individuals with predominantly lean body mass have higher EE, while fat mass is metabolically less active.[8]

Certain medical conditions can also change the REE. The use of nutritional support and certain medications can raise up to 10% this expenditure. Clinical and surgical diseases usually increase REE as part of the metabolic response to stress. Postoperatively to elective surgeries, REE can increase from 5 to 20%. Multiple fractures, extensive abdominal injury, central nervous system trauma, and severe infections may raise the REE 50 to 60%.[9]

Faisy et al.[10] found that in patients on mechanical ventilation, weight, height, body temperature, type of mechanical ventilation, and type of medication received influenced the REE. Fever is another important factor that changes the REE, so that each 1°C increase in temperature raises the REE by 11%.[8] Conversely, different equipment and methods of mechanical ventilation, as well as medications such as sedatives, painkillers, and muscle relaxants seem to reduce the metabolic and systemic stress of patients, with consequent reduction in REE.[10]

Clinical conditions that can present with REE change include acute kidney injury (AKI), a complex disorder commonly seen in critically ill patients with manifestations that can range from minimum elevations in serum creatinine to renal failure requiring dialysis.[11] Its incidence in the intensive care unit (ICU) is 20 to 40%[12] and is associated with high mortality rates, which may reach 60% in those requiring dialysis.[13] This critical population has complex nutritional needs and as part of the metabolic response to acute disease, sepsis or trauma, the BEE can be altered, leading to intense catabolism accompanied by hyperglycemia combined with insulin resistance, progressive loss of lean body mass, and severe lipolysis.[14] Such metabolic changes associated with lack of adequate nutritional support can lead to rapid and significant depletion of lean body mass and malnutrition,[15,16] as well as prolonged use of mechanical ventilation, hyperglycemia, and liver dysfunction in cases of overfeeding.[17,18]

Thus, many of the severe patients have a characteristic hypermetabolism, which aims to acutely provide energy and substrate for the immune system and coagulation pathways to fight pathogens, stop bleeding, and repair damaged tissues. Such a response is beneficial; however, it coincides with great body exhaustion including protein degradation and early onset of malnutrition, in which case the patient becomes more susceptible to infections and thus to longer hospital stays, higher hospital costs, and increased mortality.[19,20] In this scenario, underfeeding associated with increased energy demand could adversely affect the prognosis of patients.

Dvir et al.,[21] in an observational study of 50 ICU patients, showed an association between greater energy deficit and adult respiratory distress syndrome (p=0.0003), sepsis (p=0.0035), renal failure (p=0.0001), pressure ulcers (p=0.013), need for surgery (p=0.023), and total rate of complications (p=0.0001), but no association with duration of mechanical ventilation, ICU stay or hospital stay and mortality.[21] Similar results were observed by Villet et al.,[1] who also discovered a correlation between negative energy balance and clinical complications, especially infection (p<0.001).

In a study of a small group of 38 critically ill patients on prolonged mechanical ventilation, the authors found that a deficit of approximately 1,200 kcal/day was associated with independent risk of death in ICU (OR 6.12, 95CI 1.33-28.2; p=0.01).[22] In another study, Alberda et al.[23] noted that an increase of 1,000 kcal/day was associated with overall reduction in mortality of patients in intensive care (OR 0.76, 95CI 0.61-0.95; p=0.014).

On the other hand, overfeeding also has negative effects, such as respiratory and metabolic disorders, including hypercapnia, need for prolonged mechanical ventilation, hyperglycemia, hepatic steatosis, azotemia, hypertonic dehydration, metabolic acidosis, hypertriglyceridemia, and refeeding syndrome, as well as known deleterious effects related to infection and patient outcomes.[5,24] In a multicenter study conducted in 40 Spanish ICUs and that included 725 patients, Grau et al. showed that overfeeding (> 27 kcal/kg) was one of the determinants of abnormal liver function.[25] According to the study of Dissanaike et al.,[26] increased parenteral caloric intake was a risk factor for infection of the bloodstream; this association was independent of the occurrence of hyperglycemia.

According to the authors, critical patients have a number of systemic, metabolic, and hormonal changes

that can adversely affect their nutritional status. This makes the determination of REE essential for adjusting the nutritional supply and thus allows the planning of an adequate diet to ensure that energy needs are met and to avoid the complications associated with overfeeding or underfeeding.[27]

Methods for determination of energy expenditure

The calculation of energy needs is an integral part of nutritional care of critically ill patients. Determining the exact EE is one of the great difficulties in clinical practice, as acute disease and its treatment affect metabolism, increasing or decreasing the patient's EE.[28]

Several evaluation methods of EE in this population have been described, but all of them have limitations.[29] They include direct calorimetry (DC), doubly labeled water (DLW), indirect calorimetry (IC), several predictive equations, and, more recently, the rule of thumb (kcal/kg of body weight).

The use of a rule of thumb based on guidelines issued by medical societies such as the American Society of Enteral and Parenteral Nutrition (ASPEN), the European Society for Clinical Nutrition and Metabolism (ESPEN) and the Canadian Critical Care Clinical Practice Guidelines Committee (CCPG) is a common practice to estimate REE, and although there is a consensus among these entities, a few discrepancies are found.[30] US guidelines recommend 25 to 30 kcal/kg of current body weight in adults, and in the case of critically-ill obese patients, they recommend 11 to 14 kcal/kg of current body weight or 22 to 25 kcal/kg of ideal body weight (IW).[31]

DC is a method based on the use of a thermally insulated chamber to directly measure the heat generated by the body. It is considered highly precise (1 to 2% error), but with little viable applicability[32] as it requires a very sophisticated camera and permanence of the subject in the chamber for a period equal to or greater than 24 hours.[33] Thus, studies point to the efficacy and use of the indirect method.[34] A study comparing the EE of three patients during 40 days, obtained through direct and IC, showed difference of only 0.22% between the two methods (2,723 kcal/24h *vs.* 2,717 kcal/24h). Other studies in animal and human models have shown good correlation between DC and IC, with differences below 1%.[35]

The method of DLW consists in using water doubly labeled with ^{2}H and ^{18}O, which must be ingested by the subject whose disappearance rate of body fluid (water) is then monitored for 7 to 21 days, approximately. The difference between the rates of disappearance of two isotopes, corrected for body water pool, enables to estimate the carbon dioxide (CO_2) production rate that, based on IC equations, reveals the TEE of the individual.[36] The accuracy of the method is 97 to 99% compared to IC.[37] In studies with adults in energy balance, in which the results from the DLW were compared with those obtained by IC, Coward et al.[38] obtained error at 1.9±2% in the estimated production of CO_2, while Schoeller & Webb[39] obtained error at 1.5±7.6%. However, DLW is most commonly used to measure the TEE in individuals not confined to a calorimetry room, in special conditions such as lactating, in sports activities, validation of assessment instruments of physical activity and/or EE, and validation of methods to assess dietary intake. It is not commonly used in hospitals.[40]

IC is considered the gold standard for measuring REE in critically ill patients,[41,42] and measurement is based on gas exchange, with energy production from the consumption of oxygen (O_2) and production of CO_2. It is estimated that approximately 80% of EE is due to O_2 consumption, while the remaining 20% are attributed to EE due to CO_2 production.[43,44] It is considered a safe, non-invasive, and precise method, with error less than 1%, with high reproducibility and almost free of complications.[4]

The calorimeter is a simple device, portable, a type of "open circuit" that supports the patient while breathing air either connected or not to a respirator. In both situations, the samples of inspired/expired gas are collected by the device for analysis of the CO_2 fraction in expired air, O_2 fraction in the inhaled and exhaled air, and inspiratory and expiratory flows. Through analysis of these parameters, oxygen consumption (VO_2) and carbon dioxide production (VCO_2) are measured, and REE is obtained by transforming these values using the classical Weir equation:[45-47]

$$\text{Energy expenditure (kcal)} = [3.941\ (VO_2) + 1.106\ (VCO_2)] \times 1440$$

Respiratory volumes are measured in L/min, and factor 1440 expresses the number of minutes in 24 hours.

A second important result obtained from the IC is the respiratory quotient (RQ), defined as the ratio between VCO_2 emitted by body tissues and the VO_2 absorbed by them ($RQ = VCO_2/VO_2$). RQ are in a very narrow range in humans (0.67-1.2)[48] and, thus, values outside of this range suggest the presence of technical errors in measurement.

Some mechanical, environmental, and metabolic aspects must be observed to ensure test accuracy. The environment should be quiet, with dim lighting and temperature around 20°C, with the patient at rest for at least 30 minutes and fasting for 2 to 3 hours.[49] In patients who

are receiving nutritional therapy or intravenous glucose solution, the rate of infusion of solutions should be kept constant.[50] The O_2 and CO_2 analyzers must be calibrated with a known concentration of gas before each determination and periodically validated according to the manufacturer's specifications.[6] For individuals on mechanical ventilation, modifying the system to a regime of constant moisture content of the air and oxygen is not recommended for 90 minutes before measuring.[6] The inspired gas sample collection tube should be as close as possible to the patient, making sure that there are no leaks in the connections of the breathing circuit. The endotracheal tube should also be perfectly adapted and without leaks.[50] Furthermore, the fraction of inspired oxygen (FiO_2) must be stable and below 60%, since greater values increase the likelihood of errors in the results obtained.[50]

The calorimetric test duration is based on reaching the Steady State, considered a metabolic balance period where changes in VCO_2 and VO_2 are < 10% for 5 consecutive minutes or the average of the coefficient of variation (CV) for these two values is less than 5%.[7,51-56] Calorimeters typically require a 30 minute test period to reach Steady State, the first 5 minutes of the test being discarded.[7,51] Metabolic balance must be achieved in order to reduce errors and ensure the validity of the test.[54,57]

In Brazil, it is known that the application of this method to evaluate patients in hospitals is not a routine, since the equipment is expensive and requires specialized labor to be handled properly.[58]

The predictive equations comprise a commonly used alternative method to determine the energy needs according to estimates of EE due to zero cost and ease of application. There are about 190 equations published in the literature using variables such as weight, height, age, gender, and body surface.[29] The most used are the Harris-Benedict equation (1919),[48] the Mifflin-St Jeor equation (1990),[59] the Ireton-Jones equation (1992),[60] and the Penn State equation (2003),[61] described in Table 1.

The accuracy of the method in hospitalized patients has been questioned, particularly in critically ill, malnourished and elderly patients.[62,63] In addition, any occasional error in REE obtained using predictive equations can be further increased when activity and injury factors are applied to empirically adjust the needs altered in patients with acute disease.[64]

Boullata et al.[65] evaluated the efficacy of seven predictive equations, including the Harris-Benedict, the Mifflin-St Jeor, the Ireton-Jones, and the Penn State equations, to predict REE in 365 hospitalized patients, including critically ill and obese individuals. None of the equations precisely predicted the REE, regardless of age, gender, race, body mass index, and ventilatory status. Even using the global equation of Harris-Benedict, 39% of patients had imprecise REE results, with 400 kcal error above or below the REE measured by IC. In obese individuals, prediction based on the Harris-Benedict equation was more precise than any other equation in 62% of the sample. However, there was still a mean error of 47 kcal, with an agreement range between + 534 kcal and - 440 kcal.[65]

TABLE 1 Description of predictive equations.

Name of equation	Calculation of REE
Harris-Benedict	Male: $66.5 + (13.8 \times P^a) + (5 \times A^b) - (6.8 \times I^c)$
	Female: $655 + (9.6 \times P^a) + (1.8 \times A^b) - (4.7 \times I^c)$
Mifflin-St Jeor	Male: $5 + (10 \times P^a) + (6.25 \times A^b) - (5 \times I^c)$
	Female: $-161 + (10 \times P^a) + (6.25 \times A^b) - (5 \times I^c)$
Ireton-Jones	$1.925 + (5 \times P^a) - (10 \times I^c) + (281 \times G^d) + (292 \times Tr^e) + (851 \times Q^f)$
Penn State	$-6.433 + (HB^g \times 0.85) + (V_E{}^h \times 33) + (T_M{}^i \times 175)$

Note: [a]weight (kg); [b]height (cm); [c]age (years); [d]gender (1 = male, 0 = female); [e]trauma (1 = present, 0 = absent); [f]burn (1 = present, 0 = absent); [g]Harris-Benedict; [h]minutes of ventilation (L/min); [i]maximum temperature (°C); REE: resting energy expenditure.

In a prospective observational study involving 40 adult patients admitted to the ICU, the authors observed that the REE estimated using the Ireton-Jones formula overestimated REE measured by IC, obtaining a mean difference between the IC and the equation of - 353.83 kcal, ranging from - 904.77 kcal to 197.11 kcal, with a significant difference between measured and estimated EE for the same individual ($p<0.004$).[58]

Although the inaccuracy of predictive equations is shown in numerous studies, the unavailability of a calorimeter in many services causes such equation to be routinely used to assist in the estimation of energy needs, based on publications that demonstrate greater concordance between the estimated EE and that measured by IC.

Faisy et al.[10] evaluated the EE measured by IC and compared it to the value estimated by the Harris-Benedict equation. They noted that although EE on IC was 25% greater, the difference was not statistically significant when the injury factor was applied for adjustment. In another study conducted in the previous year, Cheng et al.[66] analyzed the accuracy of five predictive equations to estimate the EE of 46 patients on mechanical ventilation, including the Harris-Benedict and Kleiber and Liu equations, noting that EE can be estimated in most critically ill patients by these equations, provided that an injury factor is used.

The predictive equation of Harris-Benedict is one of the oldest and most used to date; however, it is not recommended in critically ill patients.[67,68] The Penn State University equation is the most exact and precise indicator of REE in the critically ill patients, and should be used when IC is not feasible, combined or not with the rule of thumb in order to improve precision.[42,61,69,70]

IC is the best technique to ensure exact determination of EE and consequently the ideal nutritional intake, and thus should be use whenever possible in critically ill patients.

Energy expenditure in acute kidney injury

Observational studies show a strong association between cumulative energy deficits and worse renal outcomes and survival, as well as correlation between malnutrition and increased morbidity and mortality in intensive care patients affected by AKI.[21,71] Thus, the adequate supply of nutritional requirements by determining the actual EE in this population is relevant.

When AKI is monofactorial and uncomplicated, REE does not seem to be changed, although the kidney is responsible for about 10% of the REE.[72] Studies have shown that the metabolism in non-complicated AKI, measured using calorimetry, seldom exceeds 1.3 times the BEE obtained by the Harris-Benedict equation.[10,72,73]

As AKI affects up to a third of patients admitted to the ICU, it is rarely monofactorial and non-complicated. Most commonly, it is part of a more complex disease such as sepsis, multiple organ failure, shock, trauma or high-risk surgery, with resulting hypermetabolism and hypercatabolism.[74] There is evidence that severe sepsis and septic shock are the most important causes of AKI in critically ill patients, corresponding to 50% or more of these cases in ICU. The occurrence of AKI in this critical population, in addition to the significant impact on morbidity and increased length of stay and hospital costs, is an independent risk factor for mortality in affected patients.[75]

As important as the AKI in the prognosis of these patients are comorbidities, previous nutritional status, and complications such as infection, inflammation, and ventilatory support, which alter the EE of these patients.[72,76]

Schneeweiss et al.[77] studied energy metabolism by IC in 86 patients with various forms of renal failure and in 24 control subjects. The groups were: AKI with sepsis (n=18), AKI without sepsis (n=11), chronic kidney disease (CKD) in pre-dialysis phase (n=17), CKD on hemodialysis (n=25), and patients with severe untreated azotemia (n=15). They noted that the REE was increased only in patients with AKI associated with sepsis and was not correlated with body temperature (r=0.359). Patients with septic AKI showed a 33% increase in REE, while AKI not associated with sepsis, dialysis, and uremia did not change the REE. However, the study did not evaluate the influence of dialysis in REE of patients with AKI, or sepsis in the absence of AKI.

Some studies assessed if the uremia and dialysis affect EE in CKD patients, with conflicting results. The first study, conducted over 20 years ago, showed that REE in CKD patients either undergoing dialysis or not was similar to that of healthy individuals.[77,78] Ikizler et al.,[79] in 1996, reported that patients on hemodialysis had significantly higher REE than the healthy controls matched for gender, age, and body mass index (BMI). More recent studies with larger numbers of clinically stable patients with CKD, matched by gender and age with healthy controls, showed different results. Patients with CKD on conservative treatment were hypometabolic, i.e. with REE lower than the control group,[80,81] while dialysis patients treated by hemodialysis and peritoneal dialysis showed REE similar to the controls.[82,83] When evaluating REE of patients with CKD under catabolic conditions, such as in cases of uncontrolled *diabetes mellitus*, severe hyperparathyroidism, and inflammation, hypermetabolism has been observed.[84,85] Avesani et al.,[84] when comparing the REE of diabetic and non-diabetic patients with pre-dialysis CKD, matched for gender, age, and renal function, showed that REE in the diabetic group was 12.5% (182 kcal/day) higher than that seen in non-diabetics. The same group noted that in patients with pre-dialysis CKD and subclinical inflammation (C-reactive protein levels – CRP > 0.5 mg/dL) REE was significantly higher than in patients with CRP levels < 0.14 mg/dL even after adjusting for gender, age, and lean body mass.[83]

There are very few studies evaluating REE in patients with AKI and, thus, experts tend to follow protocols used for patients in intensive care to determine the energy demand and other aspects involved in nutritional therapy.[86] There is a consensus on the recommendation of obtaining the actual EE using IC, if possible, in individuals kept under intensive care, more specifically, people with AKI.[31,87]

The negative impact of overfeeding and underfeeding in the prognosis of these patients and within this context is well-known. Determining the REE and the adequate supply of nutrients is paramount as it contributes to preserve lean body mass and energy reserves, to restore the immune function, to attenuate the inflammatory response and oxidative stress, and to reduce mortality rates in patients with AKI.

Conclusion

Determining the energy needs should be an integral part of primary care given to the patient in critical condition, considering the benefits of an adequate supply of nutrients to reduce complications and mortality. Despite its technical and financial limitations, IC proved to be the best method for assessing EE in patients under intensive care. Since there are very few studies on nutritional care of patients with AKI, recommendations for critically ill patients are usually adopted. Thus, the need for new studies that address nutritional aspects and assist in planning appropriate prescription of nutritional therapy for critically ill patients with AKI is evident.

Resumo

Gasto energético de repouso em pacientes críticos: métodos de avaliação e aplicações clínicas

Os pacientes em cuidados intensivos apresentam alterações sistêmicas, metabólicas e hormonais, que podem afetar adversamente a condição nutricional e levar à rápida e importante depleção da massa magra e desnutrição. Vários fatores e situações clínicas podem exercer influência sobre o gasto energético (GE) de pacientes críticos, como idade, sexo, cirurgias, infecções graves, medicamentos, modalidade ventilatória e disfunção de órgãos. Dentre as condições clínicas que podem cursar com alteração do GE, encontra-se a lesão renal aguda (LRA), distúrbio complexo comumente observado em pacientes críticos, com manifestações que podem variar de mínimas elevações na creatinina sérica até insuficiência renal com necessidade dialítica. Dessa forma, essa população crítica apresenta necessidades nutricionais complexas e a determinação do gasto energético de repouso (GER) torna-se essencial para o ajuste da oferta nutricional e para o planejamento de uma nutrição adequada, assegurando que as necessidades energéticas sejam atingidas e evitando as complicações associadas à hiper ou hipoalimentação. Diversos métodos de avaliação do GE nessa população foram descritos, mas todos apresentam limitações. Dentre eles, destacam-se a calorimetria direta, a água duplamente marcada, a calorimetria indireta (CI), diversas equações preditivas e, mais atualmente, a regra de bolso (kcal/kg de peso). Atualmente, a CI é eleita o método padrão-ouro.

Palavras-chave: gasto energético, paciente crítico, necessidade energética, calorimetria indireta.

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Ascorbic acid in the prevention and treatment of cancer

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Summary

This review is aimed at the systematic mapping of ascorbic acid in the prevention and/or treatment of cancer in clinical and non-clinical studies from 2011 to 2015, in order to understand dose-response variations as well as its mechanisms of action as an antioxidant and antitumor agent. Seventy-eight articles were retrieved from the PubMed/Bireme database, of which only 30 included ascorbic acid in the prevention and/or treatment of cancer. However, there are controversies regarding doses and a lack of clinical studies featuring its mechanism of action more clearly. Other studies are needed to understand dose-response variations, as well as its targeting mechanisms of action, both as an antioxidant and antitumor agent, to assist treatment and prevention of cancer, aiming at better quality of life for both patients and the general population.

Keywords: neoplasms, cancer, prevention, ascorbic acid, antioxidants.

Introduction

The word "cancer" derives from the Greek *Karkinos*, which means crab, a reference to the blood vessels infiltrated in the tumor as if they were the claws of this animal. Currently, cancer is characterized as a complex disease that involves the alteration of gene expression, sustains cell survival and proliferation, and can be modified by genomic and epigenomic factors.[1] Genomic factors are characterized by changes in the sites of the genes, promoting mutations, while epigenomic factors correspond to changes that do not alter the sequence of DNA bases but their conformation through changes in histone, methylations in DNA bases and nucleosome remodeling.[2,3]

Cancer cells operate under a high level of oxidative stress, due to high baseline levels of reactive oxygen species, oncogenic transformation, and metabolic reprogramming.[4] Oxidative stress occurs due to imbalance between the production of free radicals [superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), nitric oxide (NO), and more] and their elimination by antioxidant defense mechanisms [superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), among others], which induces cell damage caused by lipid peroxidation generating derangement and loss of function and integrity of the cell membrane, as well as DNA damage, promoting genomic instability and cell proliferation, thereby increasing the somatic mutations and neoplastic transformation.[5,6]

According to the Brazilian National Cancer Institute (INCA, in the Portuguese acronym), in 2012 there were 14.1 million cases of cancer in the world, with a total of 8.2 million deaths from the disease. It is estimated that in 2030 the global burden of cancer will be 21.4 million new cases and 13.2 million deaths, mainly due to the growth and aging of the population.[7] Among the types of cancer, breast cancer is the second most common, with a worldwide estimate in 2012 of about 1.67 million new cases. In Brazil, the estimate is about 25% of all cancer types diagnosed in women. Mortality amounts to 70% and the 5-year survival ranges from 80 to 40% depending on the country's economic development. In Brazil, the number of new cases of breast cancer was estimated at 49,000 in 2010.[8]

The etiology of breast cancer is not fully understood; it is multifactorial and includes genetic, reproductive, and environmental factors. The World Health Organization (WHO) states that consumption of fruits and vegetables can help prevent cancer, due to its composition with nutrients such as vitamins, minerals and fiber.[9] According to the INCA (2011), antioxidant foods, rich in ascorbic acid (vitamin C), carotenoids (vitamin A) and tocopherol

(vitamin E), selenium, and flavonoids, are recommended due to their antagonistic action, following the requirements presented in the Dietary Reference Intake (DRI), as they can help in the prevention of cancer, inhibiting oxidation and free radical production, and also favoring oxidative stress and even promoting carcinogenesis.[10]

Ascorbic acid (vitamin C) has been widely used in the treatment and prevention of cancer; nevertheless, the clinical results are still inconclusive. At low concentrations, it has an antioxidant role, preventing oxidation, which induces apoptosis. However, its high content can increase the production of ATP (generated by mitochondria) inducing apoptosis in tumor cell lines, via a pro-oxidant mechanism.[11] Studies show dose-dependent antineoplastic activity with influence on apoptosis, cell cycle, and cell signaling, increasing the cytotoxicity of the antineoplastic agent in cell lines of breast cancer treated with mitoxantrone and ascorbic acid.[12]

However, there are still many controversies regarding the role of vitamin C in the prevention and treatment of cancer. This review is aimed at the systematic mapping of ascorbic acid in the prevention and/or treatment of cancer in clinical and non-clinical studies from 2011 to 2015, in order to understand dose-response variations as well as its mechanisms of action as an antioxidant and antitumor agent.

Method

The survey was conducted based on a literature review on Pubmed/Bireme databases, of scientific articles derived from clinical and non-clinical studies carried out between 2011 and 2015, using the keywords "cancer" and "ascorbic acid". Seventy-six articles were retrieved, of which 30 were used in the study as they met the inclusion criteria: clinical and non-clinical studies using ascorbic acid in the prevention and/or treatment of cancer between 2011 and 2015; and not the exclusion criteria: studies that do not use ascorbic acid in the treatment and/or prevention of cancer and who are outside the established time range (Figure 1). Of the articles selected for analysis, 12 used ascorbic acid as antioxidant: two clinical and ten non-clinical studies; 18 used it as pro-oxidant, of which only one was clinical, while the remaining (17) were non-clinical studies.

Results and discussion

Ascorbic acid as antioxidant

Ascorbic acid is an essential micronutrient for human health, having antioxidant activity and participating in the production of proteins such as collagen, norepinephrine and serotonin. It is acquired through the ingestion of various plants, especially citrus fruits such as lemon and orange, and vegetables including tomatoes and broccoli, with recommended daily doses of 90 mg for men and 75 mg for women.[13]

Table 1 shows the clinical and non-clinical studies on the use of ascorbic acid as an antioxidant in the treatment and/or prevention of cancer, describing its use in several types of cancer or cell lines at different doses/concentrations and their mechanisms of action. The clinical studies (2) involved different types of cancer (pancreas, breast, kidney, lung, liver, bladder, lymphoma, prostate, colon, brain, leukemia, stomach, ovary, skin, and uterus) and doses of ascorbic acid (0.04-0.28 mM; 1-10 mM); the non-clinical studies (10) used different tumor cell lineages (MCF-7 cells in breast cancer; renal carcinoma; B16FO

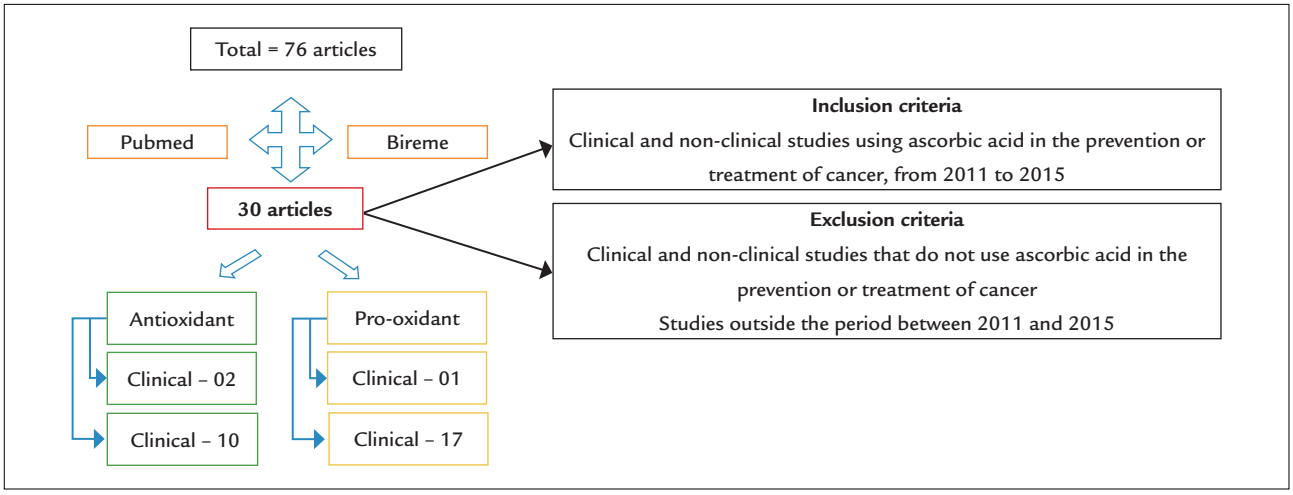

FIGURE 1 Literature search design with inclusion and exclusion criteria.

TABLE 1 Clinical and non-clinical studies using ascorbic acid as antioxidant in the treatment and/or prevention of cancer.

Study type	Type of cancer/cell	Mechanism of action	Dose/concentration	References
Clinical	Pancreas, breast, kidney, lung, liver, bladder, lymphoma, prostate, colon, and stomach	Decrease in levels of C-reactive protein and proinflammatory cytokines	0.04-0.28 mM	(25)
Non-clinical	Breast cancer in mice	Hinders metastases, tumor growth and secretion of inflammatory cytokines, and enhances tumoral encapsulation	0.85 mM	(26)
Non-clinical	MCF-7 cells in breast cancer	Attenuation of cytotoxicity, decrease in apoptosis, protection of neoplastic cells against lipid peroxidation	0.05 and 0.5 mM	(27)
Non-clinical	MCF-7 cells in breast cancer	Decrease in cytotoxicity	0.1 mM	(28)
Clinical	Pancreas, breast, kidney, lung, liver, bladder, lymphoma, prostate, colon, brain, leukemia, stomach, ovary, skin, and uterus	Decreased inflammation	1-10 mM	(29)
Non-clinical	Cells from renal carcinoma	Anti-apoptotic activity by recruiting Bcl-2	0.11 and 2.28 mM	(30)
Non-clinical	Cells from melanoma (B16FO)	Hinders metastases and tumor growth	4 mM	(31)
Non-clinical	Cells from cervical cancer (HeLa)	Modulation of markers for cancer proliferation (Ki67), invasion and metastasis (MMP-2 and -9), angiogenesis (VEGF), apoptosis (TUNEL and Bcl-2), and inflammation (COX-2, iNOS and GSTπ)	4 mM	(32)
Non-clinical	Lung cancer in ferrets	Protection against lung injury induced by exposure to cigarette smoke, by inhibiting the expression of cyclin D1	1.2 mM	(33)
Non-clinical	Cells from neuroblastoma	Anti-apoptotic activity	0.1-0.4 mM	(34)
Non-clinical	Cells from acute lymphoblastic leukemia	Decreased production of reactive oxygen species caused by 4-(hydroxyphenyl) retinamide (4-HPR)	100 µM	(35)
Non-clinical	Cells from osteosarcoma (143-B)	Limitation of the invasive potential	0.28 mM	(36)

Source: Literature search.

melanoma cells; HeLa cervical cancer cells; lung; neuroblastoma; cells from acute lymphoblastic leukemia; 143-B osteosarcoma cells), at varied doses/concentrations (0.85 mM; 0.05 and 0.5 mM; 0.1 mM; 0.11 and 0.28 mM; 4 mM; 1.2 mM; 0.1-0.4 mM; 0.28 mM).

Plants and most animals synthesize ascorbic acid using glucose. Humans, however, do not synthesize this compound as the L-gulonolactone oxidase gene does not function, and thus this vitamin is obtained through the diet as ascorbate and dehydroascorbic acid (DHA). The normal concentration of ascorbic acid in human plasma is about 40 to 80 µM, and it is at this concentration range that endogenous vitamin C acts as an antioxidant. Physiological concentrations of ascorbate demonstrated inhibition of LDL oxidation and a synergistic action with vitamin E preventing lipid oxidation of cell membranes.[14] Studies describe that intravenous ascorbic acid is more effective for raising serum levels of ascorbate than the form administered orally.[15]

Clinical studies showed that reductions in the levels of C-reactive protein and proinflammatory cytokines, resulting in decreased inflammation, are the main mechanisms antioxidant. Non-clinical studies, in turn, revealed attenuation of cytotoxicity, reduced apoptosis, protection of neoplastic cells against lipid peroxidation, modulation of markers of cancer proliferation (Ki67), invasion and metastasis (MMP-2 and -9), angiogenesis (VEGF), apoptosis (TUNEL and Bcl-2) and inflammation (COX-2, iNOS and GSTπ), decreased production of reactive oxygen species generated by 4-(hydroxyphenyl)retinamide (4-HPR), limitation of the invasive potential, also hindering metastases, tumoral growth and secretion of inflammatory cytokines, and enhancing tumor encapsulation, anti-apoptotic activity through Bcl-2 recruitment and protection against lung

injury induced by exposure to tobacco smoke, by inhibiting the expression of cyclin D1 (Table 1).

Vitamin C is an excellent reducing agent, which undergoes two successive oxidations to form the ascorbate radical ($Asc^{\cdot -}$). Ascorbate is relatively unreactive due to the stability of the unpaired electron and oxidizes ascorbic acid to DHA; this reducing agent function is what maintains the structure of enzymes, thus allowing the biochemical machinery of cells and tissues functioning normally.[14]

Low electron potential and resonance stability is what makes it an antioxidant. The authors also reported that vitamin C plays the role of collecting reactive oxygen species, acting as an antioxidant for maintaining the intracellular redox balance and minimizing the oxidative damage caused by these free radicals.[16] Corroborating these studies, other researchers cite that nutrients like vitamin A, C, and E can neutralize reactive oxygen species, derived from the imbalance between antioxidant defenses and oxidative stress caused by diseases such as cancer or its treatment. Therefore, antioxidants, such as ascorbic acid, may assist in the prevention of cancer or its treatment, reducing side effects related to chemotherapy.[17]

Ascorbic acid as an antitumor agent

Vitamin supplementation can improve the benefits and quality of life of cancer patients. However, the literature shows controversy over the treatment of cancer including ascorbic acid. Researchers report that *in vitro* studies of neuroblastoma, bladder cancer, pancreatic cancer, and other tumor types showed cytotoxic effect of ascorbic acid, while *in vivo* studies supported this anti-cancer potential of the vitamin C.[18]

Table 2 shows the clinical and non-clinical studies on the use of ascorbic acid as an antitumor agent in the treatment and/or prevention of cancer, describing its use in several types of cancer or cell lines at different doses/concentrations and mechanisms of action. Of these, only one clinical study showed patients with metastatic pancreatic cancer treated with ascorbic acid at 0.28; 0.34 and 0.56 mM doses.

Regarding the non-clinical studies (17), they used different cancer cell lineages [IOSE-385, OVCAR-3, SKOV-3 and OVCA-432 for ovary cancer; esophageal squamous cells and CP-A, CP-B, CP-C and CP-D for esophageal cancer; 23132/87 for gastric carcinoma, HT-29 colon cells, SKOV-3 ovary cells, BXPC-3 pancreatic cells, BT-20, MDA-MB-468, MDA-MB-231 and MCF-7 breast cells, U-13898, U-87 and U-251 glioblastoma cells, umbilical vein endothelial cells (HUVECs) and NHDF cells; HeLa for cervical cancer; colon carcinoma; and HEp-2 cells for laryngeal carcinoma; SK-N-MC neuroblastoma cells; PANC-1, AsPC-1, BxPC-3 and MIA PaCa-2 for pancreatic cancer; Epstein-Barr virus (EBV)-positive Burkitt's lymphoma and lymphoblastoid cells; PC3 prostate cancer cells; malignant pleural mesothelioma; NSCLC epithelial lung cancer; solid Ehrlich carcinoma; RKO and SW480 for colon cancer], in various concentrations of ascorbic acid (0.25 mM; 0.1-2 mM; 0.3 mM; 0.5 mM; 0.005-0.1 mM; 4 mM; 28.39 mM; 3-10 mM; 1-6 mM; 4.26 mM; 22.71 mM; 0.4 mM; 11.36 mM; 0.5-5 mM; 0.68 mM; 1-3 mM).

At low millimolar concentrations, ascorbic acid is able to "kill" some cell lines *in vitro*, while *in vivo* it generates superoxide radicals, hydrogen peroxide, and extracellular ascorbyl responsible for its cytotoxic activity; however, concentrations as high as 20 mM did not pose any risk to the lineage of non-malignant cells.[19] Other studies confirm that high doses of ascorbic acid are effective in cell death as seen in *in vitro* studies as well as *in vivo* tumor growth inhibition.[20] Corroborating this study, researchers describe that vitamin C can be toxic in a selective manner in some types of tumor cells as a pro-oxidant, since concentrations above physiological (0.1 mM), between 1 mM and 10 mM, are toxic for neoplastic cells *in vitro*, for example, for melanoma and neuroblastoma cells, where concentrations from 10 nM to 1 mM can induce apoptosis.[21]

Regarding antitumor mechanism of action, the clinical study reported decreased tumor size. The non-clinical studies reported inhibited cell progression by increasing the levels of H_2O_2; anti-proliferative effect of tumor cells, through interference with cell cycle (G_0/G_1) and generation of H_2O_2; cytotoxicity; modification of proteins related to apoptosis; reduction and inhibition of cell growth; reduction of serotonin levels, increasing degree of hemorrhagic necrosis and endothelial permeability; production of reactive oxygen species through the release of Ca_2^+; induced apoptosis; induced aponecrosis in cells resistant to apoptosis; inhibited cell proliferation and secretion of MMP-2 and -9, and increased secretion of TIMP-2; induced autophagy; tumor suppression; blockage of tumor progression and metastasis; activation of apoptosis and reactive oxygen species-dependent mechanisms; loss of cell viability; increased expression of p53; down-regulation of proteins (Sp1, Sp3 and Sp4) and decreased expression of genes that involve cell proliferation and angiogenesis (Table 2).

Vitamin C has been occasionally used to complement the treatment of cancer since 1974, aiding in patients' survival and quality of life. Studies in humans, animals, and *in vitro* show that antioxidants such as ascorbic acid, tocopherols, and carotenoids can inhibit the growth of neoplastic cells, inducing apoptosis, boost cell differen-

TABLE 2 Clinical and non-clinical studies using ascorbic acid as antitumor agent in the treatment and/or prevention of cancer.

Study type	Type of cancer/cell	Mechanism of action	Dose/concentration	References
Non-clinical	Cells from ovarian cancer (IOSE-385, OVCAR-3, SKOV-3 and OVCA-432)	Inhibition of cell progression by increasing the levels of H_2O_2	0.25 mM	(37)
Non-clinical	Different cell lines	Antiproliferative effect on tumor cells, through interference with cell cycle (G_0/G_1) and production of H_2O_2	0.1-2 mM	(38)
Non-clinical	AGS cells	Inhibition of cell progression, cytotoxicity, modification of proteins related to apoptosis	0.3 mM	(39)
Non-clinical	Esophageal squamous cells and Barrett's esophagus cells (CP-A, CP-B, CP-C and CP-D)	Decreased cell growth	0.5 mM	(40)
Non-clinical	Cells from gastric (23132/87), colon (HT-29), ovary (SKOV-3), pancreas (BXPC-3) and breast (BT-20, MDA-MB-468, MDA-MB-231 and MCF-7) carcinoma, glioblastoma (U-13898, U-87 and U-251), endothelial cells (HUVEC) and fibroblasts (NHDF)	Production of H_2O_2	0.005-0.1 mM	(41)
Non-clinical	Cells from cervical cancer (HeLa)	Decreased cell growth	4 mM	(32)
Non-clinical	Colon carcinoma in mice	Decreased levels of serotonin, increased level of hemorrhagic necrosis and permeability of the endothelium	28.39 mM	(42)
Non-clinical	Laryngeal carcinoma (HEp-2)	Production of reactive oxygen species through the release of Ca_2^+	3-10 mM	(43)
Non-clinical	Cells from neuroblastoma	Induction of apoptosis	1-6 mM	(34)
Non-clinical	Cells from pancreatic cancer (PANC-1, AsPC-1, BxPC-3 and MIA PaCa-2)	Aponecrosis induced in cells resistant to apoptosis	4.26 mM	(44)
Non-clinical	Cells from Epstein-Barr virus-positive Burkitt's lymphoma and lymphoblastoid cells	Production of reactive oxygen species and induction of cell death	22.71 mM	(45)
Non-clinical	Cells from neuroblastoma (SK-N-MC) *in vitro* and *in vivo*	*in vitro* – induction of apoptosis, inhibition of cell proliferation, secretion of MMP-2 and -9, and increased secretion of TIMP-2 *in vivo* – inhibition of tumor growth	Not reported	(46)
Clinical	Metastatic pancreatic cancer	Decreased tumor size	0.28; 0.43 and 0.5 mM	(47)
Non-clinical	Cells from prostate cancer (PC3) in mice	Production of reactive oxygen species, induced autophagy, tumor suppression	0.4 mM	(48)
Non-clinical	Cells from malignant pleural mesothelioma in rats	*in vitro* – synergism in the mechanism of cytotoxicity *in vivo* – blocking of tumor progression and metastasis, reduction in tumor size	11.36 mM	(49)
Non-clinical	Epithelial cells from lung cancer (NSCLC)	Induction of cell death by activation of apoptosis and via mechanism of production of reactive oxygen species, loss of cell viability	0.5-5 mM	(50)
Non-clinical	Solid Ehrlich carcinoma in mice	Inhibition of tumor growth and increased expression of p53	0.68 mM	(51)
Non-clinical	Cells from colon cancer (RKO and SW480)	Decreased cell proliferation, induced apoptosis and necrosis, down-regulation of proteins (Sp1, Sp3 e Sp4) and decreased expression of genes that involve cell proliferation and angiogenesis	1-3 mM	(52)

Source: Literature search.

tiation and inhibiting the activity of protein kinase C and adenylyl cyclase, which proves its antitumor effect, also affirming that a high-dose therapy can benefit patients by improving their prognosis and therapeutic efficacy.[22]

Studies have reported that the pro-oxidant mechanisms of ascorbic acid include an ability to reduce metal ions such as Fe^{3+} and Cu^{3+}, a process that generates free radicals such as hydroxyl radical, which interact with DNA, causing breaks in the phosphodiester bonds in addition modifications in the bases, generating induced cytotoxicity.[23] Some research indicate another antitumor mechanism of action, the proliferation of natural killers (NK) cells without affecting its normal functions. According to them, these cells have the ability to "kill" tumor cells without the need for sensitization of direction, and that ascorbic acid promotes their proliferation.[24]

Conclusion

Studies have reported the use of ascorbic acid in the prevention and treatment of cancer. However, there is controversy about its antioxidant and antitumor role. This study revealed that there are reports in the literature of the effects of ascorbic acid at different doses/concentrations as antioxidant acting by several mechanisms, including the attenuation of cytotoxicity, reduced apoptosis, protection of neoplastic cells against lipid peroxidation, decrease in tumor growth and inflammatory cytokine secretion. And as an antitumor agent, ascorbic acid acts through the inhibition of cell progression, increased levels of H_2O_2, antiproliferative effect of tumor cells, cytotoxicity, induction of apoptosis, and more. There are also incompatibilities with regard to doses/concentration of ascorbic acid, as well as the need for characterization of clinical studies and mechanisms of action. Thus, other studies are needed to understand dose-response variations, as well as its targeting mechanisms of action, both as an antioxidant and antitumor agent, to assist treatment and prevention of cancer, aiming at better quality of life for both patients and the general population.

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Resumo

Ácido ascórbico na prevenção e no tratamento do câncer

Este estudo de revisão teve como objetivo fazer o mapeamento sistemático do ácido ascórbico na prevenção e/ou no tratamento do câncer como antioxidante e/ou pró-oxidante em estudos clínicos e não clínicos, entre 2011 e 2015, para o entendimento das variações de dose-resposta, bem como dos seus mecanismos de ação como agente antioxidante e antitumoral. Nas bases de dados Pubmed e Bireme, foram identificados 78 artigos, dos quais apenas 30 apontavam o ácido ascórbico na prevenção e/ou no tratamento do câncer. Contudo, há controvérsias sobre as doses utilizadas e faltam estudos clínicos que caracterizem melhor o seu mecanismo de ação. Outros estudos devem ser realizados para o entendimento das variações de dose-resposta, bem como de seus mecanismos de ação, como agente antioxidante ou antitumoral, para auxiliar o tratamento e a prevenção do câncer, visando à melhor qualidade de vida dos pacientes e da população em geral.

Palavras-chave: neoplasias, câncer, prevenção, ácido ascórbico, antioxidantes.

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Fetal thrombotic vasculopathy: A case report and literature review

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Summary

Introduction: Fetal thrombotic vasculopathy is a recently described placental alteration with varying degrees of involvement and often associated with adverse perinatal outcomes. The diagnosis is made histologically and therefore is postnatal, which makes it a challenge in clinical practice.
Method: Case report and review of literature on the subject.
Results: The present case refers to a pregnant woman presenting fetal growth restriction, with poor obstetrical past, and sent late to our service. Even with weekly assessments of fetal vitality (fetal biophysical profile and Doppler velocimetry) and prenatal care, the patient progressed with fetal death at 36 weeks and 1 day. There was no association with inherited and acquired thrombophilia. Pathological examination of the placenta revealed fetal thrombotic vasculopathy.
Conclusion: The fetal thrombotic vasculopathy may be associated with adverse perinatal outcomes including fetal death, but much remains to be studied regarding its pathogenesis. Diagnosis during pregnancy is not possible and there is still no proven treatment for this condition. Future studies are needed so that strategies can be developed to minimize the impact of fetal thrombotic vasculopathy.

Keywords: fetal death, placental diseases, fetal growth restriction.

Introduction

Fetal thrombotic vasculopathy (FTV) is a placental change described by Redline and Pappin in 1995 that encompasses several pathological findings in fetal placental circulation: fibrinoid vasculitis, avascular villi, hemorrhagic endovasculitis and thrombi in vessels, chorionic trunk or villi.[1] These lesions limit perfusion of villi distal to the occlusion resulting in stromal-vascular karyorrhexis and avascular villi.[2,12]

Even with a variety of possible clinical manifestations, FTV can remain asymptomatic until birth, induce fetal growth restriction (FGR) or cause fetal death when there is massive placental involvement or damage to the cord. To date, no specific sonographic criteria are reliable enough for the diagnosis of prenatal FTV. It can, however, be suspected in cases of FGR, Doppler changes such as zero or reverse diastole, and a non-reassuring intrapartum cardiotocography.[3]

The objective of this study is to report a case of FTV and present a literature review on the topic.

Method

Our article presents a case report of FTV with adverse perinatal outcome admitted to our service.

Results

A 40-year old pregnant woman, 5G2Pn2A, referred to our service at 33 weeks and 4 days with a diagnosis of FGR obtained by ultrasonography performed at 31 weeks and 2 days (estimated weight 1,400 g, Hadlock chart 7th percentile). In previous obstetrical ultrasounds, performed at 23, 27, and 29 weeks, the estimated fetal weight was within the normal range for gestational age. The patient brought the result of a non-invasive test (whole blood) for assessment of fetal trisomy, which showed normal

fetal karyotype at 12 weeks, and morphological ultrasound performed in the second trimester of pregnancy with no evidence of fetal malformations.

At the first consultation in our service, she was taking enoxaparin 40 mg once daily and acetylsalicylic acid (ASA) 100 mg daily, starting 15 days before.

Family history included a brother with heart disease and chronic hypertension, and a grandfather with *diabetes mellitus*. She did not have comorbidities and her blood pressure showed no alterations in the current pregnancy. The first and third pregnancies resulted in fetal death at 22 to 28 weeks, respectively. In the first pregnancy, the patient reports increased blood pressure. The second and fourth pregnancies progressed to abortion, at 7 and 8 weeks, respectively, and the patient underwent curettage on both occasions. A difference in the current pregnancy is that the baby's father is not the same.

Pathologic examination of the placenta in the third gestation revealed multiple placental infarcts and intervillous fibrin deposition; umbilical cord and chorio-amniotic membranes were unchanged.

At her first visit, we chose to continue treatment with ASA and stop enoxaparin. Obstetric ultrasounds were scheduled every two weeks and fetal vitality tests (biophysical profile and Doppler), on a weekly basis. Delivery was scheduled at 37 weeks.

Subsequent ultrasound scans performed at 33 and 35 weeks showed estimated fetal weight of 1,829 g (11 percentile) and 2,266g (11 percentile), respectively, thus a fetus with borderline growth restriction. Fetal vitality assessments at 33, 34, and 35 weeks did not demonstrate changes in fetal biophysical profile, umbilical artery or middle cerebral artery Doppler velocimetry at those occasions.

On the day of a new evaluation of fetal vitality, scheduled at a gestational age of 36 weeks and 1 day, fetal death was confirmed. The patient was hospitalized for cervical preparation with misoprostol and subsequent induction of labor with oxytocin for resolution of pregnancy.

Fetal necropsy revealed antenatal anoxia, generalized visceral congestion, amniotic fluid aspiration, and absence of fetal anomalies. It was a female fetus weighing 1,900 g. The placenta had an oval shape and weighed 310 g. The pathological study of the placenta revealed FTV with mural thrombosis of the chorionic and intraplacental arteries, amnion nodosum, and presence of large amounts of horny scales dissecting the amnion, forming a cystic cavity between amnion and chorion (Figures 1, 2, 3).

Thrombophilia tests were performed during hospital stay and after 2 months of hospital discharge, and only

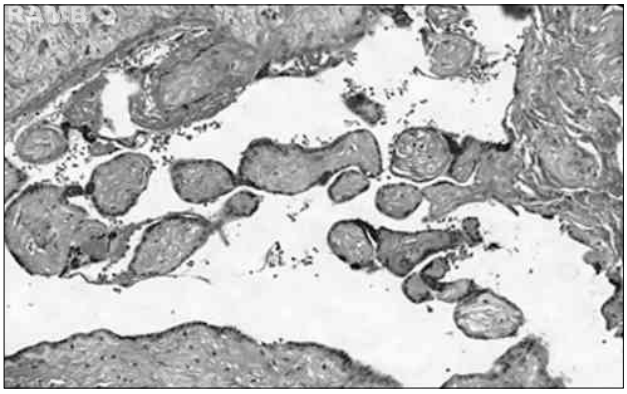

FIGURE 1 Histological section of placenta with groups of avascular villi (HE, 200x).

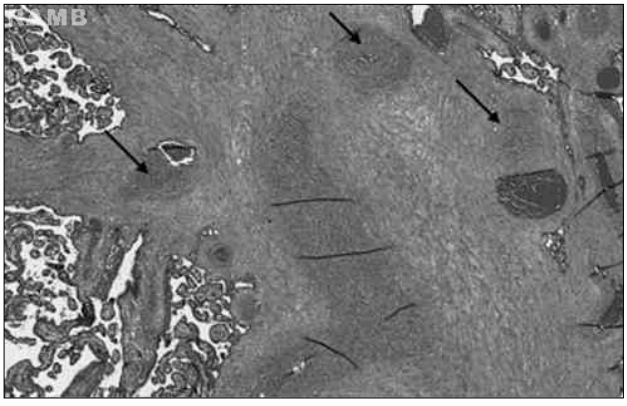

FIGURE 2 Histological section of placenta with arteries from villous trunks with thickening of the muscle wall and narrowing of the vascular lumen (arrows) (HE, 100x).

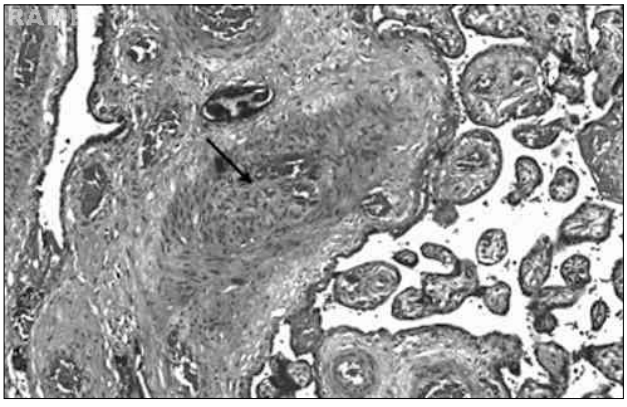

FIGURE 3 Histological section of placenta with artery from villous trunk showing occlusive thrombosis and luminal revascularization (arrow) (HE, 400x).

a mutation of the methylenetetrahydrofolate reductase (MTHFR) enzyme in homozygous form was found. Other tests, including antiphospholipid syndrome (APS), antithrombin, homocysteine, S and C protein, Factor V Leiden mutation, and prothrombin gene mutation, showed values within the normal range.

Discussion

This case demonstrates the difficulty in the management of certain patients with FGR, especially when there is an adverse obstetrical past. The thrombophilia tests showed no significant changes, even after 2 months of stillbirth. The fetal vitality tests (biophysical profile and Doppler assessment of umbilical artery, middle cerebral artery, and ductus venosus) had normal values and were repeated weekly. Fetal death occurred 6 days before the scheduled date for resolution of pregnancy. The estimated fetal weight was at the limit of what we consider small for gestational age (10th percentile). There are no sonographic criteria that might suggest FTV, which was identified only in the pathological examination of the placenta.

It is believed that the etiology of FTV is varied and complex, so that it can be summarized by changes in Virchow's triad: endothelial injury, hemodynamic abnormalities such as stasis or turbulence, and hypercoagulability. Thrombi found at the chorionic bed may lead to endothelial damage as a result of intense fetal acute inflammatory response, as in the case of chorioamnionitis. Factors related to the umbilical cord, including true knots and marginal or membrane insertions can also result in the formation of thrombi.[5] Last, hypercoagulable states due to fetal or maternal thrombophilia have also been associated with FTV.[4,11] Loh et al.[4] report a case of fetal myeloproliferative disease, which resulted in hypercoagulable state and consequent FTV.

The Pediatric Pathology Society has proposed criteria for severe FTV classification: two or more foci of 15 or more avascular villi or villous stromal-vascular karyorrhexis.[2] Such classification was studied by Chisholm et al.[6] in a retrospective cohort of 139 cases, in which 67 cases with severe FTV large vessels were associated with preeclampsia, birth by fetal indication, lower placental weight, umbilical cord abnormalities, and small for gestational age fetus. In the cases that were not classified as severe, the results were similar to those without FTV. In addition, a possible association between severe FTV and neurological damage was suggested.

In a retrospective cohort study, Saleemuddin et al.[7] studied placentas with (n=113) and without (n=216) a diagnosis of FTV and found an increase in the rate of fetal death, FGR, oligohidramnia, and a frequency nearly six times higher of fetal cardiac anomalies. Other fetal abnormalities have been reported in association with FTV. Lian et al.[9] describe a case of congenital intestinal atresia, possibly due to FTV, and Ernst et al.[1] report three cases of severe perinatal liver disease. As for neurological disorders after birth, the studies differ in respect to FTV as a causal factor. Mcdonald et al.,[8] in a retrospective cohort of 93 cases, found a relationship between FTV and the occurrence of neonatal encephalopathy. In a more recent study, Lepais et al.,[3] through a retrospective cohort analysis of 54 placentas and monitoring of newborns for 3 years, found an association between FTV and pregnancy-induced hypertension (PIH), FGR (5.4 times higher), perinatal death and early neonatal death, in addition to a greater need for caesarean sections and emergency deliveries. There was also a higher number of thromboembolic events during the follow-up of these children, while other abnormalities such as brain or cardiac impairment, or the presence of malformations, were not related to this change. Despite a higher incidence of developmental delay in the group with FTV, this finding was not statistically significant.

Magnetti et al.[10] propose that the placenta of fetuses with perinatal thromboembolic events should be examined. Leistra-Leistra et al.,[2] in turn, found no correlation between the occurrence of fetal thromboembolism and FTV or thrombophilia and FTV.

Conclusion

FTV may be related to the occurrence of adverse perinatal outcomes, including FGR and fetal death, as described in the present case. The fact that the diagnosis is only possible in the postnatal period (pathological examination) makes FTV a major medical challenge, since irreversible fetal damage may have already been caused.

In many reports, there is no association with thrombophilia, as in this case. The presence of *MTHFR* mutation, but with normal homocysteine, is not consistent with the unfavorable progression of this pregnancy.

Apart from the borderline FGR (near the 10th percentile for gestational age), there were no other relevant data that indicate a need to anticipate delivery. The outcome shown here is one of many possible in cases of FTV.

As a relatively recent abnormality, little is known about the pathogenesis, early detection and suspicion, and especially effective measures to change the unfavorable perinatal outcome. New criteria for diagnosis are highly desirable so that preventive measures can be taken during prenatal care. This is the desire of all those who deal with high-risk pregnancies.

Resumo

Vasculopatia trombótica fetal: relato de caso e revisão da literatura

Introdução: a vasculopatia trombótica fetal é uma alteração placentária recentemente descrita, com espectro variado de acometimento e, muitas vezes, associada a resultado perinatal adverso. Trata-se de diagnóstico histopatológico e, portanto, pós-natal, o que a torna um desafio para a prática clínica.
Método: apresentação de um relato de caso e revisão da literatura.
Resultados: o caso apresentado é de uma gestante com restrição do crescimento fetal, encaminhada tardiamente ao serviço, com histórico obstétrico ruim. Apesar da avaliação semanal da vitalidade fetal (perfil biofísico fetal e dopplervelocimetria) e dos cuidados pré-natais, o caso evoluiu a óbito fetal com 36 semanas e 1 dia. Não houve associação com trombofilias hereditárias e adquiridas. O anatomopatológico da placenta revelou vasculopatia trombótica fetal.
Conclusão: sabe-se que a vasculopatia trombótica fetal pode estar associada a resultado perinatal adverso, incluindo óbito fetal. Ainda há muito a ser estudado acerca de sua etiopatogenia. Não é possível o diagnóstico durante a gestação e não existe ainda qualquer tratamento comprovado para essa condição. Estudos futuros são necessários para que estratégias que minimizem o impacto da vasculopatia trombótica fetal sejam desenvolvidas.

Palavras-chave: morte fetal, doenças placentárias, restrição do crescimento fetal.

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Adult T-cell leukemia/lymphoma

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Summary

Adult T-cell leukemia/lymphoma (ATL) is a malignancy of mature CD4+ T-cells caused by human T-cell lymphotropic virus type 1 (HTLV-1). Twenty million people are believed to be infected throughout the world, mostly in Japan, Africa, the Caribbean, and South America, particularly in Brazil and Peru. ATL affects about 5% of infected individuals and is classified in the following clinical forms: acute, lymphoma, primary cutaneous tumoral, chronic (favorable and unfavorable), and smoldering (leukemic and non-leukemic). Although it is considered an aggressive disease, there are cases with a long progression. We emphasize the importance of clinical classification as an indispensable element for evaluating prognosis and appropriate therapeutic approach. Since several cases have been published in Brazil and this disease is still poorly known, we decided to make a review paper for dissemination of clinical, hematological and pathological aspects, diagnosis, and therapy. The best way to reduce the occurrence of ATL would be halting the transmission of the virus through breastfeeding.

Keywords: human T-cell lymphotropic virus 1, adult T-cell leukemia/lymphoma, T-cell lymphoma, peripheral T-cell lymphoma, mycosis fungoides, cutaneous T-cell lymphoma.

Introduction

Adult T-cell leukemia/lymphoma (ATL) is a distinct neoplasia of peripheral T-lymphocytes caused by human T-cell lymphotropic virus type 1 (HTLV-1). It was described by Uchiyama et al. (1977),[1] in southwest Japan, when HTLV-1 had not yet been discovered, through observation of many patients with a different pattern of T-cell neoplasia.[1] These authors suspected a possible viral etiology.

HTLV-1 was discovered in 1980 after being isolated from cells derived from a cutaneous lymphoma, probably a mycosis fungoides (MF) lesion. Soon after, it was correlated to ATL.[2] In 1986 and in 1990, it was correlated to two other serious diseases, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[3] and infective dermatitis associated with HTLV-1 (IDH), respectively.[4] Although most infected patients remain asymptomatic, it is believed that in up to 10% of them the disease progresses during their lifetime.[5]

Several other inflammatory and autoimmune conditions, such as polymyositis, arthropathy, Sjögren's syndrome, and facial nerve paralysis have been associated with this virus.[6] Furthermore, infected individuals are more predisposed to developing infectious and parasitic diseases, and may also develop ophthalmic diseases, such as HTLV-1 uveitis.

HAM/TSP affects the central nervous system (CNS) and is characterized by progressive spastic paraplegia, sensory disorders of the lower limbs, neurogenic bladder, and bowel rhythm changes.[3] In Bahia, it occurs associated with ATL in 14% of cases.[7] IDH almost exclusively affects child/adolescent age ranges and is characterized by infected, intense, and recurrent eczema that mainly affects the scalp, face, and skin folds.[8] It has been noted that 37.5% of cases of ATL with cutaneous involvement described in Bahia have a history compatible with IDH. Furthermore, there are some well-documented cases of IDH associated with ATL.[9-13]

Epidemiology

The frequency of ATL varies according to the prevalence of HTLV-1 in different populations. It is estimated that

there are around 5 to 10 million infected individuals worldwide. It is most highly prevalent in Japan, Africa, the Caribbean Islands, and Central and South America, particularly Peru and Brazil.[14]

In Brazil, several regions are endemic for HTLV-1. A seroprevalence study of blood donors in the capitals showed a high prevalence of infection in São Luís (10.0/1,000), Salvador (9.4/1,000), Belém (9.1/1,000), and Recife (7.5/1,000). In Salvador, a study of a population sample identified the rate of carriers of the virus as 1.8%.[15]

The risk of carriers of the virus developing ATL during their lifetime is 6 to 7% in men and 2 to 3% in women, usually after a long latency period (20 to 30 years).[16] ATL corresponds to around 33% of the cases of cutaneous T-cell lymphoma at a reference service in Bahia,[17] and occurs predominantly in those of African descent.[7]

Although this disease is considered aggressive, cases with very long progression have been recorded.[18] ATL has been observed in children and adolescents, but not frequently.[18,19]

It is believed that the route of transmission responsible for the development of ATL is vertical, through breastfeeding,[20] although HTLV-1 may also be transmitted by blood transfusion, sharing of needles and unprotected sex. In Brazil, until November 1993 there were no mandatory serological tests on blood and organ donors, and to this day there is no standardization for prenatal HTLV-1 tests.[21,22]

Pathogenesis

ATL pathogenesis is not yet completely understood. The virus multiplies in the carrier through virological synapse and mitotic division. Through the synapses, various components of the virus, including its RNA, are transferred from the infected cell to an uninfected one. Inside the newly infected cell, the viral RNA is transcribed into DNA, becoming part of the human nuclear DNA, and giving rise to a newly infected clone. Using the second mechanism, the virus induces mitotic division of the infected cell, producing other identical infected cells with the proviral DNA inserted in the same site in the human genome, thereby increasing the number of cells of the infected clone. The expression of viral genes such as *tax* and *HBZ* stimulates the proliferation of infected lymphocytes and inhibits apoptosis. However, expression of the *tax* gene is not detected in infected cells originating from patients with ATL. In about 5% of HTLV-1 carriers, continuous and prolonged stimulation induces the accumulation of genetic and/or epigenetic alterations in infected cells, which acquire greater proliferative capacity, becoming established as the major clone and leading to ATL.[23,24]

Changes in the pattern of the cytotoxic immune response by both CD8 T-cells and natural killer (NK) cells from the innate immune response may lead to the development of the disease and may be conditioned by genetic factors. In this context, specific haplotypes of the human leukocyte antigen (HLA) and killer immunoglobulin-like receptors (KIR) genes may be associated with an abnormal immune response that could contribute to or slow down the progression of ATL, as already observed in HAM/TSP.[25] There is marked evidence that MHC class I genotyping influences the course of infection with HTLV-1.[26] For example, in a population from southern Japan, class I HLA-A2 and HLA-Cw8 alleles were considered as protective factors for the development of HAM/TSP, and were associated with a lower proviral load in asymptomatic carriers.[27,28]

Clinical characteristics

The natural history, clinical characteristics, and prognosis of ATL vary greatly, serving as the basis for the classification of the disease into five clinical types: smoldering, chronic, primary cutaneous tumoral (PCT), lymphoma, and acute. The smoldering type is subdivided into leukemic and non-leukemic, and the chronic type into favorable and unfavorable.[7,29,30] The acute, lymphoma, unfavorable chronic, and PCT types are considered aggressive, while the favorable chronic and non-leukemic smoldering types have a better prognosis.[7,29] There is still no data in the literature to assess the prognosis of the leukemic smoldering type.

In our case series, the median survival time (MST) of ATL is 4 months in the acute form, 9 in the lymphoma form, 21 in the PCT form, 18 in the chronic form, and 58 months in the smoldering form.[7]

The non-leukemic smoldering form without pulmonary involvement and the PCT are considered as primary cutaneous ATL.[31]

Less aggressive types may develop into more serious forms in up to 25% of cases, and this may be associated with specific changes in the gene expression profile.[32]

Table 1 presents the suggested conduct at the first consultation of a patient with suspected ATL and proposes in the medical history and physical examination the points that require more attention.

Characterizing the clinical form (Table 2) is fundamental because it will define the prognosis and therapeutic conduct.

TABLE 1 Conduct at the first consultation of a patient with suspected ATL.

Medical history	Supplementary examinations
History of the illness	**Laboratory**
Insidious/sudden onset	Serology confirmation for HTLV-1
Neurological symptoms	Complete blood count and blood smear ("flower" cells)
Digestive symptoms	Serum LDH
Performance status[70]	Serum calcium
Personal and family history	Serum albumin (a prognostic factor in the chronic form)
Birthplace	Urea (a prognostic factor in the chronic form)
IDH in childhood	Parasitology of the feces with the Baermann technique (to rule out strongyloidiasis)
HAM/TSP	Immunophenotyping and determination of soluble IL-2, if possible
ATL	**Imaging**
Dermatological diseases	CT scan of the neck, chest, abdomen and pelvis
Rheumatologic diseases	If this is not possible, carry out at least a chest x-ray and ultrasound of the abdomen and pelvis
Ophthalmic diseases	**Pathology**
Breastfed? For how long?	Skin, in the case of cutaneous lesions
Blood transfusion	Lymph node, in the case of lymph nodes with neoplastic features
Risky behavior	Myelogram and lumbar puncture in aggressive forms
Physical examination	**Useful in selected cases**
Attention to skin lesions	Pregnancy tests for women of childbearing age
Attention to auscultation of lungs	Endoscopy of the upper digestive tract for digestive symptoms
Attention to the palpation of lymph nodes, liver, and spleen	Skeletal examination in patients with the acute form and hypercalcemia
	PET scan, if available at the center
	CT scan, MRI, and/or lumbar puncture in all patients with acute and lymphomatous forms or in patients with neurologic manifestations not related to HAM/TSP

ATL: adult T-cell leukemia/lymphoma; IDH: infective dermatitis associated with HTLV-1; HAM/TSP: HTLV-1-associated myelopathy/tropical spastic paraparesis; LDH: lactic dehydrogenase; PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging.

TABLE 2 Clinical classification of ATL (adapted from Shimoyama's classification).[7,29]

Clinical form	Lymphocytosis (> 4 x 109/L)	Atypical lymphocytes	LDH level	Hypercalcemia	Organs involved
Smoldering*	–	< 5% or ≥ 5%	≤ 1.5 x N	–	Skin and/or lungs only[¥]
PCT	–	...	≤ 1.5 x N	–	Cutaneous nodule/tumor lesions, mandatorily
Chronic **	+	≥ 5%	< 2 x N or ≥ 2 x N	–	Any organ except bone, GIT, and CNS
Lymphoma	–	≤ 1%	Variable	-/+	Lymph node, mandatorily, and/or any other organ
Acute	Usually +	Usually ≥ 5%	Usually ≥ 2 x N	+/-	Any organ and pleural effusions

*This form is divided into non-leukemic (< 5% atypical lymphocytes) and leukemic (≥ 5% atypical lymphocytes); **This form is divided into favorable and unfavorable, the latter being characterized by increased LDH (≥ 2 x N) and/or increased urea and/or decreased serum albumin; PCT: primary cutaneous tumoral; ... : not determined; LDH: serum lactic dehydrogenase; N: upper limit of the reference value; ¥skin and/or lung involvement may be lacking in the leukemic form; GIT: gastrointestinal tract; CNS: central nervous system.

Below is a list of the main characteristics of the various forms of ATL:

- **Smoldering form:** There is only involvement of the skin and/or lungs; however, involvement of these organs may be absent in the leukemic form. Lymphocytosis (≥ 4,000 cells/mL) and hypercalcemia are absent, with an increase in lactic dehydrogenase (LDH) up to 1.5 times the normal value and presence of up to 5% atypical lymphocytes in the peripheral blood. Cutaneous involvement may be identical to that in classic MF. In the leukemic variant, ≥ 5% atypical lymphocytes are observed.[29] However, in some reviews this subtype is not considered.[33,34]

- **Primary cutaneous tumoral (PCT):** The only differences in relation to the non-leukemic smoldering form are the presence of nodules or tumors on the skin and a worse prognosis.[7] In many studies, this type is included in the smoldering form.[35-37]
- **Chronic:** This is marked by lymphocytosis that may remain stable for months or years, an increase in LDH over 1.5 times the normal value, absence of hypercalcemia, with possible moderate lymphadenomegaly. There is an unfavorable subtype that is defined by low levels of serum albumin and high levels of serum LDH and/or urea, having a prognosis similar to the aggressive forms.[38] In the chronic form there is no involvement of the CNS, bone, gastrointestinal tract (GIT) or pleural effusions. There are often skin lesions, mainly in the form of disseminated papules.
- **Lymphoma:** This is characterized by marked lymphadenopathy without lymphocytosis and ≤ 1% abnormal lymphocytes in the peripheral blood. There may be increased serum LDH and serum calcium as well as involvement of the CNS, GIT and bones.[7,29] Histological proof of infiltration of T-cell lymphoma in the lymph nodes is required, associated with extranodal involvement or otherwise.
- **Acute**: This form displays high levels of lymphocytosis and atypical cells, including "flower" cells in the peripheral blood smear.[1,30] Any organ may be involved, including the CNS, GIT, and bone. Pleural effusions occur frequently.[39] Lytic bone lesions are frequent and may include up to 80% of cases.[40] A sharp increase in levels of serum LDH can also be noted. Lymphadenomegaly and cutaneous involvement are frequent. It should be taken into consideration that this form may present different aspects including, less commonly, the absence of lymphocytosis and hypercalcemia. In the absence of lymphocytosis, differential diagnosis against the lymphoma form depends on the presence of a high percentage of atypical lymphocytes in the peripheral blood.

ATL involves the skin in around 60% of cases and in all clinical forms, and is most frequent in the smoldering and chronic forms.[7] The lesions are multiple and generalized in around 50% of cases (Figure 1). Erythroderma, infiltrated plaques, papules, nodules, and tumors can be observed. Macular lesions are seen less frequently. Nodules and tumors are present in the aggressive forms (PCT, lymphoma, and acute forms). Erythroderma has been observed

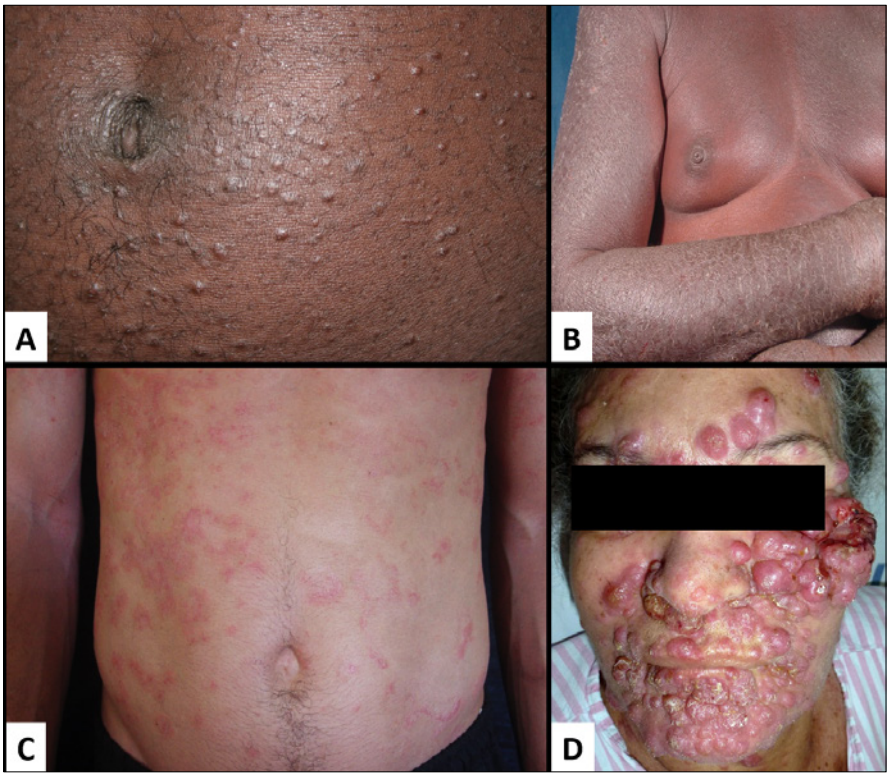

FIGURE 1 Examples of cutaneous lesions observed in ATL. A. Chronic form with papular pattern. B. Acute form showing exfoliative erythroderma. C. Smoldering form with a pattern of papules and erythematous scaly plaques. D. Primary cutaneous tumoral form.

in all clinical forms, with the exception of PCT, mimicking Sézary syndrome.[31] Although rare, vesicular lesions[41] and purpuric lesions[42] may also appear in ATL, similarly to that seen in MF. According to Sawada et al. (2011)[43] the skin lesions that correspond to cases with a worse prognosis are the erythroderma and nodular/tumor lesions. In their case series, all cases of erythroderma occurred in the acute form.

Diagnosis

Clinically, ATL diagnosis should be based on seropositivity for HTLV-1 associated with hematological and/or histopathological diagnoses of peripheral T-cell leukemia and/or lymphoma.[30]

Confirmation of infection with HTLV-1 is generally performed by enzyme-linked immunosorbent assay (ELISA), and should always be confirmed by Western blot and/or polymerase chain reaction (PCR).

Distinctive "flower" cells can be seen in peripheral blood smears, that is, medium and/or large lymphocytes with multi-lobed nuclei, densification of chromatin, and absent or small nucleoli. These are seen mostly in the acute and chronic forms (Figure 2A). These cells are considered pathognomonic of ATL and enable diagnosis alone.[44] Other atypical cells may have the following morphologies: chronic lymphocytic leukemia, lymphoblastic type, and pleomorphic with granular or vacuolar cytoplasm.[44]

Flow cytometry is an important test for the diagnosis of ATL. Most patients display a phenotype of mature CD4 cells. The following markers should be used: CD2, CD3, CD4, CD5, CD7, CD8, CD25, CD29, CD26, CD45RO, αβ T-cell, and HLA-DR receptors. Many cases of ATL do not express CD7 and CD26 and show decreased expression of CD3. The minimum markers required for this examination should include: CD3, CD4, CD7, CD8, CD25, and Ki-67.[30,31] This examination can also be performed on cerebrospinal fluid and pleural effusions.[45]

Patients with tissue infiltration should undergo a biopsy and pathological examination. Whenever possible, the ideal action is to investigate the type of viral integration in the peripheral blood mononuclear cells (PBMC) and/or fresh neoplastic tissue, which confirms the diagnosis of ATL if monoclonal.[30] The techniques used are the reverse and long-range PCR[46] and Southern blot.[47] Southern blot is mainly used when there is a greater amount of DNA (Figure 2B). These techniques are performed by few laboratories, and thus are not generally accessible. However, they are not essential to the diagnosis in most cases. Their importance is greater as scientific proof in cases with atypical aspects, such as those presenting very long progression. On the other hand, it is known that the occurrence of T-cell leukemia/lymphoma not associated with HTLV-1 is rare in patients infected with the virus.[30]

There are several differential diagnoses of ATL, including mature T-cell neoplasms such as MF, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma, and even Hodgkin's lymphoma.[7,48,49]

Anatomical-pathological aspects

In 120 cases observed in Bahia, the organs most affected by ATL were: the skin (66.7%), lymph nodes (56.7%), peripheral blood (53.3%), spleen (32.5%), bone marrow (27.5%), and liver (25%), although several other organs may be involved (data not published).

The histopathological patterns of ATL vary and mimic different types of T-cell lymphomas not associated with HTLV-1. However, in the World Health Organization's classification of cutaneous lymphomas,[50] all cases of leukemia/lymphoma associated with HTLV-1 are classified as ATL, regardless of the histological pattern and without taking into account that the pathologists can only diagnose this disease if they are aware of HTLV-1 infection. Without this information, the pathologist classifies these cases as PTCL-NOS, MF or, less often, ALCL.[51]

In cases with MF morphology, infiltration is by small and irregular cells, usually associated with epidermotropism, obliteration of the basal layer by atypical lymphocytes (Figure 3A) and Pautrier's abscesses. PTCL-NOS is characterized by moderate to marked pleomorphism (Figure 3B), and may also present epidermotropism of lymphocytes and Pautrier's abscesses. In the ALCL pattern, large, cohesive cells with abundant cytoplasm and anaplastic nuclei are noted.[31]

In ATL, the most commonly observed immunophenotype is CD2+/CD3+/CD4+/CD5+/CD7-/CD8-/CD20-/CD79a-/CD25+.[7] However, in 52 cases with cutaneous manifestation, 29% presented CD8+. It is important to include a macrophage marker in the immunophenotype, such as CD68, to differentiate the macrophages of large lymphocytes in cases with MF pattern.[17] In large-cell lymphomas, the CD30 and ALK markers are also important. The cases of ATL with ALCL pattern recorded in Bahia were CD30 and ALK-.[31] In addition, it is always important to determine the proliferative index of the ATL lesions, usually carried out using proliferation marker Ki-67 (Figure 3C). This evaluation is very important because there is a negative correlation between the proliferative index and the

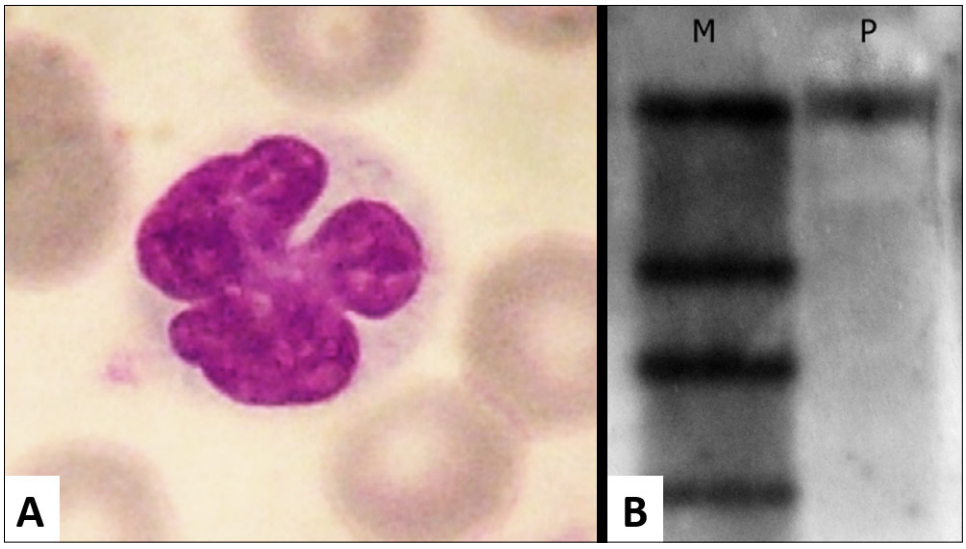

FIGURE 2 A. «Flower» cell on blood smear. B. Southern blot demonstrating monoclonal proviral integration. M: marker; P: patient.

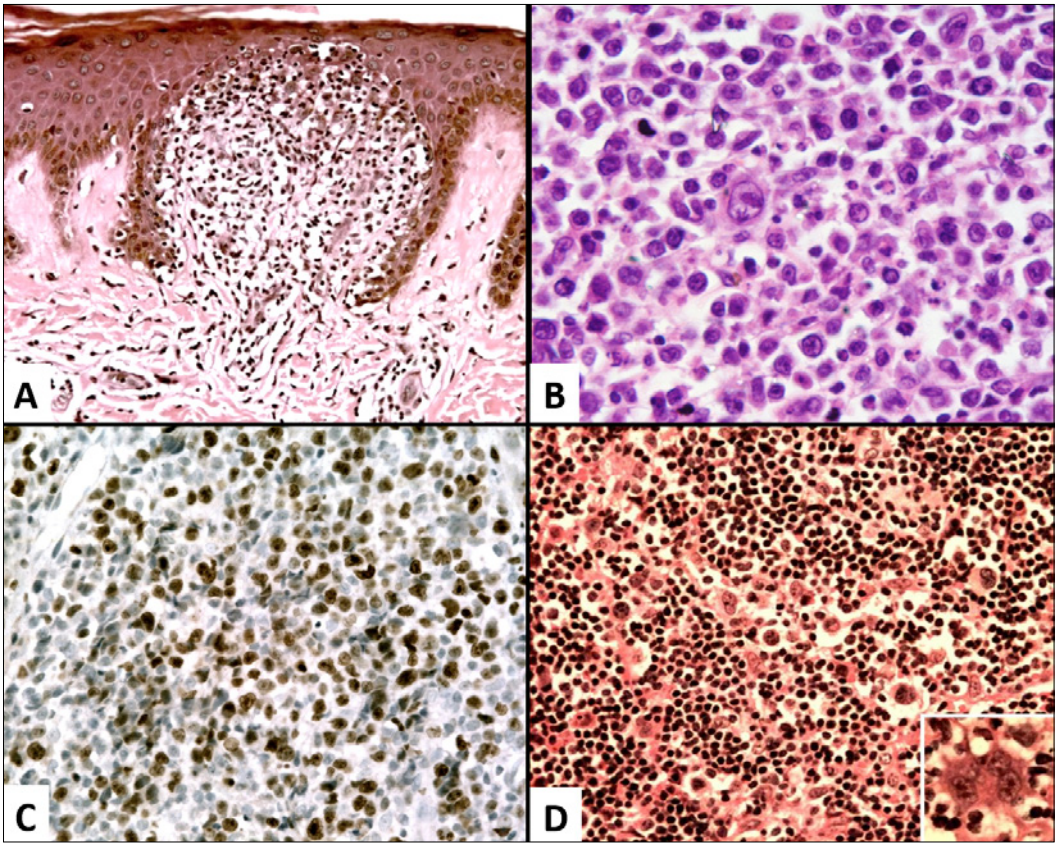

FIGURE 3 A. Skin biopsy of a patient with the chronic form and with a pattern of mycosis fungoides. Infiltration of small and medium lymphocytes in the superficial dermis, with pagetoid infiltration of the epidermis (HE, 100x). B. Skin biopsy of a patient with the primary tumor of skin form and with a pattern of peripheral T-cell lymphoma not otherwise specified. Note the accentuated cellular pleomorphism (HE, 500x). C. Biopsy of the same patient in figure B, showing a high proliferative index (Ki-67, 400x). D. Lymph node of chronic patient with a Hodgkin's lymphoma pattern. Reed-Sternberg and Hodgkin type cells seen amid a background of medium sized lymphocytes, with a T-cell phenotype (HE, 400x). A Reed-Sternberg cell highlighted in the lower right corner (HE, 560x).

MST.[7] In 60 to 70% of cases, the tumor cells express FoxP3 on the surface, which is a marker of regulatory T-cells.[52]

Confirming the stated above, a comparative study showed no significant difference between the histopathological aspects of PTCL-NOS and MF in individuals with and without infection with HTLV-1.[53]

Besides the aspects of PTCL-NOS and ALCL, a Hodgkin's type pattern may be observed in the lymph nodes, although infrequent, with a background of small and medium-sized T phenotype cells, with sparsely scattered Hodgkin and Reed-Sternberg type cells (Figure 3D). These cells are CD30, CD20, and/or CD15.[48,54] In our case series we found one case of Hodgkin type ATL among the 120 individuals studied. Rarely, ATL may be present in the lymph node presenting a pattern similar to angioimmunoblastic T-cell lymphoma.[48] It is important that pathologists consider Hodgkin-type ATL in the diagnosis of Hodgkin's disease.

As with cutaneous lymphomas in general, it is of paramount importance to differentiate between primary and secondary cutaneous ATL, as there is a statistically significant difference between them with respect to MST (48 months *vs.* 7 months).[31] In Bahia, among the cases of primary cutaneous T-cell lymphoma, 26.4% correspond to primary cutaneous ATL, while secondary ATL corresponds to 66.7%.[17] This data shows that ATL is frequent in Brazil.

Treatment

The treatment of ATL is based on the clinical type. Patients with aggressive forms, such as the acute, lymphoma or unfavorable chronic types, often receive chemotherapy. Recently, the Brazilian Ministry of Health published a guideline for ATL treatment including zidovudine (AZT) and interferon-α (IFN-α) as the first-line treatment for all clinical types, and associated chemotherapy only for lymphoma form.[55] In the United States and Europe, the association of AZT and IFN-α is the standard treatment for the leukemic forms. In Europe, chemotherapy alone is the first line treatment only for the lymphoma form of ATL, because survival with antiviral treatment alone is shorter.[56]

Traditionally, patients with the smoldering and favorable chronic forms are not submitted to specific treatments. In these forms, NB-UVB phototherapy is used for more superficial lesions and PUVA for more infiltrated lesions, with good results.[57,58] A recent study of patients with the smoldering form of ATL and cutaneous involvement demonstrated better survival in those treated with phototherapy combined with etoposide (25 to 75 mg/day for 2 to 4 weeks with a one-week interval or on alternate weeks).[35]

As such, the favorable chronic and smoldering types of ATL are considered less aggressive and should be kept under observation until possible progression of the disease, similar to management of chronic lymphocytic leukemia and smoldering myeloma. The treatment of the smoldering form with chemotherapy worsens the prognosis, which is similar to the unfavorable chronic form.[59]

Antiviral therapy using AZT and IFN was described in 1995[60] as an alternative treatment for ATL and has been used ever since. A meta-analysis with 254 patients recruited from four Western countries has been published, where all of the patients with the chronic and smoldering forms that were initially treated with AZT/IFN survived for more than 5 years. In acute patients treated initially with antivirals who had a complete response, survival at 5 years was 82%.[56] A summary of the recommendations of the 16th International Conference on HTLV-1 held in Montreal in June 2013 defined the combination of AZT and IFN as effective in the leukemic forms of ATL, which should be considered as the standard procedure and first-line therapy in this situation. In these cases, chemotherapy should only be started when a response to antivirals is not obtained.[61]

In relation to chemotherapy treatment, various combinations have been evaluated in Japan among ATL patients. However, MST ranged between 6 and 8.5 months.[62] The Japanese Clinical Oncology Group (JCOG) has conducted various clinical trials with several chemotherapeutic regimens. The best results for aggressive clinical forms (acute, lymphoma, and unfavorable chronic) were obtained with the VCAP-AMP-VECP regimen (vincristine, cyclophosphamide, doxorubicin, prednisone-doxorubicin, ranimustine, and prednisone-vindesine, etoposide, carboplatin, prednisone), which obtained a complete response rate of 40 *vs.* 25%, and an MST of 13 *vs.* 11 months, respectively, compared with the biweekly CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen. However, due to the high toxicity of this regimen, especially in patients over 70 years old, CHOP regimens are preferred.[63] As some of these drugs are not available in the United States, hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone – methotrexate, cytarabine) is acceptable as an alternative regimen.[64] Due to frequent CNS impairment in aggressive forms (from 10 to 25%) intrathecal prophylaxis is recommended.[65]

Also in relation to the severe forms, it is worth mentioning that patients are immunocompromised and at high risk for fatal opportunistic infections, therefore prophylaxis for pneumocystis pneumonia and strongyloidiasis is recommended, among others, as well as screening for tuberculosis. Control measures must be adopted for calcium in addition to observing the possible development of tumor lysis syndrome.[66]

Autologous and allogeneic bone marrow transplantation (BMT) has been attempted in ATL in order to improve the outcome of these patients. Autologous BMT does not seem to have many benefits due to frequent relapses and the occurrence of infections.[67] Several researchers refer to an improvement in survival with allogeneic BMT, especially using myeloablative regimens. However, a high mortality rate has limited its use.[68] Studies using a reduced intensity conditioning regimen show an interesting and even curative option in approximately 15% of cases, probably due to a graft *versus* tumor effect.[68] In a retrospective analysis of 386 patients in Japan treated with allogeneic BMT under any induction regimen, survival at 3 years was 33%. Four factors were associated with having a poor prognosis: being older than 50 years, being male, disease without complete remission at the time of BMT, and having an unrelated donor.[69]

Many new agents for ATL are under study with promising results in the treatment of ATL, for example, anti-CCR4 monoclonal antibody (mogamulizumabe), IL-2 fusion inhibitor (denileukin diftitox), histone deacetylase inhibitors (HDAC), purine nucleoside phosphorylase inhibitor (forodesine), proteasome inhibitor (bortezomib), etc.[68]

Prognosis

A study of 854 patients using a multivariate analysis determined the indicators of a poor prognosis as being: high performance status,[70] high levels of LDH, being aged > 40 years, more than three areas involved and hypercalcemia.[71] Most of these indicators are present in the acute form, which has the worst prognosis.[30] In relation to the chronic form of the disease, as mentioned above, patients who have high levels of LDH and urea and low levels of albumin have the worst prognosis.[38] A recent multicenter retrospective study with 807 patients newly diagnosed with the acute and lymphoma forms of ATL identified Ann Arbor clinical staging, performance status and three continuous variables (age, serum albumin, and dosage of the soluble IL-2 receptor) as independent prognostic factors.[72]

In a study in Bahia that included 70 cases of ATL assessed using a univariate analysis, the factors related to poor prognosis were: the acute, lymphoma and PCT clinical forms, a proliferative index higher than 18%, presence of large cells in the histology, and the absence of cutaneous lesions. However, cutaneous involvement predominated in the forms with a better prognosis, and was present in all cases of the smoldering form and in 90% of cases of the chronic form.[7]

Prevention

For the prevention of ATL it is also important to halt vertical transmission of the HTLV-1, with infected mothers recommended not to breastfeed and being provided with formula and suitable pediatric assistance to children, as is already the case with HIV-infected mothers.[22,73]

Given that strongyloidiasis predisposes the development of ATL due to clonal expansion of lymphocytes, and considering that this form of parasitosis may be asymptomatic, frequent investigations for such in asymptomatic carriers of HTLV-1 are important, having in mind that proper treatment of this parasitosis can reverse clonal expansion.[74] Atypical cells, including "flower" cells, can be found in 10 to 43% of asymptomatic carriers of HTLV-1, and thus they are considered as being at high risk of developing ATL.[75] These patients should be monitored at regular intervals in order to detect the early development of ATL.

Conclusion

1. Clinical classification of ATL is fundamental to determining the prognosis and therapeutic conduct.
2. ATL can simulate other T-cell lymphomas not clinically and histologically associated with the virus, such as MF, PTCL-NOS, and ALCL.
3. Serology for HTLV-1 should be performed in all patients with a diagnosis of mature T-cells leukemia/lymphoma, so that cases of ATL receive adequate orientation.
4. Although new therapeutic options are gradually improving the prognosis of ATL patients, treatment continues to be a major challenge. New studies and measures will be necessary in order to optimize therapeutic combinations.
5. It is important for the Brazilian Ministry of Health to consider the inclusion of HTLV-1 serology in prenatal programs to decrease the incidence of ATL.

Resumo

Leucemia/linfoma de células T do adulto

A leucemia/linfoma de células T do adulto (LLcTA) é uma neoplasia de células T maduras CD4+ causada pelo vírus linfotrópico para células T humanas tipo 1 (HTLV-1). Acredita-se que existem cerca de 20 milhões de pessoas infectadas em todo o mundo, principalmente no Japão, na África, no Caribe e na América do Sul, particularmente no Brasil e no Peru. A LLcTA acomete cerca de 5% dos indivíduos infectados e classifica-se nas seguintes formas clínicas: aguda, linfomatosa, tumoral primária de pele, crônica (favorável e desfavorável) e indolente (leucêmica

e não leucêmica). Embora seja considerada uma doença agressiva, há casos com longa evolução. Salientamos a importância da classificação clínica como elemento imprescindível para avaliação do prognóstico e conduta terapêutica adequada. Como já foram publicados vários casos no Brasil e essa doença ainda é pouco conhecida, decidimos fazer um trabalho de revisão para divulgar os seus aspectos clínicos, hematológicos, anatomopatológicos, diagnósticos e terapêuticos. O melhor meio de reduzir a ocorrência de LLcTA seria sustando a transmissão vertical do vírus pela amamentação.

Palavras-chave: vírus 1 linfotrópico T humano, leucemia-linfoma de células T do adulto, linfoma de células T, linfoma de células T periférico, micose fungoide, linfoma cutâneo de células T.

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Night eating syndrome: How to treat it?

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Summary

Night eating syndrome (NES) is characterized by caloric intake ≥ 25% of total daily after dinner and/or by two or more weekly nocturnal awakenings accompanied by food ingestion. Causes of NES are not entirely clear and seem to involve a desynchronization between the circadian rhythms of food ingestion and sleep, resulting in a delayed pattern of food intake. Estimates of the prevalence of NES in the general population are around 1.5%, and although much higher frequencies have been described in obese individuals, a causal relationship between NES and obesity is not clearly established. Since the first NES reports, several treatment modalities have been proposed, although, in many cases, the evidence is still insufficient and there is no consensus on the ideal approach. In order to conduct a critical review of proposed treatments for NES since its original description, a systematic search of articles published in journals indexed in Medline/Pubmed database in the period 1955–2015 was performed. Seventeen articles addressing non-pharmacological and pharmacological therapies met the selection criteria. Based on the articles analyzed, we conclude that serotonergic agents and psychological interventions, particularly cognitive behavioral therapy, have been shown to be effective for the treatment of NES. A combination of non-pharmacological and pharmacological therapies must be considered in future studies on the treatment of these patients.

Keywords: circadian rhythm, obesity, eating disorders, sleep disorders.

Introduction

Night eating syndrome (NES) was originally described by Stunkard et al., in 1955, in obese patients treated at a specialized clinic for nocturnal hyperphagia, insomnia, and morning anorexia.[1] Its main feature is a delay in the pattern of food intake, usually defined by ingestion of at least 25% of total daily calories after dinner and/or during nocturnal awakenings. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), NES is classified in the category of eating disorders not otherwise specified.[2,3]

The prevalence of NES in the general population is approximately 1.5%. In contrast, this syndrome is present in 6 to 14% of patients in clinical follow-up for weight loss and 8.9 to 42% of candidates for bariatric surgery.[4-6] High frequencies, close to 12%, have also been reported in psychiatric patients.[7] A prevalence of 3.8% was observed for NES in elderly patients with type 2 diabetes,[8] 8.6% in patients with sleep apnea,[9] and 17% in patients with restless legs syndrome.[10]

The causes of NES are not fully understood but appear to involve a desynchronization between the rhythms of food intake and sleep. Despite the delay in the circadian pattern of food intake typically observed in these patients, changes in sleep-wake rhythm (the beginning and end of the sleep time) have not been demonstrated in actigraphic and polysomnographic studies.[11,12] In normal individuals, energy homeostasis is controlled by a neurohumoral system that minimizes the impact of small fluctuations in energy balance, and leptin and insulin are critical elements in this control. The nighttime sleep period is characterized by prolonged fasting, where the en-

ergy balance is maintained through hormonal changes.[13] In patients with NES, leptin levels tend to be reduced at night, which may contribute to nocturnal awakenings accompanied by food ingestion. A reduction in the levels of ghrelin, probably due to the nocturnal food intake itself, has also been described in these individuals. Low levels of melatonin have been implicated in the desynchronization process found in NES.[14-16]

The relationship between NES and obesity is not fully understood. Studies in overweight and obese patients, usually recruited from specialized clinics, have shown a high frequency of NES compared to community controls, suggesting the existence of a relationship between NES and obesity.[5,17-20] However, epidemiological studies have not confirmed whether this association exists[5,21] and numerous cross-sectional studies show inconsistent results.[17,22-24] These contradictory results can be attributed, at least in part, to methodological issues such as differences in the operational definition of NES, small variation in body mass index (BMI) in homogeneous populations or insufficient statistical power to identify differences between groups. In an attempt to overcome the limitations of previous studies, Colles et al. (2007) recruited 431 individuals with BMI ranging from less than 18 to over 65 kg/m^2 and identified an independent association between NES and BMI.[20] Although a relationship between obesity and NES is considered probable, its exact nature remains uncertain. Adult obese patients with NES are, on average, older than obese individuals without NES, which suggests that NES leads to weight gain over time.[25] Recently, a study including 2,317 individuals showed a positive correlation between the intensity of night eating symptoms and BMI in the age group from 30 to 60 years, but not in younger individuals, suggesting that age plays an important role in the relationship between NES and obesity and the weight gain occurs only after long periods of nocturnal feeding habits.[26] A prospective study lasting 6 years found that women who get up at night to eat significantly gain more weight.[27] A longitudinal study of the variation of body weight showed that individuals who eat between 11 pm and 5 am hours gain more weight than those who do not eat during this period.[28] Although the evidence, as a whole, points to a causal relationship between NES and obesity, difficulty in controlling for several variables and external factors of environmental, socioeconomic, genetic, and behavioral nature prevents a definitive conclusion. It is reasonable to assume that in subjects with night eating habits, high intake at night hours, not offset by a similar increase in energy expenditure, leads to a positive balance and, over time, weight gain. It is also possible that NES involves a general tendency to excessive food consumption. Controlled studies to investigate the excessive food intake in patients with NES produced conflicting results.[11,15,29] Conversely, the reverse hypothesis that weight gain and obesity may influence the characteristics of NES must be considered. In this regard, individuals with limited food intake in the morning could have a more deregulated intake overnight. Furthermore, the guilt associated with weight gain could lead to a greater tendency to overeat in the privacy of one's home.[30]

The diagnosis of NES is eminently clinical. The current criteria established in the International Symposium of 2008 include evening hyperphagia, defined by consumption greater than or equal to 25% of total daily calories after dinner and/or nocturnal awakenings accompanied by food intake plus at least three of the following five: i) morning anorexia, ii) insomnia, iii) desire to eat between dinner and bedtime, iv) need to eat to fall asleep or return to sleep, and v) depressed mood, most often at night.[2] In order to screen patients and to help evaluate the response to treatment, some useful tools have been developed, including the Night Eating Questionnaire.[31,32] The main conditions to be considered as a differential diagnosis include other eating disorders, particularly the binge eating disorder, characterized by eating large amounts of food in a short time, with feeling of loss of control, depressed mood, and lack of compensatory behaviors.[4,14,33]

Eating disorders in general tend to be associated with a spectrum of clinical manifestations and behavioral changes for which a multidisciplinary approach is often considered more effective.[34] In the case of NES, although several options have been investigated, there is no consensus on the optimal treatment.[29,35-39] The aim of this study was to critically evaluate the therapeutic alternatives proposed so far for the management of this condition.

Method

We conducted a systematic search of articles published in journals indexed in the PubMed (US National Library of Medicine – National Institutes of Health) database since 1955, the year that NES was originally described, until June 2015. The keywords used in the search were: "night eating syndrome" and "nocturnal eating", with no language restrictions. The reference lists of selected articles were reviewed to expand the initial search.

Results

486 articles were retrieved (258 having as keywords "night eating syndrome"). After reading the summaries, 469 were

excluded because they did not address our subject of study. The 17 selected articles included case reports, case series, and clinical trials, involving non-pharmacological and pharmacological treatment modalities.

Non-pharmacological treatment

Administration of bright light in the morning has produced beneficial effects in patients with seasonal affective disorder, a condition in which changes in sleep and mood patterns, as well as in circadian neurobiological markers similar to those seen in NES, are observed.[40,41] This led some groups to assess its applicability in the management of patients with NES. Friedman et al. (2002) reported that a patient with NES treated with 40 mg/day of paroxetine for depressive symptoms, who underwent 14 morning sessions of phototherapy with 10,000 lux white light for 30 minutes, showed improvement of depression and symptoms of night eating. After one month, there was a recurrence of eating-related symptoms, although the intensity of depressive symptoms remained low. The authors decided to start the morning phototherapy, obtaining complete suppression of eating-related symptoms after 12 sessions.[42] Subsequently, the same group reported the case of a non-obese patient with NES and depression, who underwent morning phototherapy with 10,000 lux of white light for 30 minutes; after 14 sessions, improvement of depression and symptoms of NES was observed.[43]

The effect of progressive muscle relaxation therapy on stress, mood, hunger, and eating pattern was evaluated by Pawlow et al. (2003) in 20 individuals with NES randomly assigned to a treatment or control group. In the latter, patients remained at rest for the same time duration of the therapy session. There were two sessions lasting 20 minutes each, carried out one week apart. The levels of stress, relaxation, and salivary cortisol were determined before and after each session. In addition, in the first and eighth day, the authors evaluated the mood. It was observed that progressive muscle relaxation reduces the levels of stress, anxiety and salivary cortisol immediately after the session. This technique was associated with increased morning hunger and reduced night eating.[44]

Cognitive behavioral therapy (CBT) has been successfully used in the management of various conditions, including depression, insomnia, and some eating disorders. Allison (2012) proposed a brief but intensive model of CBT for NES that includes information on NES, guidance on sleep hygiene and healthy nutrition, self-monitoring of eating habits, exercise, and relaxation strategies.[45] A non-controlled pilot study with 25 participants (19 female) on the use of CBT in cases of NES showed an improvement in symptoms and weight loss.[46]

Vander Wal et al. (2015) conducted a clinical trial involving patients with symptoms of NES randomized to receive only educational measures, educational measures, and relaxation with exercise, or educational measures and relaxation without exercise. The three groups showed a reduction in symptoms of NES, depression, anxiety, and perceived stress. The reduction in the percentage of food eaten after the last meal was higher in the group with educational measures and relaxation without exercise. These results suggest that educational measures associated with relaxation techniques have a promising role in the management of patients with this condition.[47] Studies on non-pharmacological treatment of NES are summarized in Table 1.

Pharmacological treatment

It is believed that neuroendocrine alterations associated with changes in the rhythm of food intake are important in the pathogenesis of NES. It has been suggested that in these patients there would be a relative deficiency of postsynaptic serotonin in the mesencephalic nuclei, caused by hyperactivity of the carrier system, which would lead to a defect in the regulation by the central nervous system of sleeping and feeding rhythms. Thus, the use of selective serotonin reuptake inhibitors (SSRIs), which reduces the binding of serotonin transporters and increases postsynaptic serotonin, could restore circadian function and satiety.[15,39] Favorable results of the use of SSRIs to treat obesity[48,49] and other eating disorders such as anorexia nervosa and binge eating disorder have been reported.[50-52] Miyaoka et al. (2003) prescribed paroxetine (n=3) or fluvoxamine (n=1), SSRIs, to four patients with NES characteristics and reported effective control of nocturnal eating episodes after 2 to 3 weeks of treatment.[37] In an open clinical trial with 17 participants with NES characteristics, O'Reardon et al. (2004) evaluated the effect of other SSRI, sertraline, for 12 weeks on the number of awakenings, nocturnal food intake, and ingestion of food after dinner, and observed an improvement of all the aspects evaluated in all patients. Five patients had significant weight loss, close to 5 kg on average.[38] O'Reardon et al. (2006) conducted a randomized double-blind placebo-controlled study to assess the efficacy of sertraline for 8 weeks in 28 patients with NES. The authors reported a significant reduction in the number of awakenings with nighttime eating. In addition, an average weight reduction of about 3 kg was observed in the sertraline group but not in the placebo group.[53]

TABLE 1 Summary of studies involving non-pharmacological treatment of patients with night eating syndrome.

Author	Study type	Treatment	Sample characteristics	Duration	Result
Friedman, 2002[42]	Case report	Phototherapy 10,000 lux for 30 minutes	1 female aged 51 years with NES, obese	14 days	Improvement of depressive symptoms and nocturnal eating
Pawlow, 2003[44]	Controlled clinical trial	PMR	20 participants with NES (intervention, n=10; control, n= 10)	1 week	Reduction of nocturnal appetite and increased morning hunger
Friedman, 2004[43]	Case report	Phototherapy 10,000 lux for 30 minutes	1 male aged 46 years with NES, not obese	14 days	Improvement of depressive symptoms and NES
Allison, 2010[46]	Non-controlled clinical trial	CBT	25 participants with NES (19 women)	12 weeks	Improvement of depressive symptoms and NES; weight loss
Vander Wal, 2015[47]	Controlled clinical trial	CBT, exercise, and education	44 patients with NES (education, n=14; CBT without exercise, n=15; CBT with exercise, n=14)	3 weeks	Improvement of NES using any of the three interventions

NES: night eating syndrome; PMR: progressive muscle relaxation; CBT: cognitive behavioral therapy.

Stunkard et al. (2006) conducted an open clinical trial, at distance, to evaluate the effectiveness of sertraline in the treatment of NES. Patients who spontaneously sought the help of researchers via website, email or phone were asked to fill the Night Eating Questionnaire and underwent a structured interview to determine the presence of NES. Fifty participants were treated with sertraline, which was prescribed by their own doctors. To evaluate the response, the questionnaire was completed every 2 weeks and the interview repeated at the end of 8 weeks. The researchers reported improvement in nocturnal hyperphagia, nocturnal awakenings with food intake, and depressive symptoms.[54] Vander Wal et al. (2012) conducted a randomized placebo-controlled trial of 40 patients with NES to evaluate the effect of escitalopram, an other SSRI, for 12 weeks, and found no difference between groups in the reduction of the symptoms of NES assessed based on the Night Eating Questionnaire, weight loss, mood, and adverse events.[55] In contrast, Allison et al. (2013), in a clinical trial involving 31 patients with NES to evaluate the use of escitalopram, found a significant reduction in nocturnal hyperphagia and nocturnal awakenings accompanied by food intake, measured based on the Night Eating Symptom Scale, after 12 weeks.[56]

The use of topiramate, an agonist of gamma aminobutyric acid, in patients with NES has been reported by some authors. Winkelman (2003) observed a reduction in nocturnal awakenings with food intake, improved sleep and weight loss in two patients who failed prior treatments with psychotherapy and pharmacotherapy.[35] Tucker et al. (2004) reported the case of a 40-year-old obese woman treated with topiramate for 8 months, who achieved reduction in episodes of nocturnal awakenings accompanied by food intake.[36] Cooper-Kazaz (2012) reported the case of a non-obese female patient under treatment for depression with venlafaxine, who developed NES and weight gain. She received topiramate for 6 weeks, with improvement of night eating symptoms, sleep quality, self-esteem and well-being, and weight loss.[57]

A decrease in nocturnal melatonin levels in patients with NES has been reported.[15] Based on this finding, agomelatine, an agonist of the MT1 and MT2 receptors, has been considered as an option for treatment of NES.[58,59] Milano et al. (2013) gave agomelatine (25 mg/day during the first 3 weeks and 50 mg/day in the subsequent weeks) for 12 weeks to five patients with symptoms of NES and depression, and observed improvement in clinical symptoms, mood, and number of nocturnal awakenings, as well as weight reduction.[60] Given the strong association between NES and changes in the sleep-wake and eating cycles, in addition to the frequent finding of depressive symptoms and low melatonin levels, new studies are required in order to properly assess the efficacy of agomelatine to treat this syndrome. Studies on the pharmacological treatment of NES are summarized in Table 2.

Conclusion

This critical review of the literature on the treatment of NES in the last 60 years shows that the number of studies is still insufficient, especially regarding controlled clinical trials with adequate sample size and methodology. The results above suggest that serotonergic agents and psychological interventions such as the CBT can be effective in the treatment of NES. Among the SSRIs, sertraline was the drug most studied for this condition. Preliminary reports of beneficial effects of topiramate and agomelatine justify further studies involving these substances and

TABLE 2 Summary of studies involving pharmacological treatment of patients with night eating syndrome.

Author	Study type	Treatment	Sample characteristics	Duration	Result
Miyaoka, 2003[37]	Case series	Paroxetine (3 cases); fluvoxamine (1 case)	4 patients with NES	2 weeks	Effective control of episodes of nocturnal eating after 2-3 weeks of treatment
Winkelman, 2003[35]	Case series	Topiramate	2 patients with NES	N/I	Improved night eating, weight loss; the symptoms of NES returned one month after the end of treatment
Tucker, 2004[36]	Case report	Topiramate	1 female aged 40 years	9 months	Improvement of symptoms of NES, sleepiness; weight loss
O'Reardon, 2004[38]	Open clinical trial	Sertraline	17 participants with NES (12 women)	12 weeks	Reduction in the number of awakenings; improvement in night eating
O'Reardon, 2006[48]	Double-blind, randomized, placebo-controlled trial	Sertraline	34 participants with NES (sertraline, n=17; placebo, n=17)	8 weeks	Improvement in symptoms of NES and in quality of life; weight loss
Stunkard, 2006[49]	Open clinical trial	Sertraline	50 participants with NES	Not informed	Improvement in nocturnal hyperphagia, nocturnal awakenings with food intake, and depressive symptoms
Cooper-Kazaz, 2012[52]	Case report	Topiramate	1 female aged 54 years with NES and depression	3 months	Improvement in symptoms of NES, sleep quality and self-esteem
Vander Wal, 2012[50]	Controlled randomized clinical trial	Escitalopram	40 participants with NES (escitalopram, n=20; placebo, n=20)	6 weeks	Improvement in symptoms of NES and weight loss did not differ between the groups
Allison, 2013[51]	Open clinical trial	Escitalopram	31 patients with NES (21 women)	12 weeks	Improvement in NES and depressive symptoms
Milano, 2013[55]	Case series	Agomelatine	5 patients with NES (3 women)	10 weeks	Improvement in symptoms of NES and depression; weight loss
Milano, 2013[54]	Case report	Agomelatine	1 female aged 39 years with NES and depression	3 months	Improvement in mood and symptoms of NES; weight loss

NES: night eating syndrome; N/I: not informed.

similar medications. Similarly, an initial report of benefits obtained with phototherapy suggests that chronobiological treatments can be useful and should be further examined. Finally, in view of the complexity of the manifestations of NES and its frequent association with obesity, mood disorders, and other comorbidities, the combination of non-pharmacological and pharmacological therapies coupled with a multidisciplinary approach needs to be considered in future studies on the treatment of these patients.

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Resumo

Síndrome do comer noturno: como tratar?

A síndrome do comer noturno (SCN) caracteriza-se por ingestão calórica ≥ 25% do total diário após o jantar e/ou por dois ou mais despertares noturnos semanais acompanhados de alimentação. As causas da SCN não estão totalmente esclarecidas e parecem envolver uma dessincronização entre os ritmos circadianos de alimentação e sono, resultando em um atraso do padrão alimentar. Estimativas da prevalência de SCN na população geral estão em torno de 1,5% e, embora frequências bem mais elevadas

tenham sido descritas em obesos, uma relação de causalidade entre SCN e obesidade não está claramente estabelecida. Desde os primeiros relatos da SCN, várias modalidades de tratamento têm sido propostas, embora, em muitos casos, a evidência ainda seja insuficiente e não exista um consenso sobre a abordagem ideal. Com o objetivo de realizar uma revisão crítica dos tratamentos propostos para a SCN, desde sua descrição original, foi realizada uma busca sistemática de artigos publicados nos periódicos indexados na base de dados MedLine / Pubmed entre 1955 e 2015. Dezessete artigos, abordando terapias não farmacológicas ou farmacológicas, preencheram os critérios de seleção. Com base nos artigos analisados, conclui-se que os agentes serotonérgicos e intervenções psicológicas, particularmente, a terapia cognitivo-comportamental, têm mostrado eficácia no tratamento da SCN. Uma combinação de terapias não farmacológicas e farmacológicas precisa ser considerada em estudos futuros sobre o tratamento desses pacientes.

Palavras-chave: ritmo circadiano, obesidade, transtornos alimentares, transtornos do sono.

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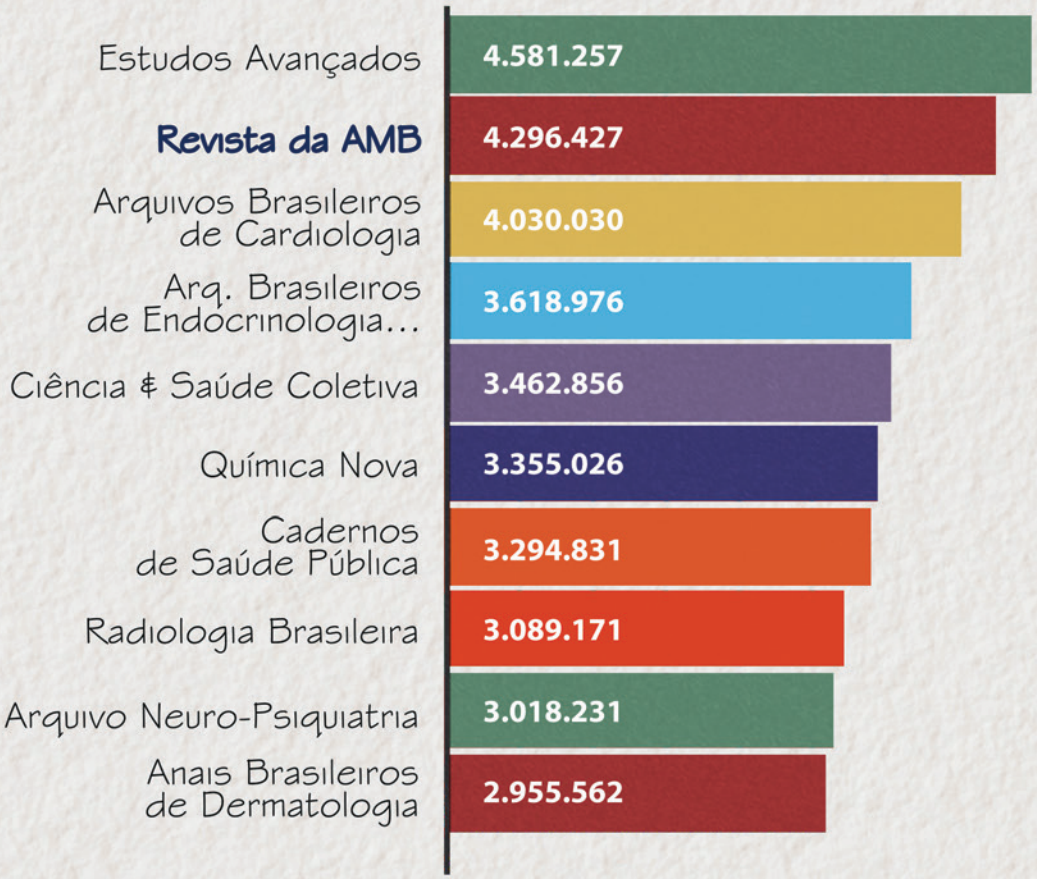

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