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Postal code: 01333-903
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SUMMARY

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INVITED REVIEW

Isoflavones derived from *Glycine max* (L.) Merr. in the treatment of vaginal atrophy: A new frontier

Isoflavonas derivadas do *Glycine max* (L.) Merr. no tratamento da atrofia vaginal: nova fronteira

Sônia Maria Rolim Rosa Lima[1]*, Adriana Bittencourt Campaner[1], Antonio Pedro Flores Auge[1]

[1]Department of Obstetrics and Gynecology, Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, SP, Brazil

*Correspondence:
lima@silber.com.br

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During the climacteric, many changes take place, caused both by the decrease of estrogens and other hormones and by the effects of aging itself.[1] Complaints of vasomotor alterations, sleep disturbance, mood changes, and genitourinary symptoms (GUS) are common. GUS affect up to 50% of women in this period. They may be chronic and progressive and their lifelong improvement is unlikely. They can range from mild to severe and are not exclusive to sexually active women. Despite this, many are unaware that such symptoms result directly from the decline in estrogen associated with menopause, and that there are treatments available.[2]

Due to a common embryological origin, the bladder, the urethra and the genitals have similar responses to hormonal changes, especially to estrogens. The atrophic process that accompanies the hypoestrogenism can be verified in the epithelium and in the pelvic support tissues. The mucous membranes become thinner, also causing genital prolapse, vaginal and urinary symptoms become frequent and intense, the vaginal microbiota changes, and vaginal pH becomes more alkaline influencing women's lives globally.[3]

Despite the many safe and effective options for treating the changes caused by vulvovaginal atrophy (VVA), only a minority of women (about 25% in the Western world and probably much less in other areas) seek medical help.[4] One of the possible reasons for this behavior is the adverse publicity (not currently justified) disclosed in recent years for the use of hormone replacement therapy (HRT) in menopause.

It is worth mentioning that local treatment of VVA is not associated with the possible risks of systemic HRT. Among the reasons for not seeking treatment for VVA complaints are cultural ones and an understandable reluctance to discuss such issues, particularly with a male doctor. On the other hand, doctors also fail to inform about the possibilities of treatment for atrophic vaginal symptoms.[5]

Phytoestrogens are plant-derived chemical substances structurally or functionally similar to estradiol. The main phytoestrogen used as a treatment for women in the climacteric are isoflavones, polyphenolic flavonoids found naturally in plants such as *Glycine max* (L.) Merr and *Trifolium pratense* L.[6] Isoflavones contain a phenolic ring in a position analogous to estradiol, which allows them to occupy their receptors in different tissues, and may present actions similar to endogenous estrogen.[7]

Isoflavones have been used topically to prevent and delay skin aging in postmenopausal women. They act on the skin inhibiting tyrosine kinase, preventing the expression of mRNA encoding collagenases and elastases (metalloproteinases), and thus hindering the degradation of extracellular matrix fibers. Topical use of isoflavones in the skin can lead to epidermal proliferation, increased synthesis, and decreased enzymatic degradation of dermal collagen.[8,9]

To date, studies analyzing the effects of isoflavones derived from dry extract of *Glycine max* (L.) Merr, administered vaginally on vaginal epithelium, on morphometric features, the behavior of estrogen receptors, the vaginal flora, and endometrium are scarce. Research was conducted with postmenopausal women comparing the effects of isoflavones derived from dry extract of *Glycine max* (L.) Merr, conjugated equine estrogens and placebo administered vaginally on the vaginal epithelium and endometrium. As a result, there was improvement in the symptoms of vaginal atrophy with a significant increase in the values of cell maturation, similar to those obtained with conjugated estrogens, both superior to the placebo group. After treatment, in serum FSH and estradiol concentrations, none of the groups had an increase in endometrial thickness.[10]

Another study of the same product administered vaginally in another group of postmenopausal women evaluating the symptoms of vaginal dryness and dyspareunia, vaginal epithelial morphology, and estrogen re-

ceptor expression, resulted in significant improvement of symptoms after treatment in the Treated Group compared with the Placebo Group, with increased vaginal epithelial thickness and percentage of immunopositive cells to estrogen receptors.[11]

As for the vaginal microbiota, we know that resident bacteria of the genital tract obtain the glycogen used in their nutrition from the local epithelium and, by producing lactic acid, they constitute a protective factor against the proliferation of pathological bacteria. The concentration of glycogen available for this microbiota depends on the developmental conditions of the urogenital epithelium, including the presence of estrogenic hormones, among other factors. Therefore, the hypoestrogenism typical of the climacteric phase allows a pathological microbiota to develop. The analysis of the vaginal microbiota is thus a tool for understanding the health condition of the urogenital tract. There are unsatisfactory attempts to improve urogenital health with hormone therapy and oral therapy with phytoestrogens, but these approaches are associated with the presence of adverse reactions and unconfirmed therapeutic outcomes, respectively. On the other hand, the application of phytoestrogens vaginally appears to be satisfactory due to the possibility of local action with little systemic interaction and a pharmacodynamics typical of phytomedicines. We highlight a pioneering study that evaluated the vaginal flora of women treated with isoflavones derived from *Glycine max* (L.) Merr, for the purpose of alternative (vaginal) route of phytoestrogens.

A study was conducted on the effects of isoflavones derived from *Glycine max* (L.) Merr on the vaginal microbiota of postmenopausal women who did not present systemic symptoms, had the exclusive complaint of vaginal atrophy, and applied topically a gel with the active product for 90 days, compared with a placebo. Vaginal pH, serum concentration of estradiol and symptoms of genital atrophy were also analyzed.

The microbiota found in both groups was similar at T0, T30 and T90 days, with the prevalence of acidophilic species, namely coagulase-negative *Staphylococcus, Enterococcus* sp*, Escherichia coli* and *Bacillus* sp, with variation in the isoflavones group. Regarding vaginal pH, there was a statistically significant reduction in T30 and T90 in the isoflavones group, which did not occur in the placebo group. As for FSH, there was no significant difference in the times studied. With respect to the Questionnaire on Symptoms of Urogenital Atrophy, it was observed that in the isoflavones group there was improvement in all symptoms while in the placebo group only dryness and pruritus improved after 90 days of treatment. Thus, vaginal isoflavones appear to be an important alternative for the treatment of symptoms of genital atrophy in postmenopausal women, including those with contraindications to hormonal therapy, resulting in vaginal pH close to that of women of reproductive age, an increase in acidophilic species, including those potentially pathogenic – without causing infection – and improved urogenital health.[12]

Isoflavones administered vaginally present as an important alternative for the treatment of the symptom of genital atrophy thus constituting a new frontier within gynecology.

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Guidelines for the treatment of lung cancer using radiotherapy

Diretrizes para tratamento de câncer de pulmão com radioterapia

Authorship: Brazilian Society of Radiotherapy (SBR)

Participants: Michael J. Chen[1], Paulo Eduardo Novaes[1], Rafael Gadia[1], Rodrigo Motta[1]

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[1]Sociedade Brasileira de Radioterapia (SBR)

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

Grades of recommendation and levels of evidence

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

Objective

The aim of this guideline is to evaluate the most appropriate radiotherapy technique to treat patients with lung cancer.

Description of evidence collection method

Through the elaboration of four relevant clinical questions related to the proposed theme, we sought to present the main evidences regarding safety, toxicity and effectiveness of the presented radiotherapy techniques. The study population consisted of male and female patients of all ages with lung cancer, regardless of histological type, staging or presence of comorbidities. For this, a systematic review of the literature was carried out in primary scientific databases (Medline – PubMed; Embase – Elsevier; Lilacs – Bireme; Cochrane Library – Record of Controlled Trials). All articles available through April 31, 2015 were considered. The search terms used in the research were: ((lung cancer) OR (lung carcinoma)) AND (IMRT OR intensity modulation OR intensity modulated) AND (conventional OR 2D OR two dimensional OR bidimensional OR standard OR conformal OR 3D OR tridimensional OR CRT OR three dimensional). The articles were selected based on critical evaluation using the instruments (scores) proposed by Jadad and Oxford. The references with greater degree of evidence were used. The recommendations were elaborated from discussions held with a drafting group composed of four members of the Brazilian Society of Radiotherapy. The guideline was reviewed by an independent group, which specializes in evidence-based clinical guidelines. After completion, the guideline was released for public consultation for 15 days, and the suggestions obtained were forwarded to the authors for evaluation and possible insertion in the final text.

Introduction

Radiotherapy is an integral part of the multidisciplinary treatment of lung cancer.

In small cell lung cancer, radiotherapy is performed after chemotherapy (adjuvant) in tumors staged as extensive disease,[1] and concomitantly in tumors staged as localized disease.[2]

In non-small cell lung cancer, radiotherapy is indicated before or after surgery (adjuvant), with the purpose of making them surgically resectable or to prevent relapse of locoregional disease and tumors with positive margins,[3,4] while in unresectable tumors, it is preferably associated with chemotherapy.[5]

Radiation therapy has progressed in recent decades due to advances in computerized systems that allow the recognition of internal structures in the body. This recognition is done based on the patient's imaging investigation, usually computed tomography. A more accurate dose distribution that reaches the area intended to be treated while sparing normal organs derives from the information sent to the radiation device from a previously configured treatment planning system. This release

dosage form is known as conformal technique. The software shows the radiation dose distribution inside the patient's body and creates dose-intensity graphs on each target organ or volume. It is thus possible to know the potential toxicity of these organs and whether the tumor is being adequately treated.[6]

Even though the conformal technique allows for dose assessment at irradiated site, sparing healthy organs, it does not provide ways of protecting tissues in close contact with irradiation treatment targets. The intensity-modulated radiation beam technique was developed to solve this problem. It allows the prescribed dose to "fit" within the contour of the site to be irradiated, allowing maximum protection of areas not intended for treatment.

In the thoracic region, which houses several radiation-sensitive organs, such as the heart, esophagus, spinal cord, and lungs, conformal radiotherapy is the minimally recommended technique for patient safety.[6]

Based on clinical experience with complications of radiotherapy, a dose-limiting standard according to the volume of a normal organ was created and published in 2010, the Quantitative Analysis of Normal Tissue Effects in the Clinic (Quantec).[7] The recommendation was developed by the joint work of several researchers, authors, reviewers and support professionals. It is currently recommended throughout the world as a practical guide to performing radiotherapy on all parts of the body. Such dose quantification can only be established from the shaped technique.

For the reasons given above, conventional radiotherapy has been abandoned whenever the treatment site is close to radiation-sensitive organs (for example, the chest), since this technique does not provide any information on dose distribution in these organs. In this case, both the locoregional control of the disease is dose-dependent and appears to be directly related to survival,[8] and residual lung function after treatment seems to be an important factor related to quality of life in survivors.[9]

1. Is there superiority in dose distribution for irradiation of lung cancer with intensity modulated radiation therapy (IMRT) compared to conformal radiotherapy?

There are no prospective phase III studies comparing conformal radiation therapy and IMRT for any chest cancer. Therefore, other factors should be weighed and considered to choose the best radiotherapy technique. These factors include, for example: dosimetric advantage, technology accessibility, financial aspects, and decision to escalate the dose or maintain the restriction of doses released on a critical organ.[10]

IMRT can improve the physical and biological conformability of the dose and enable its scaling within the target volume, which makes it possible to release higher doses to target subvolumes such as the hypoxic areas or those capturing high SUV on PET-CT, with no need to increase the number of fractions, and maintaining a low dose exposure to healthy tissues.[11]

Virtual simulation studies have shown that IMRT may be more appropriate than conformal radiotherapy for patients with large tumor volumes and difficult position within the thoracic anatomy, cases in which protection of normal surrounding structures is a priority. These studies presented a 7% reduction in the irradiated lung volume with more than 10 Gy, and 10% with more than 20 Gy. Volumes of heart and esophagus irradiated with up to 50 Gy, as well as volumes of lung tissue irradiated between 10 and 40 Gy, were also reduced with IMRT compared to conformal radiotherapy.[12] (D)

For bronchial neoplasms close to critical organs (esophagus, heart, brachial plexus), IMRT may have dosimetric advantages compared to 3DCRT.[10] (D)

Other points to consider include: IMRT can release greater low dose volumes in areas of healthy lung, it may result in failures outside the therapeutic margin leading to differences in sterilization of lymph nodes incidentally not included in the target volume, and the lower dose rate may be less lethal for neoplastic cells.[13]

2. Is there less toxicity in the use of IMRT in relation to conformal radiotherapy for lung cancer?

Toxicity related to radiotherapy external to primary lung tumors can be temporally divided into acute or late. Anatomically, it is divided into pulmonary and esophageal, because these are the main organs to manifest adverse reactions to radiation.

Comparing IMRT with conformal radiotherapy of lung tumors, two studies had as their main toxicity outcome, i.e., pulmonary toxicity:

1. A retrospective study of 290 patients showed that at month 6, treatment-related grade ≥ 3 pneumonitis rates reached 8% (95CI 4-19%) with IMRT and 22% (95CI 17-29%) with conformal radiation therapy. At month 12, treatment-related grade ≥ 3 pneumonitis rates reached 8% (95CI 4-19%) with IMRT and 32% (95CI 26-40%) with conformal radiation therapy (p=0.002).[14] (B)
2. Another retrospective study with 409 patients being treated reported a significant difference (p=0.017), both 6 and 12 months after radiation, in favor of IMRT

with 90% of patients without treatment-related pneumonitis, versus conformal radiotherapy, with 75% free of this toxicity.[15] **(B)**

Toxicity to normal tissue is the major obstacle to be dodged in order to make it possible to release a suitable dose, aiming at better tumor control. One of the tissues most sensitive to radiation is the lung. Depending on the lung volume receiving a given dose, as well as other factors (pulmonary reserve, radiobiological factors, concomitant therapy), patients may not present with acute symptoms, but only asymptomatic pulmonary fibrosis evidenced in the radiation field (typically 12 months or longer after treatment), transient moderate pneumonitis (typically 2-6 months after radiotherapy), or a more symptomatic, severe, or even fatal disease. Thus, volumetric parameters such as V20 (percentage of pulmonary volume receiving ≥ 20 Gy), V10 and V5, and pulmonary mean dose have been shown to be the most important predictive factors for severe pulmonary toxicity.[14,16-18]

The lung is the thoracic organ most sensitive to the deleterious effects of radiation, but this does not mean that it is the only limiting anatomical structure to restrict the appropriate dose release. Spinal cord, esophagus, and heart are also restrictive. The spinal cord, for example, should be protected from doses > 45 Gy.

The esophagus does not have a critical dose limit such as the spinal cord, but acute damage caused by radiation can be identified even at modest doses depending on the volume irradiated. Significant esophageal morbidity is routinely reported, which often limits the administration of an appropriate treatment, using optimal dose and without interruptions, especially if concomitant with chemotherapy and/or whenever mediastinal lymph nodes should be addressed.[19,20]

A recently published retrospective study with 223 patients showed that the rate of patients with severe esophagitis requiring feeding tube was 5% with IMRT versus 17% with conformal radiotherapy (p=0.005).[11] **(B)**

3. Is there an impact on quality of life that justifies the use of IMRT compared to conventional and conformal radiotherapy?

One of the goals when we offer a modality of treatment for any type of cancer is the preservation or improvement of the patients' quality of life. However, because it is an outcome that is difficult to assess due to both subjectivity and the scarcity of objective tools for its measurement, there is little information on the subject.

The best study that evaluated the impact on quality of life of lung cancer patients treated with different radiotherapy techniques was published as a summary, not providing the full text. This was a randomized clinical trial whose main objective was to evaluate the impact of treatment on the survival of patients with locally advanced lung cancer after high-dose radiotherapy (60 Gy x 74 Gy). As a secondary outcome, information regarding quality of life was prospectively collected using instruments validated for patients with lung cancer, and the following results were found:[21] **(A)**

1. Of the 419 patients included in the study, 45% underwent IMRT and 55% underwent conformal radiotherapy. The two groups were equally distributed in terms of patient characteristics, except for tumor size that tended to be larger in the IMRT group.
2. In all, 357 patients completed the questionnaires to assess quality of life before treatment. The questionnaires used were as follows: "Functional Assessment of Cancer Therapy-Trial Outcome Index" (FACT-TOI), "Physical Well Being" (PWB), "Functional Well Being" (FWB) and "Lung Cancer Subscale" (LCS).
3. Twelve (12) months after the end of treatment, patients who underwent IMRT presented better quality of life than those treated with conformal radiotherapy, according to all of the questionnaires evaluated. All differences were statistically significant.

4. Is there a difference in effectiveness, local control or overall survival between IMRT, conformal and conventional radiotherapy?

Based on a comparison between IMRT and conformal radiotherapy for lung tumors, two studies evaluated disease control and survival outcomes:

1. A retrospective study included 223 patients with small cell lung cancer and evaluated two consecutive historical cohorts. The authors found no difference in local control, locoregional control, incidence of distant metastases, disease-free survival, and overall survival for patients undergoing chemotherapy and IMRT compared with conformal radiation therapy.[11] **(B)**
2. Another retrospective study included 496 patients with non-small cell lung cancer and assessed two consecutive historical cohorts. The authors found better overall survival for patients undergoing concomitant chemotherapy and IMRT compared with conformal radiation therapy. In this study, median survival was 16.8±16.3 months with IMRT and 10.2±6.4 months with conformal radiotherapy (hazard ratio = 0.64 [0.41-0.98], p=0.039).[15] **(B)**

A retrospective study conducted from multi-institutional databases also evaluated the role of radiotherapy techniques in patient survival, demonstrating the superiority of IMRT or conformal techniques compared to the conventional technique, with 5-year survival rates of 14% for IMRT or conformal radiotherapy compared with 11% for conventional radiotherapy (p=0.0001). Another similar study demonstrated a better overall survival in the comparison between the IMRT or conformal radiotherapy techniques and the conventional technique, but did not demonstrate superiority of IMRT over conformal radiotherapy in terms of survival.[22,23] **(B)**

Conclusion

Treatment with IMRT can provide more conformality and protect more critical structures than conformal radiotherapy, also allowing the dose escalation within the target, without prolonging the treatment time. It is particularly indicated for "superior sulcus" (Pancoast tumors), paravertebral and paracardiac tumors and in complex clinical situations in which conformal radiotherapy does not enable the release of non-toxic doses to organs at risk.[24]

IMRT significantly reduces the risk of worsening quality of life in lung cancer patients undergoing radiation therapy.

There is less toxicity with the use of IMRT compared with conformal radiotherapy for primary lung tumors, particularly regarding the rates of grade ≥ 3 pneumonitis and requiring feeding tube.

There is also longer survival with the use of IMRT or conformal radiotherapy in relation to conventional radiotherapy, but not with IMRT compared with conventional radiotherapy.

Conflict of interest

The authors declare no conflict of interest.

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Rupture of the myocardium in autopsied MI hearts

Valesca Bizinoto Monteiro[1], Bianca Gonçalves Silva Torquato[1], Guilherme Ribeiro Juliano[1], Bárbara Cecílio da Fonseca[1], Flávia Aparecida de Oliveira[2], Daniel Ferreira da Cunha[3], Camila Lourencini Cavellani[1], Luciano Alves Matias da Silveira[1]*, Mara Lúcia da Fonseca Ferraz[1], Vicente de Paula Antunes Teixeira[1], Edson Luiz Fernandes[4]

[1]Sector of General Pathology, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba, MG, Brazil
[2]Sector of General Pathology, Universidade Federal de Goiás (UFG), Goiânia, GO, Brazil
[3]Department of Internal Medicine, UFTM, Uberaba, MG, Brazil
[4]*In memoriam*

Study conducted at Universidade Federal do Triângulo Mineiro (UFTM), Uberaba, MG, Brazil

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***Correspondence:**
Address: Av. Frei Paulino, 30
Uberaba, MG – Brazil
Postal code: 38025-180
drluciano@hotmail.com

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Summary

Although myocardial rupture occurs in only 2% to 4% of cases of acute myocardial infarction (AMI), there is a high mortality rate due to acute cardiogenic shock. We present the anatomopathological findings of three cases of myocardial rupture in autopsied hearts in the last 30 years, with a diagnosis of cardiac rupture in acute myocardial infarction. In these 30 years the percentage of AMI with myocardial rupture was 0.2%. Risk factors for post-AMI myocardial rupture include older age, atherosclerosis, diabetes mellitus and systemic arterial hypertension.

Keywords: autopsy, cardiac rupture, cardiogenic shock, myocardial infarction.

Introduction

Although the rupture of the myocardium occurs in only 2 to 4% of the cases of acute myocardial infarction (AMI), it is associated with high mortality mainly due to the state of acute cardiogenic shock. This occurs in about 90% of the ruptures of the left ventricular free wall and in 50% of the cases with rupture of the septum, with 5 to 24% of deaths being caused by AMI.[1] The clinical/physical signs and symptoms include chest pain, dyspnea, bradycardia and shock.[2] The main risk factors for cardiac rupture in patients not treated with thrombotic medication include older age, female gender, and the concurrence of systemic arterial hypertension, smoking habit, sedentary life style and diabetes mellitus.[2]

Myocardial rupture post-AMI occurs in total arterial occlusion as often as in cases with low collateral flow to the infarcted area.[3] The most affected coronary arteries are the right (46%), the left anterior descending (42%), and the left circumflex (11.53%).[4] Although rupture may involve the intraventricular septum and the papillary muscle, the free wall of the left ventricle is by far the most common.[5] About 95% of cardiac ruptures occur in the first week, with 40% of the cases within the first 24 hours post-AMI. Rupture rarely occurs after the 10th day, when scarring has already taken place.[5,6] The anatomopathological findings of three cases of rupture of the myocardium, as a complication of a recent AMI, are presented.

Method

In our study, three cases of myocardial rupture post-AMI were studied in individuals autopsied at the Clinical Hospital of the Triângulo Mineiro Federal University (Uberaba – Minas Gerais – Brazil). Our investigation includes all the cases of autopsied patients in the last 30 years, during the period from 1979 to 2009, with a diagnosis of cardiac rupture as a result of a recent acute myocardial infarction. The anatomopathological findings are presented, as well as the importance of carrying out the autopsies in order to confirm the diagnosis. Our study was approved by the Research Ethics Committee of UFTM with protocol number 56433316.3.0000.5154.

Results

Autopsy findings

Case 1: Female patient, 52 years, non-white, married, housewife, born in Montes Claros (Minas Gerais), residing in Canal São Simão (Goiás). The patient was brought to the hospital in a clinical state suggestive of AMI, progressing with the appearance of a precordial systolic murmur, and died before surgery on January 19, 1979. The cause of death was

ischemic heart disease. In the anatomopathological examination, the heart weighed 310 g and the heart weight to body weight ratio was 0.57%. There had been a recent transmural infarction measuring about 3 cm in length in the lower third of the interventricular septum and anterior wall of the left ventricle, with rupture of the septum and consequent interventricular communication in the lower front portion of the septum, measuring about 1 cm in diameter. There was severe atherosclerosis in the left coronary artery and its branches, especially in the anterior descending and the circumflex branches, with a recent thrombus in the anterior descending artery. Passive hepatic congestion (weight 1,490 g) and renal congestion (right kidney weight 140 g; left 150 g) with atherosclerosis and degenerative phenomena in the tubules were observed, as well as pulmonary (weight of the right lung 480 g; left 400 g), encephalic (weight 1,000 g) and inferior limb edema. Moderate atherosclerosis in the aorta with atheroma and fibrous plaques was also observed.

Case 2: Male patient, 67 years, white, single, born in Santa Juliana (Minas Gerais), residing in Uberaba (Minas Gerais), agricultural worker, died on August 22, 1980. He presented hypertensive and ischemic heart disease. There had been a recent infarction with intracardiac thrombosis, affecting the lower third of the interventricular septum in its right half, apex of the left ventricle and right ventricle, measuring in its largest diameters about 4.5 by 3.5 cm. Rupture in the apex of the right ventricle with 0.4 cm in length and hemopericardium. Atherosclerosis was found in the left coronary, especially in the front interventricular branch, calcification and recent thrombosis. The lungs were edematous.

Case 3: Male patient, 67 years, white, married, born in Ipiau (Bahia), residing in Uberaba (Minas Gerais), retired carpenter, died on August 23, 2007. The patient had diabetes mellitus, was admitted to the emergency room in a state suggesting non-controlled asthma or chronic obstructive lung disease. He died suddenly on the 4th day, after lung function stabilization. On autopsy, hypertensive heart disease and ischemic heart disease were verified. There was global hypertrophy of the myocardium, especially in the left ventricle, with cardiac weight of 470 g and the heart weight to body weight ratio was 0.71%. A recent infarction was observed, in accordance with the upper-posterior region of the left ventricle, next to the coronary circumflex artery, measuring about 2.0 by 1.0 cm, with a recent rupture of 0.5 cm, and consecutive hemopericardium (Figure 1). There was marked atherosclerosis of the aorta, especially of the thoracic portion and its main branches. The lungs presented edema and congestion (right lung 435 g; left 494 g).

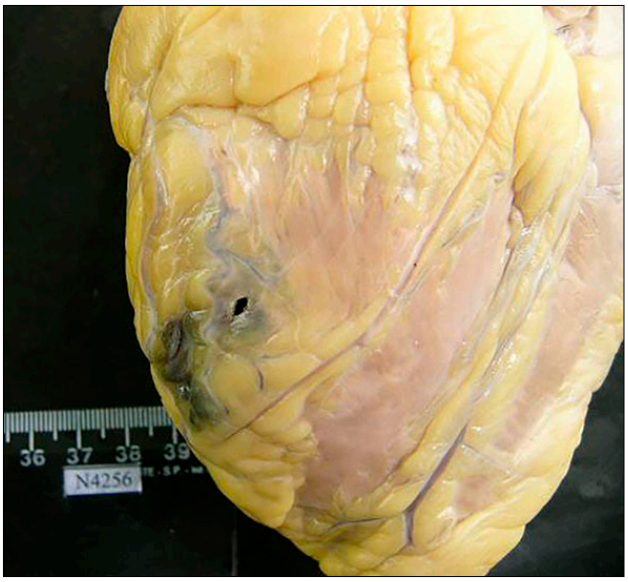

FIGURE 1 Case 3: Heart with a recent infarction corresponding to the upper-posterior area of the left ventricle and a recent rupture of 0.5 cm.

Discussion

Our study includes all the cases of autopsied patients in the last 30 years, during the period from 1979 to 2009, with a diagnosis of cardiac rupture as a result of a recent, acute myocardial infarction. In this period, the percentage of AMI with rupture of the myocardium was 0.2%.

Risk factors for rupture of the myocardium post-AMI include older age, diabetes mellitus and systemic arterial hypertension. In only one case, that of the patient who developed interventricular communication, there was doubt regarding the pre-death diagnosis. Rupture of the right ventricle with hemopericardium is also rare, and, to our knowledge, has never been reported in a series of cases.[5,6]

Ventricular rupture post-AMI occurs in 1 to 4% of cases, and is responsible for about 5% of premature deaths after acute myocardial infarction.[1] Strong suspicion and confirmation by means of echocardiography are important for the diagnosis and eventual surgical intervention, which is currently the only way of treating this condition.[4-6]

Although there is a worldwide trend of a lower number of autopsies, this diagnostic method continues to be important as a form of quality control of the clinical diagnosis made while the patient is alive, and the verification of the agreement of the methods. Autopsies are not only important for medical teaching, but may also help to elucidate unexpected deaths, including those of hospitalized patients, as in the case of our series.

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Resumo

Ruptura do miocárdio em corações com IM autopsiados

Embora a ruptura do miocárdio ocorra em apenas 2 a 4% dos casos de infarto agudo do miocárdio (IAM), está associada a alta mortalidade, principalmente em decorrência do estado de choque cardiogênico agudo. São apresentados os achados anatomopatológicos de três casos de ruptura do miocárdio de pacientes autopsiados nos últimos 30 anos, com diagnóstico de ruptura cardíaca em decorrência de IAM. Nesse período, a porcentagem de IAM com ruptura do miocárdio foi de 0,2%. Os fatores de risco para ruptura do miocárdio pós-IAM incluem idade avançada, arteriosclerose, *diabetes mellitus* e hipertensão arterial sistêmica.

Palavras-chave: autópsia, choque cardiogênico, infarto do miocárdio, ruptura cardíaca.

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Nutritional knowledge and body mass index: A cross-sectional study

Julia Luzzi Valmórbida[1], Maíra Ribas Goulart[1], Fernanda Michielin Busnello[1], Lúcia Campos Pellanda[1,2*]

[1]Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil
[2]Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia (IC/FUC), Porto Alegre, RS, Brazil

Study conducted at Instituto de Cardiologia/Fundação Universitária de Cardiologia, Porto Alegre, RS, Brazil

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***Correspondence:**
Instituto de Cardiologia/Fundação Universitária de Cardiologia
Address: Av. Princesa Isabel, 370, 3º andar
Porto Alegre, RS – Brazil
Postal code: 99620-000
pellanda.pesquisa@gmail.com

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Summary

Objective: To verify the knowledge about food and nutrition and its association with the nutritional status of obese patients with noncommunicable diseases (NCDs), and to identify the relationship between information sources and level of knowledge.
Method: Cross-sectional study that included 263 outpatients of a cardiology referral hospital in Porto Alegre, Rio Grande do Sul, Brazil. The participants filled out a questionnaire on socioeconomic data and knowledge about food and nutrition and had their nutritional status evaluated by body mass index (BMI), waist circumference (WC) and waist-hip ratio (WHR).
Results: BMI showed a significant inverse association with the percentage of correct answers (p=0.002), as well as WC (p=0.000) and WHR (p<0.001). This was also true for education (p<0.001) and female gender (p=0.005) compared to males. More than 60% of patients reported using television and 23% reported using newspaper as sources of nutritional information.
Conclusion: Our study revealed a significant association between BMI and the level of knowledge about foods, showing that there is need for more information on obesity-related NCDs for greater understanding by patients.

Keywords: obesity, knowledge, attitudes and health practices, nutrition, chronic disease.

Introduction

Chronic noncommunicable diseases (CNCD) were responsible for 38 million deaths worldwide in 2012.[1] These include diabetes mellitus (DM) and high blood pressure (HBP). It is known that an increased body mass index (BMI) is related to an increase in CNCDs and that the specific treatment of obesity can also act in the control of other CNCDs.[2] In Brazil, 12.5% of men and 16.9% of women are obese.[3] Therefore, weight loss is a primary goal in public health strategies directed to this population.

In order to promote healthier eating habits and improve self-care regarding CNCD, it is important for the population to gain knowledge about food and nutrition,[4-6] especially those related to healthy food choices and nutritional recommendations.[7] Several studies have found a relationship between dietary knowledge and obesity,[8-11] as well as nutritional status.[12]

Considering that the understanding of these issues is important for advancing the treatment of CNCDs, the objective of our study is to describe the knowledge about diet and nutrition and its relation with the nutritional status of obese patients with CNCD who attend a cardiology outpatient clinic.

Method

Patients

This cross-sectional study was carried out with patients attending the general outpatient clinic of the SUS (Brazilian public health system) in a reference hospital randomly selected between May and July 2009. The sample was calculated using a 95% confidence interval, with a margin of error of 6%, estimating an average of 70% of correct answers in the questionnaire, resulting in a minimum of 225 patients. Considering the possibility of losses, the final sample consisted of 263 patients.

Patients with BMI greater than or equal to 30 kg/m^2, individuals aged 20 years or older and who agreed to participate by signing a Free and Informed Consent Form (FICF) were included.

Patients who presented diseases that caused obesity and water retention, presence of edema, liver disease or nephropathy were excluded. Our study was approved by the institution's ethics committee.

Data collection procedure

Nutritional status was evaluated based on BMI, waist circumference (WC) and the waist-hip ratio (WHR). In order to measure weight and height, participants were positioned on their feet, with their heels joined, arms along their sides, legs stretched, shoulders relaxed, and head in the horizontal plane; they were all barefoot and wearing light clothing. Both height and weight were measured using an anthropometric scale, Filizola brand, located in a private place, in the waiting room of the outpatient clinic. WC was measured while the patient was standing up, just after breathing out, 1 cm above the iliac crest. Hip circumference was assessed on the widest circumference of the buttocks. All of these measurements were performed with an inelastic tape measure.

After the anthropometric evaluation, the patients answered a questionnaire with thirteen questions. The questionnaire was initially consisted of questions about personal and sociodemographic identification, such as sex, age, formal education, risk factors, food choice and sources of food information. There were also 20 questions to assess the level of general knowledge about food and nutrition, such as sugar, fat, fiber and salt content in foods, as well as sources of dietary cholesterol. The questionnaires were applied by a researcher trained for such activity in the waiting room of the outpatient clinic.

The questionnaire was adapted from Parmenter and Wardle,[13] since there were no other similar studies applied in the adult Brazilian population. Questions about sources of information about foods and influences on food choice were multiple choice, with the possibility of selecting more than one option for each of the questions, as well as questions concerning sugar, fat and sodium contents in foods. In all other questions about diet and nutrition, patients could select only one of the alternatives presented.

Statistical analysis

The database was assembled using Excel 2003, while the statistical analyzes were performed using SPSS software version 17.0.2.

Means and standard deviation or median and minimum and maximum values were used to present continuous variables, while absolute (n) and relative (%) frequencies were used for the categorical variables. Continuous variables were analyzed using Pearson correlation, and categorical variables were analyzed using Spearman correlation. We used Student's t-test to compare means, and Chi-square test to analyze associations. In all comparisons, a critical alpha of 0.05 was considered.

Results

The study totaled 263 participants. The sample was consisted of 52% of female subjects, with 66.5% of married individuals. Regarding education, 43.4% reported not having completed elementary school. The mean age was 56.7 years and the mean BMI was in the obesity range (32.48 kg/m^2), as shown in Table 1. The general characteristics of the population are presented in Table 1. BMI, WC and WHR of both sexes are described in Table 2. The mean of correct responses according to different characteristics is described in Figure 1.

TABLE 1 General characteristics of the population.

Variables	N (%)
Female	138 (52.5)
Married	175 (66.5)
Elementary school, incomplete	114 (43.4)
High school diploma	70 (26.6)
	N±SD
Mean age	56.7±12.9 years
Mean BMI	32.48±3.41 kg/m^2

SD: standard deviation.

TABLE 2 Mean BMI, WC and WHR for men and women.

	BMI (kg/m^2)	WC (cm)	WHR
Women	33.36±4.2	109.92±10.11	0.95±0.05
Men	32.26±2.1	112.57±7.43	1.00±0.05
Total of the sample	32.84±3.41	111.09±9.00	0.97±0.06

BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio.

The BMI showed an inverse and significant association with the percentage of correct answers (p=0.002), as well as WC (p<0.001) and WHR (p<0.001). However, after stratification by sex, there was a significant association between women when correlating the percentage of correct answers with BMI (p<0.001) and WC (p<0.001). Among men, there was a significant association between the percentage of correct answers and WHR (p=0.002).

Regarding "dieting or adopting food restrictions," 39.2% (103) answered affirmatively. Nevertheless, 88.2% of the participants stated that they presented some CNCD in addition to obesity.

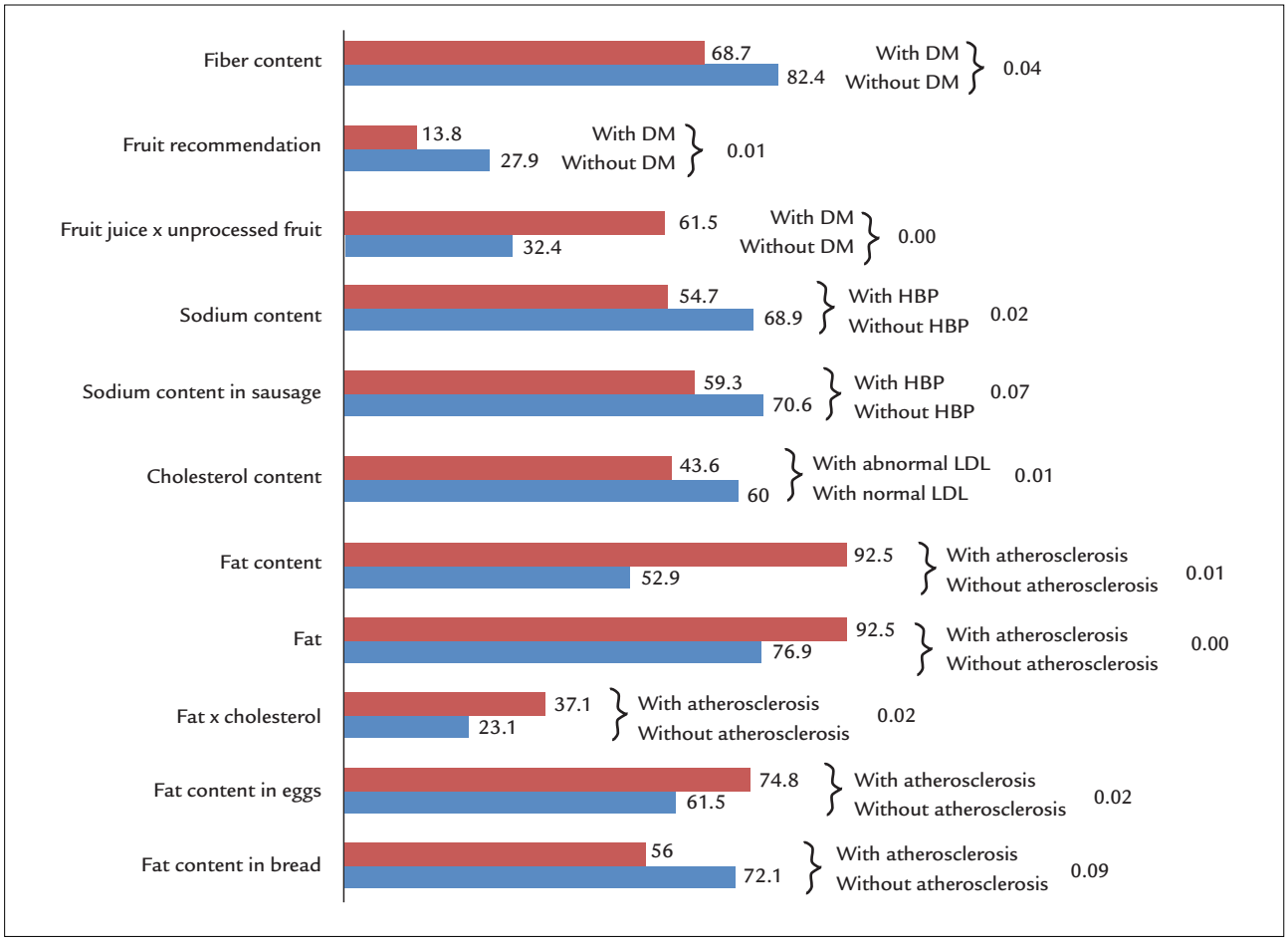

FIGURE 1 Relation between the presence of chronic noncommunicable disease and the mean of correct responses in percentages and p-value.

When asked about the factors that most influence food choice, the most commonly reported alternative was "attempt to maintain a healthy diet" (53%), followed by "taste of the food" (31%) and "routine" (24%). The level of knowledge of the patients who chose the alternative "taste" as one of the main influences in food choice was significantly lower than those who did not choose this alternative. Those who claimed to choose food items in accordance to a diet or to follow a healthy diet had a higher degree of knowledge than those who did not.

Regarding the main sources of information about food and nutrition, 67.3% of the patients (177) pointed to television as one of the main sources, followed by health professionals (29%), newspaper (23%) and nutritionists (16%).

Discussion

The main finding in our study was an inverse and significant correlation between BMI and WC/WHR, as well as the percentage of the participants' correct answers.

Even though some findings do not corroborate the results of the study,[14-18] these are still relevant data. By demonstrating that the level of knowledge about food and nutrition has a significant impact on the nutritional status (noting that participants who scored less in the questionnaire had the worst results for BMI, WC and WHR), we can justify the importance of developing public policies to raise awareness of healthy eating habits and self-care among individuals presenting CNCDs.

In our study, both men and women had high WC and WHR. WC and WHR have a known relation with the amount of abdominal fat, and high values are indicators of risk for the development of cardiovascular disease.

The participants obtained a middling score on the questionnaire, similar to that found in other studies,[19,20] except for O'Brien et al.,[21] who found a good level of knowledge. Formal education was related to the mean of correct answers, and low levels of education are probably related to the result found, which is in agreement with the literature.[22] Differently from another study, our results showed

that women performed better,[23] which can be explained by a culture in which women are responsible for buying food and preparing meals for the whole family.[17]

Among the three main sources of food information, two are media-related. It is known that media exposure can influence the food choices of adults as well as the amount of food, and the time spent in front of a television screen is related to the higher consumption of high energy foods.[16,24,25] Participants who chose "health professionals" or "nutritionists" among the alternatives as important sources of information on food and nutrition did not perform better than those who did not mention these professionals as relevant sources. This reinforces once again the importance of health professionals paying special attention to the diet of patients, especially those with CNCDs.

Most study participants stated that food choice is heavily influenced by an attempt to maintain a healthy diet, even though only 39.2% indicates any food restriction. However, pointing out that eating choice is influenced by the attempt to maintain a healthy diet or to lose weight resulted in a higher percentage of correct responses. Thus, these patients are probably really concerned with choosing the foods that will be part of their meal, and in order to achieve that goal one must know and take an interest in nutritional recommendations, which is achieved through behavioral programs and nutritional education.[26]

The performance of participants for whom food choice is made primarily based on the taste of food was worse than those who did not choose this alternative. This finding is quite consistent in showing less concern about the items that will make up the meals and the diet as a whole, which also reflects less attention and interest in getting information on this subject.

More than 90% of patients correctly answered questions of a more general nature and those involving sodium and fat content of certain foods. However, some aspects should be considered: 88.2% of the patients reported having some other CNCD besides obesity and only 39.2% are doing some type of dietary control. Less than 10% of the participants had already heard about the "Food Guide for the Brazilian Population" or the "Ten steps for a healthy diet," materials developed by the Ministry of Health, which should be used for food guidance and advice for Brazilians. Finally, less than 30% of the patients stated that a physician or other health professional was among the main sources of information about nutrition, this shows that this topic should be further developed at the time of the consultations and that access to nutrition needs to be expanded. This accounts for the fact that nearly 40% of patients claim to believe that soft drinks are fattier than milk. Therefore, it is up to the health professional to guide patients by indicating educational programs[27] that address issues related to the importance of a varied diet to control risk factors[28] and the nutritional composition of foods, especially for lipids, which are important risk factors for coronary artery disease.[8]

The questionnaire used in our study is considered a limitation, since there is no valid instrument for this population and, therefore, we needed to adapt a previously developed instrument.

Conclusion

There was a significant association between the degree of knowledge about diet and the BMI of the participants, demonstrating the need to develop the autonomy of patients with CNCD, especially with respect to generating knowledge that enables healthy food choices, implementing programs for disease prevention and health promotion.

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Resumo

Conhecimento nutricional e índice de massa corporal: um estudo transversal

Objetivo: Verificar os conhecimentos sobre alimentação e nutrição e sua associação com o estado nutricional de pacientes obesos portadores de doenças crônicas, e identificar a relação das fontes de informação com o nível de conhecimentos.

Método: Estudo transversal realizado com 263 pacientes ambulatoriais de um hospital de referência em cardiologia em Porto Alegre, RS. Os indivíduos preencheram um questionário sobre dados socioeconômicos e conhecimentos sobre alimentação e nutrição, tendo seu estado nutricional avaliado por meio de índice de massa corporal (IMC), circunferência da cintura (CC) e relação cintura quadril (RCQ).

Resultados: O IMC apresentou associação inversa e significativa com o percentual de acertos (p=0,002), assim como a CC (p<0,001) e a RCQ (p<0,001). E também a escolaridade (p<0,001) e o sexo feminino (p=0,005) em relação ao masculino. Mais de 60% dos pacientes relataram utilizar televisão e 23% jornal como fontes de informação sobre alimentação.

Conclusão: No presente estudo, houve associação significativa entre IMC e nível de conhecimento sobre alimentação, demonstrando que há necessidade de maior

divulgação sobre as doenças crônicas não transmissíveis (DCNT) para que haja maior entendimento por parte dos pacientes.

Palavras-chave: obesidade, conhecimentos, atitudes e práticas em saúde, nutrição, doença crônica.

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Pain-induced depression in the elderly: Validation of psychometric properties of the Brazilian version of the "Geriatric Emotional Assessment of Pain" – GEAP-b

Carla Bezerra Lopes Almeida[1]*, Ricardo Humberto Félix[1], Maysa Seabra Cendoroglo[2], Fania Cristina Santos[2]

[1]Affiliated Physician of the Osteoarticular Disease and Pain Service, Division of Geriatrics and Gerontology (DIGG), Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil
[2]PhD Professor, DIGG, Unifesp, São Paulo, SP, Brazil

Summary

Objective: In order to introduce an instrument within our midst that allows a comprehensive clinical evaluation of pain-induced depression in the elderly, we proposed the translation, cross-cultural adaptation into Brazilian Portuguese, and study of the psychometric properties of the "Geriatric Psychosocial Assessment of Pain-induced Depression" (GEAP) scale. This instrument was especially developed for the screening of depression associated with chronic pain in the elderly.
Method: We performed translation and cross-cultural adaptation of the GEAP scale, whose psychometric properties were analyzed in a sample of 48 elderly individuals. Sociodemographic data and information related to chronic pain were ascertained, as well as those related to depression. The GEAP-b scale was applied at three different times on the same day by two different interviewers (I1 and I2), and after 15 days by one of those interviewers (I3).
Results: The GEAP-b proved to be an easy-to-apply instrument with a high internal consistency value, according to the Cronbach's alpha coefficient (0.835). The reproducibility of the instrument was optimal, achieving intraclass correlations of 98.5 and 92% for interobserver and intraobserver, respectively. There was "considerable" agreement (between 0.419 and 1.0) for each GEAP-b item, except for item 19, according to the kappa statistic. As for the validity of the GEAP-b criterion, positive and statistically significant correlations were obtained for pain, according to GPM-p (r=49.5%, p<0.001), and depression, according to GDS (r=59%, p<0.001), both values being considered regular (between 40-60%).
Conclusion: The GEAP-b scale has proven to be reliable and valid in the screening of pain-related depression in the elderly.

Keywords: elderly, chronic pain, depression, cross-cultural comparison, validation studies.

Study conducted at the Division of Geriatrics and Gerontology (DIGG), Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil

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***Correspondence:**
Address: Rua Francisco de Castro, 105
São Paulo, SP – Brazil
Postal code: 04024-002
dra.carlabezerra@gmail.com

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Introduction

About 50% of the community's elderly and 80% of those living in long-term care facilities experience chronic pain.[1] These individuals are more likely to suffer from depression, and therefore are more at risk of increased intensity, frequency and duration of pain.[2] This direct relation was demonstrated in a study in which patients with multiple pain symptoms were three to five times more likely to have depression, while those with a "single" symptom of pain were twice as likely to have this mood disorder.[2]

Elderly individuals with depression and chronic pain, compared to those with depressed mood only, have more suicidal ideation, sleep disorders and personality disorders, in addition to longer hospitalizations and greater use of the health system.[3] A vicious cycle takes place that interferes with the adequate treatment of both comorbidities.[4] Thus, adequate diagnosis of pain-induced depression cannot be established unless depression and pain are examined concomitantly rather than through separate assessment tools.[5]

Studies with individuals with chronic pain and depression have shown that less than half of those with depression were correctly diagnosed, with consequent treatment impairment.[2] The "Geriatric Emotional Assess-

ment of Pain" – GEAP scale was developed to identify the level of depression induced by pain, which in turn is defined as depression triggered by chronic pain mainly due to beliefs about pain that are formed around the socialized meaning of convictions about pain by older adults at two levels: catastrophization and perceived deficiency.[5] We attempted to test a biopsychosocial multidimensional assessment basis and to identify the level of pain-induced depression in elderly people with chronic pain, thus improving pain management in those individuals.

The GEAP scale is a tool to evaluate pain-related depression in the elderly,[5] and its use by health professionals in Brazil would enable a more consistent assessment of pain-induced depression in the aging population. This resource would allow early action, and less functional, social, psychological and health damages in the elderly with pain.

Method

This was a methodological, descriptive and analytical study, approved by the Ethics Committee of the Federal University of São Paulo in 2014 (CEP No. 528,139).

For translation and cross-cultural adaptation of the GEAP scale, we followed the methodology by Guillemin et al.[6] First, the text of the questionnaire in English was translated into Portuguese by two independent Brazilian translators, qualified and aware of the translation objectives. The translations obtained were compared to one another, originating a version that was back translated into English. This version was compared with the original in English by two native English-speaking translators with knowledge of the Portuguese language, unaware of the proposed objectives.

For cross-cultural adaptation, some equivalences were obtained: 1) Semantic equivalence, based on the comparison of grammatical and vocabulary aspects, refers to the fact that many words in a language may not have equivalents in other languages; 2) Idiomatic equivalence, which involves a vast research of dictionaries, refers to the difficulty of translating certain idiomatic expressions as the meaning of words is sometimes neither fixed nor stable; 3) Transcultural or experimental equivalence, that is, the cross-cultural context of the original expressions must have "content validity" in Brazilian Portuguese and meaning for the Brazilian population, always having in mind that the original version of the instrument will be used in a different country; 4) Conceptual equivalence, refers to the idea that some words can be semantically equivalent without presenting "concept equivalence." In this last stage, we assembled a committee of five specialists from different areas who were experienced in the elderly: a geriatrician, a physiotherapist, a psychologist, an occupational therapist and a nurse. Thus, the final version of the instrument was obtained: the GEAP-b (Chart 1).

The instrument comprised 25 yes or no questions, structured into three different social levels of pain: eight questions about beliefs about pain, eight about perceived deficiency, and nine questions about pain interference in cognition. The total GEAP score is obtained by summing

CHART 1 GEAP-b – Translated version, adapted transculturally to Brazil.

GEAP-b	Yes	No
1. Did the pain leave you physically disabled?		
2. Because of the pain, did you isolate yourself from others?		
3. Is the pain treatment too expensive for you?		
4. Has the pain changed your sleeping habits?		
5. Has the pain affected your appetite?		
6. Does pain keep you from doing the activities you enjoy doing?		
7. Does pain prevent you from relaxing?		
8. Do you believe that your pain has no solution?		
9. Does being physically active only cause you more pain?		
10. Does the pain make you feel like you cannot go on living?		
11. Does pain prevent you from planning the future?		
12. Does pain make you feel worthless?		
13. Is pain a punishment for bad things you have done to others in the past?		
14. Does pain lead to bad things in your life?		
15. Will the pain prevent you from ever being happy again?		
16. Does pain make you not control how you feel?		
17. Is it true that you will never be able to do anything for yourself because of the pain?		
18. Do you constantly complain of pain?		
19. Does telling the doctor about your pain only make things worse?		
20. Do you deal with the pain just by lying in bed?		
21. Do you stop doing everything when you feel pain?		
22. Is it true that you will never understand what causes your pain?		
23. Does your family tell you that with pain it is difficult to live with you?		
24. Have your parents ever talked about physical pain?		
25. Do you talk to your friends about your pain?		

the number of affirmative answers. The classification is given as follows: 0-5 points, little or no pain-induced depression; 5-9 points, moderate pain-induced depression; and 10 or more points, severe pain-induced depression.[1]

For the study of the psychometric properties of the newly created instrument, elderly individuals aged 80 years or older, participants of the "Longevos Project" of the Division of Geriatrics and Gerontology (DIGG) of the Federal University of São Paulo (Unifesp) were selected between May 2014 and January 2015.[7] This project refers to a longitudinal epidemiological study that includes long-lived individuals of both sexes, residents of the community, who are able to walk without assistance (but can use walking aids). Those with cognitive impairment diagnosed after clinical evaluation and/or cognitive tests; severe acute or chronic decompensated acute disease; under current treatment with dialysis, chemo or radiotherapy; hospitalized in the past 3 months; with sequelae from stroke or myocardial vascular accident; with impaired visual or auditory deficits; and those who were totally dependent on others for basic daily activities were excluded.

Thus, our population was composed of a convenience sample, obtained from a non-probabilistic sampling method dependent on the collection of data from members of the population that were conveniently available to participate in the study. Individuals with chronic pain lasting six months or longer, as defined by the International Association for the Study of Pain (IASP),[8] and with pain intensity greater than or equal to 3, according to a visual numeric scale (VNS) of pain,[9-12] were included. All participants signed a free and informed consent form.

Sociodemographic characteristics were obtained, as well as the medications used for pain and depression, and data on chronic pain, which was measured unidimensionally based on VNS, and multidimensionally according to the Geriatric Pain Measure (GPM-p).[13] Depressive symptoms were tracked according to the Geriatric Depression Scale (GDS), short version.[14,15]

The GEAP-b was applied by two independent interviewers (I1 and I2) on the same day and after 15 days without any intervention during the period, followed by a third evaluation by one of the interviewers (I3). This was done in order to obtain reliability and validity, as recommended by methodological studies on measurement instruments.[16] Reliability was analyzed based on internal consistency (correlations between items) and reproducibility (test-retest and inter-observer analysis).

During the validation process some methods are proposed, including "face validity" (if the instrument measures what is supposed to be measured) and "content validity" (if the object of measurement is representative), both obtained in the transcultural adaptation process.[17] "Construct validity" (evaluates previously operationalized constructs using empirical data) was also proposed, but not obtained due to the absence of an instrument considered gold standard for measurement of depression in patients with chronic pain. Then, we obtained the "criterion validity", which assessed the degree of efficacy in the prediction of pain-induced depression[18] based on the correlation between the GEAP-p score and the assessments of depression and pain using GDS and GPM, respectively.

For statistical analysis, we used SPSS version 17 and Microsoft Excel 2010. For the characterization of the distribution and the frequency of qualitative variables, we adopted the Equivalence Test for Two Proportions, for the Internal Consistency we used Cronbach's Alpha Coefficient, and for reproducibility Student's t-test, Intraclass Correlation Coefficient (ICC) and Kappa Concordance Index. Also, the Pearson correlation was used for validation. The significance level was set at 5%.

Results

The sample consisted of 48 elderly individuals with mean age of 87.5±4.1 years (81-99 years). The participants were predominantly female (79.2%), white (79.2%), widows/widowers (58.3%) and presented low formal education (60.4% studied for 1 to 4 years).

Most used pain medications regularly (64.6%), either classic analgesics (56.3%) or drugs with adjuvant action on pain (31.3%). Antidepressants were used by 45.8% of the sample.

Chronic pain had a mean duration of 9.26 years and intensity was mainly moderate (35.4%) or severe (54.2%), according to VNS. In the multidimensional analysis (GPM-p), it was considered mainly moderate (68.8%). Regarding the nature of pain, there was a predominance of nociceptive (79.2%), mainly in the joints (81.3%).

Depression was identified in 39.6% of the elderly according to the GDS scale. The prevalence among participants of moderate pain-induced depression was 33.3% and severe in 20.8%. 45.8% of the sample had mild or no depression.

In the evaluation of the psychometric properties of the GEAP-p, starting with the reliability according to its internal consistency, high values of Cronbach's alpha were obtained: 0.835 for I1, 0.834 for I2 and 0.795 for I3. For reproducibility, three analyzes were performed. According to the paired Student's t-test, no significant inter-observer (I1 and I2) and intraobserver (I1 and I3) differences were observed, with a coefficient of variation greater than 50% indicating heterogeneity (Table 1). The

ICC showed excellent results, with 98.5% interobserver correlation (I1 and I2) and 92% intraobserver correlation (I1 and I3). According to the analysis of agreement between the interviewers for each item of the instrument in question, using Kappa statistics, statistically significant concordances were obtained between I1 and I2 and I1 and I3, which were considered good, with a single exception for item 19 (I1 and I3) (Table 2).

TABLE 1 GEAP reproducibility, according to paired Student's t-test.

GEAP-b	I1	I2	I3	p-value
Total	48	48	42	
Mean	6.67	6.58	6.86	
Median	6	5.5	6	
Standard deviation	4.62	4.60	4.28	
Coefficient of variation (%)	69	70	62	
Min	0	0	0	
Max	21	21	18	
Confidence interval	1.31	1.30	1.29	
Correlation I1/I2				0.605
Correlation I1/I3				0.360

TABLE 2 Intraobserver and interobserver agreement, according to the Kappa index.

	I1/I2		I1/I3	
	Kappa	p-value	Kappa	p-value
Question 1	0.750	<0.001	0.571	<0.001
Question 2	0.727	<0.001	0.494	0.001
Question 3	0.762	<0.001	0.690	<0.001
Question 4	0.865	<0.001	0.642	<0.001
Question 5	0.735	<0.001	0.690	<0.001
Question 6	0.775	<0.001	0.586	<0.001
Question 7	0.845	<0.001	0.669	<0.001
Question 8	0.787	<0.001	0.561	<0.001
Question 9	0.645	<0.001	0.518	0.001
Question 10	0.833	<0.001	0.876	<0.001
Question 11	0.829	<0.001	0.651	<0.001
Question 12	0.899	<0.001	0.666	<0.001
Question 13	1.000	<0.001	0.482	<0.001
Question 14	0.862	<0.001	0.618	<0.001
Question 15	0.850	<0.001	0.639	<0.001
Question 16	1.000	<0.001	0.659	<0.001
Question 17	0.550	<0.001	0.419	0.006
Question 18	0.858	<0.001	0.654	<0.001
Question 19	0.657	<0.001	-0.050	0.746
Question 20	0.644	<0.001	0.641	<0.001
Question 21	0.813	<0.001	0.556	<0.001
Question 22	0.695	<0.001	0.738	<0.001
Question 23	0.897	<0.001	0.540	<0.001
Question 24	0.492	<0.001	0.774	<0.001
Question 25	0.775	<0.001	0.738	<0.001

I1: Interviewer 1; I2: Interviewer 2; I3: Interviewer 3.

As for validation, according to the Pearson statistic, the GEAP-b showed a positive and significant correlation with depression (GDS) and pain (GPM), respectively: r=59% and r=49.5%, both considered regular (between 40-60%).

Discussion

We obtained an instrument that the elderly were able to understand easily, GEAP-b, which is simple to apply and requires little time (about 5 minutes). We have included a unique long-lived sample, which is the portion of the elderly population that grows the most throughout the world,[19] mostly comprising females (79.2%) and similar to that found in the scientific literature considering the population over 80 years old (feminization of aging).[20]

Regarding pain, we observed the presence of impacting pain, with a majority of participants referring moderate to severe intensity, a rather prolonged duration (9.26 years), and high impact on the life of the elderly according to the GPM-p (social engagement, pain while walking, pain during vigorous activities, and more). This finding is similar to another Brazilian study conducted in the city of Londrina, which found a higher prevalence of moderate to severe pain (60.4%) among the elderly in the community.[21]

The diagnosis of possible depression, according to GDS, was found in almost 40% of patients, reaching 54% in pain-induced depression. This mood disorder is about two to three times higher among individuals with chronic pain, and there is a vicious cycle of worsening pain in patients with depression and vice versa, leading to losses directly proportional to the intensity of the illnesses.[22-25] In population studies, the prevalence of depression in individuals with chronic pain is 18%, and in primary services the incidence reaches 37 to 56%.[22] Onder et al. found a 19.5% prevalence of depression in a European population of long-lived patients with chronic pain.[26]

Analyzing the measurement properties of GEAP-b, firstly referring to its internal consistency, we verified that

it was considered good or excellent. That is, good or excellent reliability was observed for the vast majority of items in this instrument.

For reproducibility, and according to the Kappa agreement that evaluates the extent to which the variability represents the mean, very good results (I1-I2 and I1-I3) were obtained, except for agreement in item 19, which did not compromise the reproducibility. Thus, GEAP-b can be considered an instrument of good reliability.

In the validation process, face and content validities were considered adequate, and especially, the criterion validity. For the latter, we observed statistically significant, regular and positive correlations of GEAP-b with "multidomain" depression and pain. In the case of positive correlations, the higher the GEAP-b score, the higher the level of pain-induced depression observed.

The existence of a gold standard evaluation test would certainly help and enrich the GEAP validation process. A larger sample and comparison studies with other instruments for screening and assessing the severity of depression (such as the Hamilton Depression Scale – HAM-D and the Montgomery-Asberg Depression Rating Scale – MADRS) are valuable in enhancing the validity of this instrument.

The GEAP was applied by interviewers, and a self-assessment by most of the study participants is not possible due to their difficulty in reading the questions in the questionnaire, which was probably due to the low educational level (60.4% studied from 1 to 4 years) of the sample, and can be considered another limitation of our study.

Self-application of the GEAP by the patient is feasible and can be performed in the waiting room of the physicians' offices, and also by other health professionals. This measure is relevant, since there is an increase in the interest of researchers in studying aging and its consequences. Chronic pain in the elderly, as well as chronic pain associated with depression, would thus be important in clinical practice, since these conditions are associated with compromising outcomes. Further research is needed, and the cut-off points require additional validation in the Brazilian medical setting.

Conclusion

We obtained an instrument of easy applicability and good understanding by the elderly: the GEAP-b. It was appropriately translated and adapted transculturally to Brazil, and after the analysis of its measurement properties, proved to be reliable and valid for the identification of pain-induced depression in the elderly.

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Depressão dor-induzida em idosos: validação das propriedades psicométricas da versão brasileira do "Geriatric Emotional Assessment of Pain" – GEAP-b

Objetivo: A fim de se introduzir no nosso meio um instrumento que permitisse uma avaliação clínica abrangente da depressão dor-induzida em idosos, propôs-se a tradução, adaptação transcultural para o Brasil e estudo das propriedades psicométricas do "Geriatric Psychosocial Assessment of Pain-induced Depression" (GEAP). Esse instrumento foi desenvolvido especialmente para rastreio da depressão associada à dor em idosos.
Método: Foram realizadas tradução e adaptação transcultural do GEAP, cujas propriedades psicométricas foram analisadas em uma amostra de 48 idosos. Foram apurados dados sociodemográficos e relacionados a dor crônica, além de depressão. O GEAP-b foi aplicado em três momentos distintos, em um mesmo dia por dois entrevistadores diferentes (E1 e E2), e após 15 dias por um daqueles entrevistadores (E3).
Resultados: O instrumento GEAP-b mostrou-se ser de fácil aplicação e alto valor de consistência interna, de acordo com o coeficiente alfa de Cronbach (0,835). Teve reprodutibilidade ótima, segundo as correlações intraclasses: valores de 98,5 e 92%, interobservador e intraobservador, respectivamente. As concordâncias para cada item do GEAP-b foram "consideráveis" (entre 0,419 e 1,0), excetuando-se a concordância para o item 19, segundo a estatística kappa. Para a validade de critério do GEAP-b, correlações positivas e estatisticamente significativas foram obtidas para a dor, segundo o GPM-p (r=49,5%; p<0,001), e para a depressão, segundo o GDS (r=59%; p<0,001), com ambos os valores considerados regulares (entre 40 e 60%).

Conclusão: O GEAP-b demonstrou ser confiável e válido no rastreio da depressão associada à dor em idosos.

Palavras-chave: idoso, dor crônica, depressão, comparação transcultural, estudos de validação.

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Subclinical atherogenesis in patients with mild psoriasis: A role for IL-6?

Michelle Larissa Zini Lise[1]*, Talita Siara Almeida Baptista[2], Laura Esteves Petersen[2], Moisés Evandro Bauer[2], Cláudia Almeida Lopes Ungaretti[3], Elton Torres[3], Karen Harter[3], Henrique Luiz Staub[1]

[1]Doctor, PhD, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil
[2]Doctor. Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil
[3]Doctor, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

Summary

Introduction: A link of psoriasis with subclinical atherosclerosis has been postulated and cytokine network might intermediate this association. Few data are available in patients with mild psoriasis. We evaluated carotid intima-media thickness (cIMT) in drug-free psoriatic individuals and controls. In parallel, we searched for associations of cIMT with disease activity indexes and serum interleukins (IL) in psoriatic patients.
Method: An experienced radiologist performed the cIMT analyses. Cytokine concentrations were assessed by flow cytometry. Disease activity was evaluated based on psoriasis area and severity index (PASI) as well as body surface area (BSA).
Results: Sixty-five (65) patients and 64 controls were studied. Mean age of patients (50.9 years) did not differ from controls (p=0.362). A low PASI and BSA (< 10) prevailed (69.2% and 56.9%, respectively). Median levels of IL-12p70, TNF-α, IL-1β and IL-10 were significantly lower in cases than in controls (adjusted p<0.05), while IL-6 and IL-8 medians did not differ between groups (adjusted p>0.05). Smoking habit and diabetes mellitus predominated in cases (p=0.002). An altered cIMT (≥ 0.9 mm) was more frequent in cases than in controls (23.8% versus 8.5%, adjusted p=0.045). Mean cIMT was higher in cases with a borderline significance (p=0.057). cIMT scores did not correlate to PASI (rs=0.066; p=0.250) or BSA (rs=0.175; p=0.185), but did correlate significantly with serum IL-6 (rs=0.26; p=0.005).
Conclusion: Subclinical atherosclerosis was more frequent in patients with mild psoriasis than controls. cIMT in psoriatic individuals correlated with serum IL-6, pointing to an eventual proatherogenic role of IL-6 in these patients. Newer studies should clarify the connection of atherogenesis with cytokines in psoriasis.

Keywords: psoriasis, atherogenesis, intima-media thickness, inflammation, IL-6.

Study conducted at Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

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***Correspondence:**
Mãe de Deus Center
Address: Av. Soledade, 569/912, Torre Alfa
Porto Alegre, RS – Brazil
Postal code: 90470-340
dramizini@yahoo.com.br

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Introduction

Psoriasis is a chronic, inflammatory disorder characterized by skin or joint (or both) manifestations.[1] Up to 2% of the general population can be affected.[1,2] It is the most prevalent autoimmune disease in the United States of America.[3]

Psoriasis can occur at any age, with no difference in gender.[4] A concordance rate of 70% in monozygotic and up to 20% in dizygotic twins has been documented, indicating a genetic background for the disease.[4] Thus, psoriasis is currently considered as a genetically-determined autoimmune disorder.[5,6]

Its pathogenesis is complex, including changes in innate immunity[5] and increased production of pro-inflammatory cytokines.[7] The latter generates proliferation of keratinocytes and activation of neutrophils and endothelial cells in the skin.[8] Adaptive immunity also plays an essential pathogenetic role in psoriasis, and T cells remain the most important cellular players in this context.[9]

Psoriasis can affect any area of the body, including mucous membranes. The most common clinical form (90% of cases) is plaque or vulgar psoriasis, characterized by well-delimited erythematous-desquamative plaques symmetrically distributed.[10]

An increased frequency of systemic conditions such as smoking, metabolic syndrome (MetS), cardiovascular disease and obesity have been reported in psoriasis.[8,11-16] Such comorbidities are probably mediated by T-helper 1 (Th1) cytokines.[17] The association of psoriasis with accelerated atherogenesis is currently a topic of major interest.

In recent years, carotid intima-media thickness (cIMT) has been adopted as a marker of subclinical atherosclerosis and as a robust predictor of cardiovascular events.[18] cIMT is a non-invasive marker of early arterial wall changes. It is a practical, low-cost and reproducible procedure, easily assessed by B-mode ultrasound.[19]

An increased burden of subclinical atherosclerosis (as assessed by cIMT) was recently demonstrated in patients with plaque psoriasis.[20] Nevertheless, data on patients with mild psoriasis are scarce. In the current study, we compare the cIMT of drug-free psoriasis patients and healthy controls. We also correlated cIMT with psoriasis disease activity indexes and a panel of pro- and anti-inflammatory cytokines.

Method

This cross-sectional study included patients over 18 years of age with psoriasis followed in the Outpatient Clinic of Hospital São Lucas (HSL). All patients signed a free and informed consent form, and the study was approved by the local ethics committee.

We included patients of both sexes, with psoriatic lesions for at least three months. Patients were diagnosed with psoriasis and classified into different forms of disease by a trained dermatologist according to a previously established description.[21] The control group comprised individuals without psoriasis, older than 18 years. These were volunteers or subjects allocated from hospital staff.

Exclusion criteria for both groups were: a) use of hormonal or non-hormonal anti-inflammatory drugs and immunosuppressants in the last three months; c) other autoimmune diseases; d) history of organic brain injury, or neurological disorder such as epilepsy or dementia; e) renal failure; f) active neoplasm under treatment; g) history of organ transplant; h) infection within 15 days prior to sample collection; i) pregnancy.

Both groups were studied as to age, sex, phototype, hypertension, history of stroke or myocardial infarction (MI), current smoking habit, body mass index (BMI), metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), dyslipidemia (i.e., use of antilipemic drugs), and family history of stroke or MI.

An experimented radiologist, blinded to clinical data and cytokine concentrations, performed all cIMT measurements using a high-resolution 10 MHz linear transducer. A cIMT ≥ 0.9 mm was considered as altered.[22]

Body surface area (BSA) and the psoriatic area severity index (PASI) were used to assess disease activity. BSA[23] and PASI[24] above 10 were considered increased. The soluble cytokines IL-6, IL-12p70, TNF-α, IL-10, IL-1β and IL-8 were simultaneously measured by flow cytometry using Cytometric Bead Array (CBA) Human Inflammatory Cytokine Kit (BD Biosciences). Quantitative results were generated using FCAP Array v1.0.1 software (Soft Flow Inc., Pecs, Hungary).

Results were presented as mean and standard deviation (SD) for data normally distributed, or median (interquartile interval) for non-parametric data. Categorical variables were expressed as percentages and compared using Chi-square or Fisher test. The Welsh test was used to compare mean values. For comparison of continuous variables, Student's t-test was employed. The Spearman coefficient was adopted to calculate correlations among continuous variables. A logarithmic transformation of asymmetric data was done to perform Covariance Analysis (ANCOVA) for confounding factors. Statistical analysis was performed using the Statistical Package for Social Sciences, SPSS 21.0 Statistics (IBM, Chicago, IL, USA). P-values < 0.05 were considered significant. The study was approved by the hospital's ethics committee.

Results

Sixty-five (65) patients and 64 controls were studied. In the psoriatic population, the age of disease onset (mean plus standard deviation, SD) was 31.6±16.0, and mean disease duration was 19.3±13.4 years. Psoriasis vulgaris was diagnosed in 55 patients (84.6%). Family history of psoriasis was referred by 28 patients (43.1%). Mean PASI was 6.60±6.56; PASI > 10 was demonstrated in 20 patients (30.8%). Mean BSA was 11.8±12.4; BSA > 10 was seen in 28 patients (43.1%).

Clinical data from patients and controls are shown in Table 1. Lower phototypes were significantly more frequent in controls, whereas current smoking and T2DM significantly prevailed in cases. Mean BMI and occurrence of MetS did not differ in cases and controls. Likewise, frequency of hypertension, dyslipidemia, previous stroke or MI and family history of stroke or MI proved to be similar in both groups.

Serum cytokine concentrations of cases and controls are seen in Table 2. IL-12p70, TNF-α, IL-10 and IL-1β medians were lower in cases than controls ($p<0.05$). After adjustment for confusion factors (phototype, T2DM, current smoking and alcohol abuse) using ANCOVA, results were maintained for the all the aforementioned cytokines. IL-6 and IL-8 concentrations did not differ in groups.

TABLE 1 Clinical characteristics of psoriatic patients and controls.

Characteristics	Cases (n=65)	Controls (n=64)	p
Age (mean±SD)	51.0±14.5	49.20±12.4	0.454#
Males	33 (50.8%)	32 (50%)	>0.999*
Phototype			0.042*
2	12 (18.5%)	24 (37.5%)	
3	44 (67.7%)	35 (54.7%)	
4	8 (12.3%)	3 (4.7%)	
5	1 (1.5%)	2 (3.1%)	
Body mass index (mean±SD)	27.1±6.1	26.8±3.9	0.337*
Type 2 diabetes mellitus n (%)	10 (15.4)	2 (3.1)	0.030*
Dyslipidemia n (%)	21 (32.3)	31 (48.4)	0.074*
Hypertension n (%)	20 (30.8)	15 (23.4)	0.429*
Metabolic syndrome n (%)	11 (16.9)	12 (18.8)	0.822*
Current smoking	18 (27.7%)	4 (6.3%)	0.002*
Current alcohol intake n (%)	49 (75.3)	58 (90.6)	0.034*
Depression n (%)	17 (26.2)	10 (15.66)	0.194*
Personal history of stroke n (%)	1 (1.5)	0 (0)	>0.999*
Personal history of heart attack n (%)	1 (1.5)	1 (1.6)	>0.99*
Family history of stroke n (%)	19 (29.2)	20 (31.3)	0.849*
Family history of heart attack n (%)	22 (33.8)	24 (37.5)	0.715*

n: sample number; SD: standard deviation; #Student t-test; *Fisher test.

TABLE 2 Cytokine concentrations (pg/mL, median) in psoriatic patients and controls.

Characteristics	Cases (n=65)	Controls (n=64)	p*	p**
IL-12p70 (pg/mL) ME(IR)	4.86 (4.23-5.42)	5.23 (4.69-5.77)	0.042	0.036
TNF-α (pg/mL) ME(IR)	5.29 (4.45-5.64)	5.78 (5.15-6.32)	0.001	<0.001
IL-10 (pg/mL) ME(IR)	7.36 (6.64-8.04)	7.70 (7.19-8.35)	0.014	0.028
IL-6 (pg/mL) ME(IR)	6.86 (6.01-7.98)	6.63 (6.10-7.64)	0.912	0.378
IL-1β (pg/mL) ME(IR)	6.48 (6.06-7.14)	7.01 (6.44-7.56)	0.042	0.006
IL-8 (pg/mL) ME(IR)	6.46 (5.28-8.90)	6.54 (5.86-7.88)	0.808	0.540

n: sample number; ME: median; IR: interquartile range; *Mann-Whitney test. **Data adjusted for phototype, diabetes mellitus, current smoking and alcohol intake using ANCOVA.

Altered cIMT (≥ 0.9 mm) was detected in 23.6% of psoriatic individuals and in 8.5% of controls, showing statistical significance (p=0.045, Fisher test adjusted for phototype and current smoking). Mean cIMT of psoriatic individuals (0.67±0.30) was higher than that of controls (0.59±0.13) with a borderline significance (p=0.057, Welsh test).

In psoriatic patients, cIMT scores did not correlate with PASI (rs=0.066, p=0.250) or BSA (rs=0.175, p=0.185). cIMT scores correlated significantly with IL-6 concentrations (rs=0.26, p=0.005) (Figure 1), but not with other cytokines (rs<0.3, p>0.05). No correlation of cIMT with serum cytokines was observed in controls (rs<0.3, p>0.05).

Discussion

Our study looked into a potential link of psoriasis with subclinical atherogenesis. For such, we evaluated cIMT in cases and healthy controls. Subsequently, we investigated a possible association of cIMT with an index of disease activity and cytokine profile. Overall, our psoriatic population comprised middle-age individuals with long duration disease. Psoriasis vulgaris largely predominated.

Most of our patients presented mild disease, evidenced by low BSA and PASI scores. The decision of including patients that did not use anti-inflammatory drugs or immunosuppressants certainly yielded a bias towards milder disease. Smoking and T2DM significantly prevailed in psoriatic individuals, but other variables of clinical relevance such as hypertension, dyslipidemia and MS were similar in both groups.

Compared to controls, our patients with psoriasis presented low concentrations of pro-inflammatory cytokines (IL-12p70, TNF-α, IL-1β), even after adjustment for

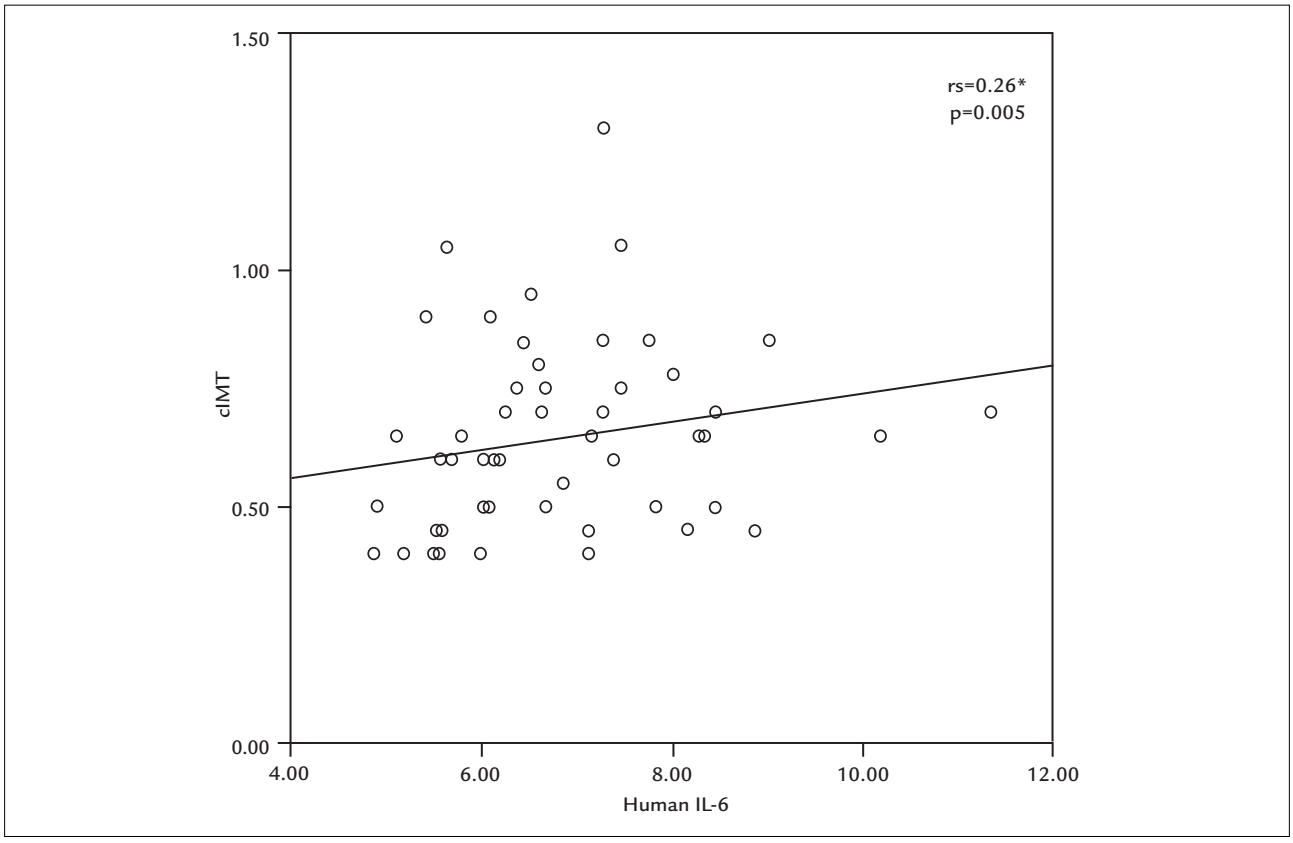

FIGURE 1 Correlation of cIMT scores with IL-6 concentrations (pg/mL) in patients with psoriasis.
cIMT: carotid intima-media thickness; *Spearman coefficient.

confusion factors. It has been postulated that Th1, Th17 and Th22 cytokines play an important pathogenetic role in psoriasis; indeed, interferon (IFN)γ, IL-2, IL-17A, IL-17F, IL-22, IL-26, and TNF-α were all increased in serum and lesional skin.[25] Also different from our findings, a 2005 study obtained high serum concentrations of TNF-α, IFN-γ, IL-6, IL-8, IL-12 and IL-18 in active psoriatic patients as compared to controls.[26]

In our study, the predominance of patients with mild and inactive disease might explain the low profile of pro-inflammatory cytokines. Of note, serum levels of IL-12/23p40 and IL-17 were equivalent in psoriatic individuals and controls, according to a recent study.[27] In 2003, supporting our findings, low levels of IL-12 were reported in psoriatic patients.[28] Thus, data regarding the role of pro-inflammatory cytokines in psoriasis are far from clear.[25-28]

Abnormal cIMT (≥ 0.9 mm) was more frequent in our psoriasis patients than in controls, which remained significant after adjustment for confusion factors. Bearing in mind that psoriasis is linked to an increased risk of atherosclerosis, a common mechanism explaining both disorders could probably involve the Th1 and Th17 network,[29] but the fundamental mechanisms connecting the two disorders are not fully known.

A recent meta-analysis confirmed that patients with psoriasis have an increased risk of subclinical atherosclerosis according to cIMT and brachial artery flow-mediated dilation.[30] To date, augmented risks of cardiovascular disease, obesity, DM and MetS have been documented particularly in patients with moderate to severe psoriasis.[31] Our data demonstrate, probably by the first time, subclinical atherosclerosis in drug-free patients with mild disease. Moreover, increased cIMT in cases did not correlate with MetS. We have also found that cIMT scores of psoriatic patients did not correlate with disease activity as measured by PASI and BSA.

In the current study, the relationship of cIMT with IL-6 concentrations appeared to be complex. Even though IL-6 concentrations did not differ between cases and controls, cIMT, interestingly, correlated with IL-6 in psoriatic individuals. Such correlation was not seen in controls, suggesting that intrinsic factors linked to psoriasis play a role in this scenario.

Knowingly, IL-6 is a pro-inflammatory cytokine produced by activated monocytes, mast cells, fibroblasts and tumor cells. Note that keratinocytes are also an established source of IL-6, which might indicate a role for this cytokine in the skin proliferation proper of psoriasis.[32] IL-6 is also able to induce release of other pro-inflammatory cytokines (IL-23, IL-17) by neutrophils.[33]

IL-6 measurement seems to be a good predictor of future vascular risk in healthy populations. IL-6 levels correlate with endothelial dysfunction and arterial stiffness. Also, it might relate to plaque destabilization and adverse outcomes in acute ischemia. Of note, genetic variations in IL-6 signaling apparently affect the rates of vascular events.[34]

If IL-6 plays a proatherogenic role in psoriatic individuals, this might be plausible. In low-density-lipoprotein-receptor-deficient mice, IL-6 expression accelerated atherosclerosis.[35] Recently, circulating IL-6 was associated with atherosclerosis in HIV-positive patients independently of traditional risk factors for cardiovascular disease.[36] A link of subclinical atherogenesis with serum IL-6 in patients with mild psoriasis has not been previously reported.

The association of psoriasis with cardiovascular morbidity is now a matter of major interest. Even though methotrexate and anti-TNF agents are probably cardioprotective in psoriasis, there have been concerns with an excess of cardiovascular events in users of the newer anti-interleukin-12p40 antibodies.[37] Currently, drugs targeting the C-reactive protein/IL-6/IL-1 axis, such as colchicine, methotrexate, tocilizumab and canakinumab (all potentially useful in psoriasis), are being tested to prevent cardiovascular events in high-risk populations.[34]

Our study has limitations. The overall sample was restricted by the rigid inclusion criteria (drug-free individuals). cIMT would probably be higher in patients with more severe and active disease, eventually allowing further associations with activity index and/or cytokines. On the other side, by dealing with drug-free patients, our study was less prone to confounding factors and masking bias.

Conclusion

Our cIMT findings revealed subclinical atherosclerosis in psoriatic individuals with mild disease. The established correlation of cIMT with IL-6 levels points to a possible proatherogenic role of IL-6 in mild psoriasis. Further research may clarify the link of atherogenesis with the cytokine network, particularly IL-6, in psoriatic populations.

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Aterogênese subclínica em pacientes com psoríase leve: um papel para IL-6?

Introdução: Foi postulada uma ligação entre psoríase e aterosclerose subclínica. A rede de citocinas pode intermediar essa associação. Poucos dados estão disponíveis em pacientes com psoríase leve. Avaliamos a espessura íntima-média carotídea (cIMT) em psoriáticos e controles livres de medicação. Paralelamente, pesquisamos a associação de cIMT com os índices de atividade de doença e interleucinas séricas (IL) em pacientes com psoríase.
Método: Um radiologista experiente procedeu à análise do cIMT. As concentrações de citocinas foram avaliadas por citometria de fluxo. A atividade da doença foi avaliada pelo índice de gravidade (PASI) e pela área de superfície corporal (BSA).
Resultados: Sessenta e cinco (65) pacientes e 64 controles foram estudados. A idade média dos pacientes (50,9 anos) não diferiu dos controles (p=0,362). PASI e BSA baixos (< 10) prevaleceram (69,2% e 56,9%, respectivamente). As medianas de IL-12p70, TNF-α, IL-1β e IL-10 foram significativamente menores nos casos do que nos controles (p<0,05 ajustado), enquanto as medianas de IL-6 e IL-8 não diferiram nos grupos (p>0,05 ajustado). Tabagismo e *diabetes mellitus* predominaram nos casos (p=0,002). Um cIMT alterado (≥ 0,9 mm) foi mais frequente nos casos do que nos controles (23,8% *versus* 8,5%, p=0,045 ajustado). A média de cIMT foi maior nos casos com significância *borderline* (p=0,057). Os escores de cIMT não se correlacionaram com o PASI (rs=0,066; p=0,250) ou o BSA (rs=0,175; p=0,185), mas se correlacionaram significativamente com a IL-6 sérica (rs=0,26; p=0,005).
Conclusão: A aterosclerose subclínica foi mais frequente em pacientes com psoríase leve do que nos controles. Em psoriáticos, cIMT correlacionou-se com níveis de IL-6 no soro, apontando para um eventual papel pró-aterogênico para a IL-6 nesses pacientes. Novos estudos devem esclarecer a ligação da aterogênese com citocinas na psoríase.

Palavras-chave: psoríase, aterogênese, espessura médio-intimal, inflamação, IL-6.

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Opioids and immunosupression in oncological postoperative patients

José Luis Bonilla-García[1]*, Manuel Cortiñas-Sáenz[2], Esperanza del Pozo-Gavilán[3]

[1]FEA Anestesiología y Reanimación, Complejo Hospitalario Universitario de Huelva, Huelva, Spain
[2]FEA Anestesiología y Reanimación, Hospital Torrecárdenas, Almería, Spain
[3]Departamento de Farmacología e Instituto de Neurociencias, Facultad de Medicina, Universidad de Granada, Granada, Spain

Summary

Introduction: Recent animal studies demonstrated immunosuppressive effects of opioid withdrawal resulting in a higher risk of infection. The aim of this study was to determine the impact of remifentanil discontinuation on Post-Anesthesia Care Unit (PACU)-acquired infection after a schedule of sedoanalgesia of at least 6 days.
Method: All patients over 18 years of age with a unit admission of more than 4 days were consecutively selected. The study population was the one affected by surgical pathology of any origin where sedation was based on any hypnotic and the opioid remifentanil was used as analgesic for at least 96 hours in continuous perfusion. Patients who died during admission to the unit and those with combined analgesia (peripheral or neuroaxial blocks) were excluded. Bivariate analysis was performed to determine risk factors for infection acquired in the unit. A comparative study between periods of 6 days before and after the cessation of remifentanil was performed. Paired samples test and McNemar test was used for quantitative and categorical variables, respectively.
Results: There were 1,789 patients admitted to the PACU during the study and the population eligible was constituted for 102 patients. The incidence rate of PACU-acquired infection was 38 per 1,000 PACU days. Ventilator-associated pneumonia was the most frequently diagnosed PACU-acquired infection. *Pseudomona aeruginosa* was the most frequently isolated microorganism. Hospital mortality was 36.27%. No statistically significant differences were seen in the incidence of HAI in cancer patients in relation to discontinuation of remifentanil (p=0.068).
Conclusion: The baseline state of immunosuppression of cancer patients does not imply a higher incidence of HAI in relation to the interruption of remifentanil. It would be of interest to carry out a multicenter PACU study that included immunological patterns.

Keywords: remifentanil, morphine, opioid, healthcare-associated infections, unit-acquired infection, withdrawal, immunosuppression, critical care, mortality.

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***Correspondence:**
Address: Ronda exterior norte s/n
Huelva, Huelva – Spain
Postal code: 21005
joseluisbonilla86@gmail.com

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Introduction

Oncological pathology is a complex problem characterized by high prevalence and incidence. The use of the various opioid drugs has increased exponentially each year in chronic benign and malignant pain.[1] Many of its primary effects on organic systems are diverse, complex, and not fully known.[2]

Potential results and long-term effects of sedoanalgesia in the field of anesthesiology and critical medicine evoke increasing interest and importance, especially after the advent of oncologic surgery.[3,4] It is suggested that different anesthetic and/or analgesic techniques may influence the rates of surgical infection, cancer recurrence, post-surgical chronic pain, need for transfusion of blood products, episodes of cardiac ischemia, neurological ischemia and cognitive dysfunction in the elderly and neonates.[5] The possible mechanisms by which sedoanalgesia in critically ill patients favors the presence of healthcare-associated infections (HAI) in a classical way are a possible prolongation of the exposure to several risk factors, the presence of micro-aspirations, changes in microcirculation and in gastrointestinal motility.[3]

Sedoanalgesia modifies immune function, but its actual clinical importance is unknown. Studies by Helmy et al.[6] and Hermann et al.[7] show that different hypnotic drugs such as propofol, midazolam and sevoflurane can produce pro-inflammatory or anti-inflammatory immune changes. The antioxidant properties of propofol have been related to its anti-inflammatory effect and therefore are described as contributing to the alteration of neutrophil phagocytosis against certain bacteria.[8] As for midazolam, its role is described as a suppressor of the innate immune response.[8] Moreover, it is linked with the inhibition of the release of cytokines, and thus of interleukins (IL) 1 and IL-6 in the central nervous system.[9]

On the other hand, multiple investigations in animals and humans demonstrate the immunosuppressive effects of opioids[10] and, therefore, administration of these drugs has been associated with increased susceptibility to certain bacterial and viral infections.[11] Morphine is associated with decreased lymphoproliferative processes, natural killer (NK) lymphocyte activity, and interferon-γ and IL-2 production.[2]

The relation between opioids and impaired immune function is constantly referred to in the medical literature, and there is a consensus that opioids act in the modulation of the immune system. Currently, there is a growing interest in elucidating the possible influences of opioid use in the management of patients with pain.[2,12] Traditionally, as documented since the 9th century, there has been an increase in the incidence and severity of infections among opiate users. The potential target of the immunosuppressive effect of opiates is not fully understood, but different investigations appear to indicate bidirectional connections between the neural, endocrine and immune systems, placing it peripherally based on the expression of the MOP receptor on immune cells with implications at the central nervous system level.[12,13]

The administration of opioids affects the immune system in different degrees and manners.[2] The clinical relevance of this immunological role is not well-known. The mechanisms of immunomodulation of opioids may be in vitro or in vivo (Table 1). In the first case, there is a change in the phagocytic and chemotactic function of neutrophils and monocytes with increased apoptosis of lymphocytes and phagocytic cells.[14] In vivo investigations seem to relate changes in the downregulation of protein C, somatostatin and nitric oxide with a decline in NK cell function, suppression of inflammatory cytokines with a sympathetic nervous system activation that promotes high levels of norepinephrine and which could be related with immune suppression.[2,12,15]

There is a close relation between cancer, inflammation, sepsis and immunity.[16] This relationship is based on the interaction that is produced between the inflammatory cells in the presence of several cytokines. A state of immunosuppression may be influenced by the underlying disease itself, the surgical and anesthetic-analgesic techniques, chemo and radiotherapy employed.

There is a wide variety of opiates used by different routes, such as morphine, fentanyl, hydromorphone, oxycodone, tapentadol, buprenorphine, tramadol, codeine, alfentanil, sufentanil, remifentanil, etc.[17] Because of their widespread use, the immunological effects of opioid drugs receive considerable attention, knowing that the changes induced by these drugs in the immune system may affect surgical outcomes or a variety of chronic pathological processes. On the other hand, we are starting to learn and

TABLE 1 Main changes in NK cell immune function with different opiates.

Opiates	In vitro studies Cellular series		In vivo studies Cellular series			
	Animals	Humans	Animals		Humans	
			No Surgery	Yes Surgery	No Surgery	Yes Surgery
Morphine	=, ↓	=, ↓	=, ↓	↑,=, ↓	↑,=, ↓	=, ↓
Fentanyl	?	?	=, ↓	↓, ↑	=, ↑	=, ↓
Remifentanil	?	?	↓	?	=	?
Sufentanil	?	?	↓	?	?	↓
Meperidine	↓	?	?	?	?	=
Methadone	=, ↓	=, ↓	=, ↓	?	=, ↓	?
Buprenorphine	?	?	=, ↓	=, ↑	?	?
Tramadol	?	?	=, ↑	↑	?	↑

↑: Increase; ↓: Decrease; =: Neutral effects; ?: Data not available.

understand that not all opioid drugs have the same profile and therefore do not induce the same immunomodulatory effects (Table 1).[18] The clinical relevance of these effects is unknown and there are no recommendations for the use of opioids in various clinical situations regarding the immunological consequences of these drugs.

Animal studies suggest that opiates withdrawal induces a state of immunosuppression that would increase the risk of infections[19] and, thus, changes in immunomodulation caused by certain drugs may be responsible for a part of the HAI-related complications in critical medicine. Recently, it was reported that anesthetic techniques and different sedoanalgesia regimens could be an important confounding factor when comparing sepsis mortality investigations.[11] Therefore, due to the inconsistent results of investigations in animal and human models, the clinical relevance of the suppression of the immune system caused by hypnotics and opiates is unclear.[20]

The aim of our investigation was to assess the hypothesis that remifentanil discontinuation is associated with an increase in HAI rates in a subpopulation of critical post-surgical patients according to the etiology of the underlying disease.

Method

After approval by the Hospital Ethics Committee, a prospective and observational study of a historical cohort in a 6-bed Post-Anesthesia Care Unit (PACU) was conducted during the years 2010-2012.

All patients older than 18 years hospitalized at the unit for more than 4 days were consecutively selected. The investigated population included surgical patients of any origin sedated with any hypnotic and treated with remifentanil as analgesic opioid infused continuously for at least 96 hours. Patients who died during the stay in the unit and those under combined analgesia (peripheral or neuraxial blocks) were excluded.

Doses of midazolam, propofol and remifentanil are described in the unit's sedoanalgesia protocol (Figure 1) and are in accordance with the guidelines of the Society of Critical Care Medicine.[21] Withdrawal syndrome is treated following the strategy of sequential sedation.

The main variable in our investigation was the number of healthcare-associated infections acquired in the PACU during the days of hospitalization. We also considered the incidence density, defined as the number of infections acquired in the unit per 1,000 days of hospitalization.

The cutoff point for differentiating early and late HAIs was determined as 6 days before and after cessation of remifentanil.

There is a nosocomial infection surveillance system with systematic and routine detection of multiresistant microorganisms. Only the infections confirmed by the Microbiology Service were considered in our study. A number of nosocomial infections were defined according to the definitions adopted by the Centers for Disease Control and Prevention (CDC).[22]

Other variables included age; sex; APACHE II (Acute Physiology and Chronic Health Evaluation II) classification; ASA (American Society of Anesthesiologists) index; McCabe score; number and type of comorbidity; cause of hospitalization; number of surgical re-interventions; previous antibiotic treatment; length of stay in critical care; Ramsay scale; rate of central and arterial venous catheter usage; closed urinary catheters and mechanical ventilation; number of re-intubations; tracheotomy; duration and type of antimicrobial agent; dose of remifentanil, midazolam or propofol; use of neuromuscular blocking drugs; and mortality.

Recommendations based on the guidelines of the Sociedad Española de Anestesiología y Reanimación adapted to the local epidemiology of bacterial resistance of our critical care unit were adopted for the empirical treatment of infectious processes.[23]

In patients with sepsis at hospitalization, vigorous resuscitation with fluids and hemodynamic support measures were initiated, including vasopressors in case of hypotension or lactate > 4 mmol/L, low-dose corticosteroids in patients with septic shock, invasive mechanical ventilation for pulmonary protection, blood glucose control between 150-180 mg/dL, assessment of the need for surgical intervention or percutaneous drainage, bacterial cultures and introduction of empiric antimicrobial treatment, as advocated in the Surviving Sepsis Campaign.[24]

The data analysis was performed with Stata statistical software version 7.0. The results are presented as number, percentages for categorical variables, and mean with their standard deviation for the quantitative variables. Univariate analysis was used to determine the factors associated with nosocomial infection. Qualitative variables were compared using Pearson's Chi-square test or Fisher's exact test, as appropriate. Quantitative variables were compared using the Mann-Whitney test or Student's t-test. Statistical significance was defined as $p<0.05$. In patients with nosocomial infection, exposure to potential risk factors was taken into account until the onset of the last episode of infection. Patients with various infections were considered at risk until the last episode. A comparative study was carried out between 6 days before and

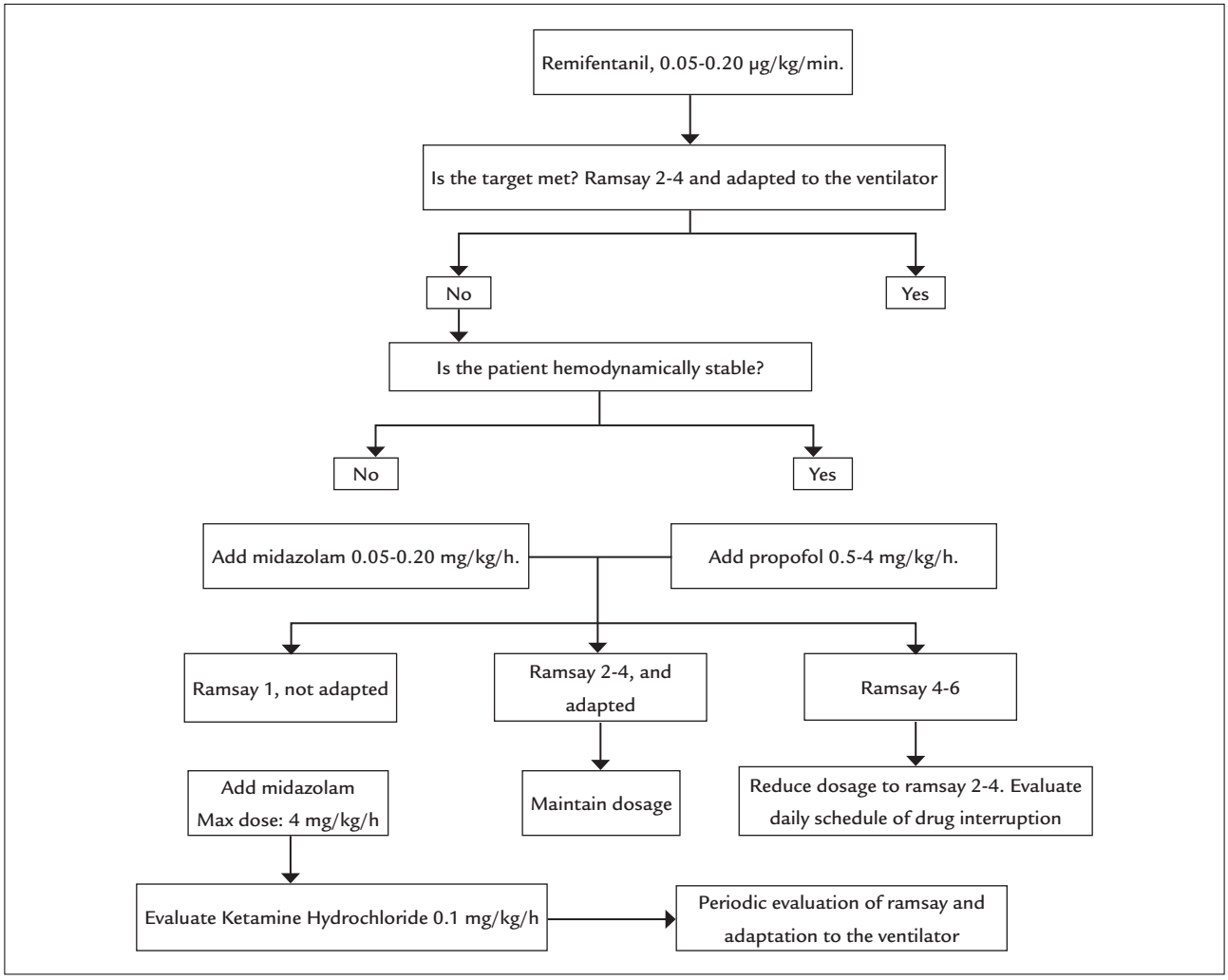

FIGURE 1 Unit's sedoanalgesia protocol.

after the cessation of remifentanil, the cutoff point being the day of cessation of this drug. For these comparisons, paired samples and the McNemar test were used for the quantitative and categorical variables, respectively.

Results

The number of patients who were admitted to the Post-Anesthesia Care Unit during the investigation period was 1,789. After applying the inclusion and exclusion criteria, the eligible population consisted of 102 patients whose analgesia protocol was the intravenous infusion of remifentanil for at least 96 hours. The hospital mortality of the cohort was 36.27%.

The demographic and prognostic characteristics of the population are summarized in Table 2 and the clinical variables in Table 3. Fifty-nine cases (59/57.84%) of hospitalizations at the unit were urgent. The main etiology for hospitalization was the occurrence of secondary peritonitis after urgent surgeries (23.52%).

Ninety percent (90%) of the patients were treated with simultaneous sedation with hypnotics, while the others did not receive sedative drugs. Remifentanil infusion during the investigation period was 11.45±11.57 days (Table 4).

The most frequent HAI was pneumonia associated with mechanical ventilation, and *Pseudomonas aeruginosa* was the most frequently isolated microorganism. The rate of use of medical devices in the investigated population admitted to PACU and treated with remifentanil for at least 96 hours is shown in Table 5.

Figures 2 and 3 show the number of HAI in a temporal relation with the administration and cessation of remifentanil according to the underlying disease (oncological and non-oncological patients of the cohort). There were no

TABLE 2 Demographic and prognostic characteristics of the cohort investigated.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
Age in years	65.57±12.03	63.89±10.31	0.236
Sex (male)	29	21	0.443
ASA > 2	41	21	0.132
McCabe Score			
Good prognosis	13	14	
Poor prognosis	20	15	0.129
Fatal prognosis	21	6	
Death expectations	9	4	
APACHE II	16.41±6.89	13.41±8.22	0.025
Underlying comorbidity			
Hemodynamic	34	19	0.606
Respiratory	24	20	0.191
Renal	17	9	0.660
Hepatic	9	7	0.621
Immunosuppression	27	15	0.661
Diabetes mellitus	34	4	<0.001
Number of comorbidities			
≤ 2	13	16	<0.001
> 2	50	23	

TABLE 3 Clinical characteristics of the cohort.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
Length of stay in PACU (days)	17.17±13.37	12±10.62	0.021
Length of hospital stay (days)			
Pre-PACU	4.28±3.88	3.25±2.35	0.069
Post-PACU	14.74±20.18	12.71±15.93	0.297
Global	36.36±24.93	27.94±22.70	0.044
Mortality			
PACU	17	8	0.460
Post-PACU	10	2	0.143
Type of urgent surgery	29	14	0.314
Reintubation	19	9	0.436

PACU: Post-Anesthesia Care Unit.

TABLE 4 Type of sedoanalgesia administered to the patients in the cohort.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
Remifentanil	5	3	0.657
Days of remifentanil	13.11±12.92	8.76±8.48	0.032
Midazolam and remifentanil	31	14	0.188
Days of midazolam	14.83±13.36	10.64±11.07	0.155
Propofol and remifentanil	27	22	0.183
Days of propofol	8.40±6.02	6.21±2.90	0.060

TABLE 5 Utilization rate of medical devices in the investigated population admitted to a post-surgical critical care unit (CCU) and treated with remifentanil for at least 96 hours.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
CVC	63	38	-
Days of CVC	20.15±16.17	16.30±12.99	0.106
IMV	63	39	-
Days of IMV	12.09±8.34	7.94±5.47	0.003
Tracheotomy	20	5	0.031
Days of tracheostomy	9.8±3.42	11±6.22	0.342
UC	63	39	-
Days of UC	21.19±16.17	16.48±11.07	0.056

CVC: central venous catheter; IMV: invasive mechanical ventilation; UC: closed urinary catheter.

statistically significant differences in the incidence of HAI in the oncological patients regarding remifentanil cessation using the Mann-Whitney U test (p=0.068) (Table 6).

Discussion

Sepsis is a critical problem in all areas of clinical medicine.[25,26] New and complex immunological investigations conducted during sepsis suggest that immunosuppression is the determinant of mortality in severely ill patients.[27-29] A shift in the traditional sepsis paradigm focuses on immunostimulation to improve clinical outcomes as a key to new therapeutic options.

The main finding in our study is a quasi-significance and the existence of two temporal patterns of post-surgical patient behavior after opioid withdrawal according to the underlying disease or etiological diagnosis (Figures 2 and 3), which is why these patients should be monitored closely for the consequences of a delayed diagnosis.[30] We observed a high incidence of HAI within 6 days after the discontinuation of opioid analgesia (remifentanil) in the population of oncological patients, with an antagonistic pattern among non-oncological postoperative patients. This different pattern in cancer patients hospitalized in our unit has been described by other authors in relation to the use of opiates, as reported by Schwacha et al.[31] in burn patients and by Nseir et al.[32] in critically ill patients after a multivariate analysis.

Patient characteristics play a key role in the risk of infection,[33] while, in the surgical setting, duration of mechanical ventilation, patient severity based on the APACHE-II index, albuminemia, and time of hospitalization prior to intervention are known factors favoring HAI.

Analyzing the characteristics of our cohort, we observed a homogeneous distribution of the sample in both groups in terms of age and sex (oncological and non-oncological), although they are not fully comparable due to differences in severity at hospitalization, comorbidity number and days of stay in PACU, which are factors predisposing to nosocomial infection,[34] and which could partially justify the differences in the incidence of HAI between groups.

Severity at hospitalization, days of mechanical ventilation and patient immuno-depressive states were factors associated with HAI acquisition in our post-surgical critical care unit. These results are in agreement with the results obtained by Nserir et al of the risk factors for HAI acquisition in critically ill patients.[32]

In our series, the high utilization rate of intrinsic risk medical devices is characteristic. These devices, along with artificial nutrition and the use of immunosuppressive therapies, are identified as extrinsic risk factors for infection.[35] The justification for these high ranges of device use may be the generalized involvement of organs and systems that are produced in patients affected by severe infections and who will require ventilatory, hemodynamic and diuretic support, as well as continuous monitoring of body functions, to assess the effectiveness of the measures put in place for treatment. In the medical literature, intubation and presence of central vascular catheter are the most prevalent extrinsic risk factors in hospital acquired infection,[36] which coincides with our investigation.

Our study does not determine whether acute use and discontinuation of remifentanil are independent risk factors for nosocomial infection, unlike results reported by Nseir et al.[32] This study showed, after a logistic regression analysis, that there is a high incidence of nosocomial infection during the 4 days after cessation of remifentanil-based analgesia.

In this context, cancer is a pathology closely related to the immune system. Cancer generates a state of immunosuppression that causes the patient to present an

TABLE 6 Analysis of multiple non-parametric Mann-Whitney U-test for nosocomial infection in a post-surgical critical care unit.

Measures	6 days pre-remifentanil cessation	6 days post-remifentanil cessation	Type of patient
Mean±SD	4.00±1.27	7.00±2.78	Oncological patients
	6.00±1.23	1.14±1.07	Non-oncological
	10.00±1.67	6.86±2.85	Global
T mean at 5%	4.06	6.94	Oncological patients
	6.06	1.10	Non-oncological
	10	6.73	Global
95CI	2.67-5.33	4.44-9.56	Oncological patients
	4.67-7.33	0.15-2.15	Non-oncological
	8.24-11.76	4.22-9.50	Global
p-value	0.068		Oncological patients
	0.002		Non-oncological
	0.030		Global

TD: typical deviation; T mean: trimmed mean; CI: confidence interval.

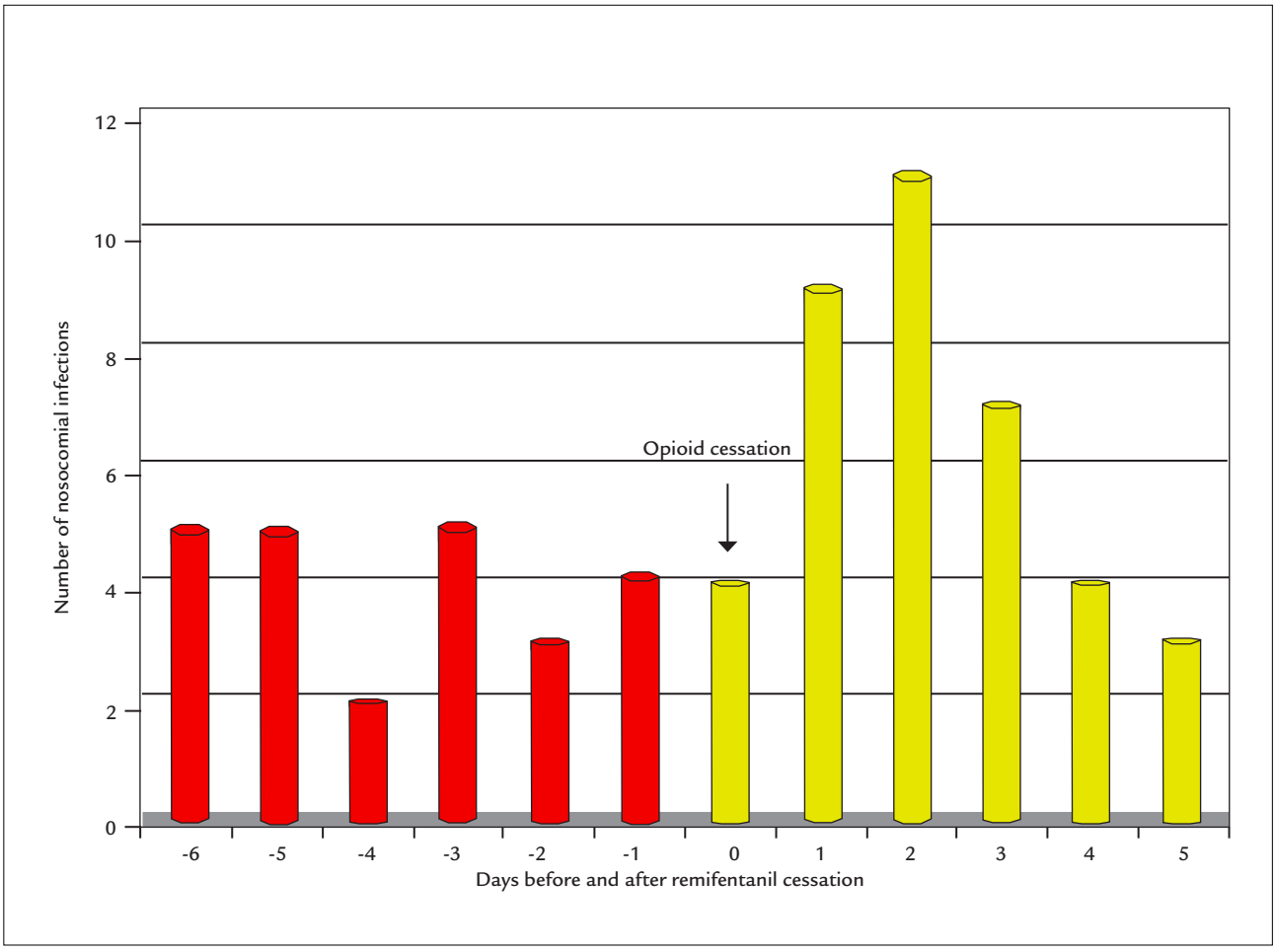

FIGURE 2 Time relation between healthcare-associated infections (HAI) and intravenous remifentanil analgesia in oncological patients in a Post-Anesthesia Care Unit (p=0.068).

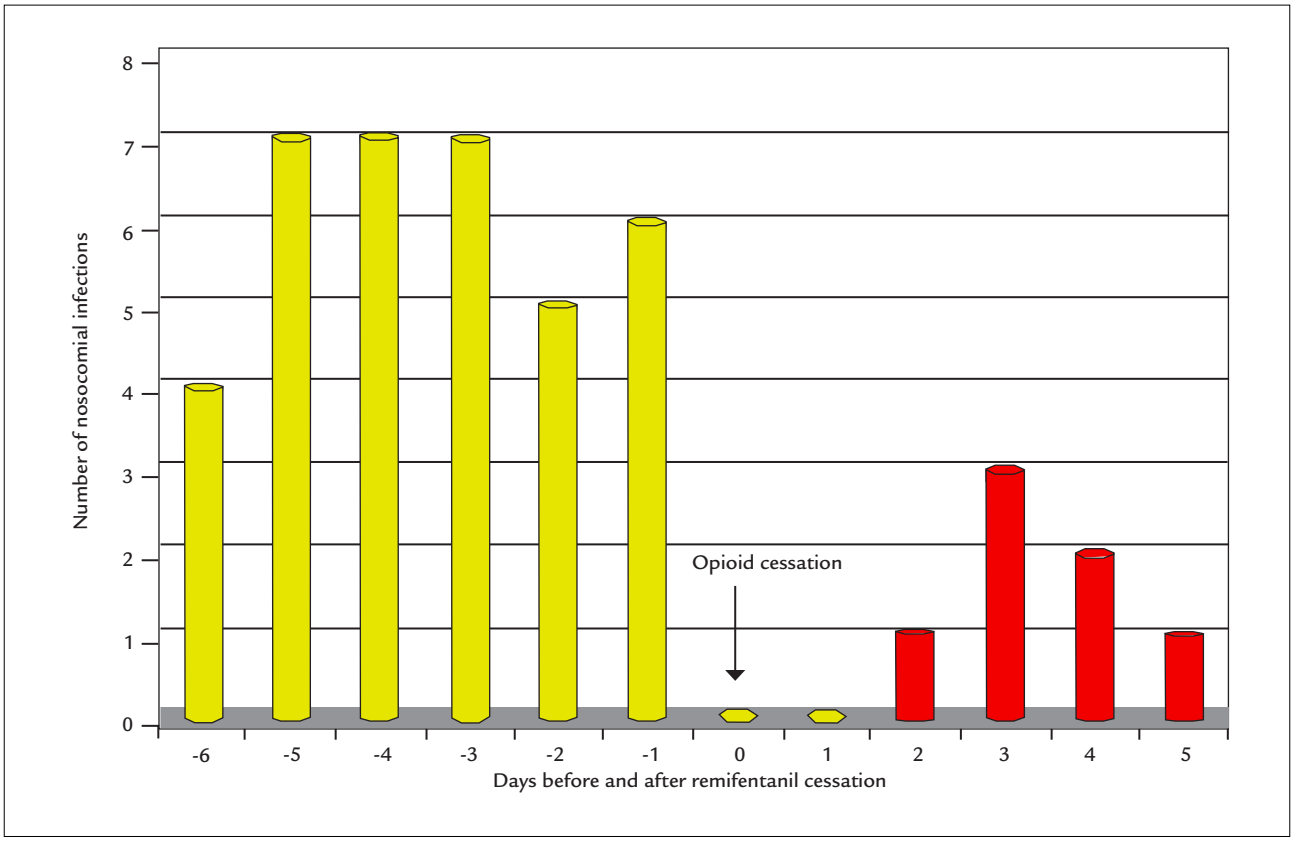

FIGURE 3 Time relation between healthcare-associated infections (HAI) and intravenous remifentanil analgesia in non-oncological patients in a Post-Anesthesia Care Unit (p=0.002).

increased risk of infectious disease. Likewise, there appears to be an inverse relationship in which immunosuppression would increase the risk of oncological pathology.[37] Several investigations clearly show contradictory data regarding the immunological action of opioids in the perioperative period.[38,39] A study by El Solh et al.[38] reveals that morphine administration in patients undergoing coronary revascularization is associated with an increased risk of nosocomial pneumonia. In contrast, Spies et al.[39] indicate that low doses of morphine protect against the development of nosocomial pneumonia after cancer surgery. Our results appear to be more in agreement with the first group cited.

Several investigations describe the immunomodulatory properties of opiates depending on the acute or chronic use and dosage.[7,40,41] Several other studies indicate that morphine is the opioid with the highest degree of impact on the immune system, which is transient with fentanyl and non-existent with tramadol and buprenorphine. As for remifentanil, the available studies show discordant results. Therefore, each substance appears to have a different effect and synthetic opioids appear to have less immunological impact due to weak interaction with leukocyte opioid receptors. This weak association described for synthetic opioids could also partially explain our results.

The use of potent immunosuppressive drugs or analgesia required by this type of patients, presented as the top rungs of the WHO analgesic ladder, may increase the risk of nosocomial infection.[42] On the other hand, many of them receive surgical treatment, which also presupposes an increase in the immunosuppression of the patient caused by both the surgery itself and the anesthesia used during the procedure, although in our investigation all patients were operated under general anesthesia, with no associated regional techniques.

Our sedation protocol is based on recommendations established in the literature. For both short-term sedation and prolonged sedation, it is recommended to use propofol for superficial sedation in hemodynamically stable patients, with special attention to triglyceridemia. Midazolam should be used in hemodynamically unstable patients with no need for frequent neurological assessment, while remifentanil and/or propofol are indicated for sequential and dynamic sedation, and ketamine is contraindicated as prolonged infusion.[43,44]

The use of the drugs is related to the modification of immune cellular functions through several mechanisms not yet fully known. In this sense, the investigation by Helmy et al.[6] shows that different hypnotic drugs can produce pro-inflammatory or anti-inflammatory immunological changes. This fact may suggest a bias in our analysis.

Although there is a change in immunity in patients treated with propofol[8] or midazolam[9] which might be biased in our investigation due to differences between these drugs, we have to say that in our cohort there are no differences in their use between oncological and non-oncological patient groups, although there may be a difference in the time of use.

In our cohort, as we indicated before, oncological and non-oncological patient groups are not fully comparable due to differences in severity at hospitalization, number of comorbidities and days of stay in the critical care unit, which are factors that predispose to infection[31] and may partially justify the differences in the incidence of nosocomial infection between groups. However, other immunomodulatory perioperative factors should be considered, such as hypothermia, pain, stress, steroid use, blood transfusion, etc., which may be associated with enhanced immunosuppression and function as confounding factors in the different human studies.[2,45] Immunosuppression presented by critical oncological patients is a complex multifactorial process that depends not only on the oncological disease itself, but also on the diagnostic and therapeutic measures used to solve or improve the patient's clinical condition, their genetic characteristics, comorbidities, multiorgan dysfunction, etc.

We can identify different limitations in our work, especially sample size and the fact that the study is being performed in a single critical care unit. Secondly, the possible occurrence of infra-sedation or over-sedation, with the possible immunological and infectious changes that this may cause, and which were not considered in the present investigation. Thirdly, there is no control group. Lastly, the lack of results for immunological markers related to cancer disease, which would allow us to better identify the relation between cancer, immunosuppression, remifentanil-related suppression, immunosuppression and healthcare-associated infection.

In conclusion, the baseline immunosuppression status of oncological patients does not lead to an increased incidence of HAI related to remifentanil discontinuation.

This is a fascinating topic, current in critical care medicine and with relevant grey areas, so it may be of interest to carry out a multicentric PACU investigation that includes immunological standards to confirm the results of studies that postulate a immunomodulatory, and not only immunosuppressive, effect of the different sedoanalgesia strategies in critical patients.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Opioides e imunossupressão em pacientes oncológicos pós-cirúrgicos

Introdução: Recentes pesquisas utilizando animais demonstraram efeitos imunossupressores depois da suspensão de opiáceos, associados a um maior risco de infecção nosocomial. O objetivo desta investigação foi determinar o impacto da interrupção do opioide remifentanilo em uma Unidade de Reanimação Pós-cirúrgica (URP) nas infecções associadas aos cuidados da saúde depois de uma pauta de sedoanalgesia de ao menos 6 dias.
Método: Foram relacionados de forma consecutiva todos os pacientes maiores de 18 anos com internação na unidade superior a 4 dias. A população investigada foi aquela afetada por patologia cirúrgica de qualquer origem, na qual a sedação esteve baseada em qualquer hipnótico e como analgésico, foi utilizado o opioide remifentanilo durante pelo menos 96 horas em perfusão contínua. Foram excluídos os pacientes que faleceram durante a internação na unidade e aqueles com analgesia combinada (bloqueios periféricos ou neuroaxiais). Foi realizada uma análise bivariante para determinar fatores de risco para a infecção adquirida na unidade. Foi realizada uma investigação comparativa entre períodos dos 6 dias anteriores e posteriores à interrupção de remifentanilo. Utilizamos o teste de amostras pareadas e a prova de McNemar para as variáveis quantitativas e categóricas, respectivamente.
Resultados: O número de pacientes internados na URP durante o período de investigação foi de 1.789. Depois

de aplicar os critérios de inclusão e exclusão, a população elegível ficou constituída por 102 pacientes. A densidade de incidência de infecção de forma global foi de 38 por cada 1.000 dias de internamento. A pneumonia associada à ventilação mecânica foi a infecção adquirida mais frequente e *Pseudomona aeruginosa*, o micro-organismo mais frequentemente isolado. A mortalidade hospitalar foi de 36,27%. Não foram observadas diferenças estatisticamente significativas na incidência de IACS em pacientes oncológicos em relação à descontinuação de remifentanilo (p=0,068).

Conclusão: O estado basal de imunossupressão dos pacientes oncológicos não implica uma maior incidência de IACS em relação à interrupção do remifentanilo. Seria interessante a realização de uma investigação multicêntrica de URP que incluísse padrões imunológicos.

Palavras-chave: remifentanilo, morfina, opiáceos, infecções nosocomiais, infecção associada aos cuidados da saúde, síndrome abstinência, imunossupressão, cuidados críticos, mortalidade.

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The importance of risk factors for the prediction of patients with invasive pulmonary aspergillosis

Selçuk Kaya[1]*, Eda Gençalioğlu[1], Mehmet Sönmez[2], Iftihar Köksal[1]

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
[2]Department of Hematology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Summary

Objective: Invasive pulmonary aspergillosis (IPA) is a major challenge in the management of immunocompromised patients. Despite all the advances in diagnosis, it remains a problem. The purpose of our study was to investigate the risk factors associated with IPA seen in patients with hematological malignancies.
Method: A total of 152 febrile neutropenia (FEN) patients with hematological malignancies aged over 18 years and receiving high-dose chemotherapy or stem cell transplant between January 1, 2010, and December 31, 2012 were included in the study. Sixty-five (65) cases with IPA according to the European Organization for the Research and Treatment of Cancer and Infectious Diseases Mycoses Study Group criteria were enrolled as the case group, while 87 patients without IPA development during concomitant monitoring were enrolled as the control group. Incidence of IPA was 21.4% (3/14) in patients receiving bone marrow transplant (allogeneic 2, autologous 1) and those cases were also added into the case group. The two groups were compared in terms of demographic, clinical and laboratory findings and risk factors associated with IPA investigated retrospectively.
Results: Presence of relapse of primary disease, neutropenia for more than 3 weeks, presence of bacterial infection, and non-administration of antifungal prophylaxis were identified as risk factors associated with IPA.
Conclusion: It may be possible to reduce the incidence of the disease by eliminating preventable risk factors. Predicting those risks would, per se, enable early diagnosis and treatment and, thus, the mortality rate of these patients would unquestionably decline.

Keywords: invasive pulmonary aspergillosis, hematologic neoplasms, risk factors, early diagnosis, treatment outcome.

Study conducted at the Department of Infectious Diseases and Department of Hematology, School of Medicine, Karadeniz Technical University, Trabzon, Turkey

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***Correspondence:**
Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Karadeniz Technical University, Farabi Hospital
Address: Kalkınma street
Trabzon – Turkey
Postal code: 61080
eselkaya@gmail.com

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Introduction

Invasive pulmonary aspergillosis (IPA) is the most common form of invasive aspergillosis and a cause of mortality. The prevalence of IPA has increased in association with the heavy chemotherapy regimens applied in patients with hematological malignancies in recent years. Development of IPA has a negative impact on prognosis as it delays treatment of the patient's primary disease while also causing significant economic losses due to treatment costs for the fungal infection.[1,2]

Various risk factors associated with disease development such as long-term deep neutropenia, long-term broad spectrum antibiotic and corticosteroid use, and allogeneic bone marrow transplant (BMT) have been described.[1,2] Identification of risk factors is important in terms of preventing the disease developing and allowing early treatment in cases of suspected infection. Thus, based on this idea, we planned to investigate the risk factors for development of IPA in patients with hematological malignancies in the light of the current literature.

Method

Following clinical research ethical committee approval, the study was performed retrospectively including febrile neutropenic patients with hematological malignancies hospitalized for treatment at the Karadeniz Technical

University Faculty of Medicine Internal Diseases Department Hematology Clinic.

All patients with febrile neutropenia (FEN) with possible, probable or proven IPA according to European Organization for the Research and Treatment of Cancer and Infectious Diseases Mycoses Study Group (EORTC/MSG)[3] criteria were enrolled as the case group, while 87 patients without IPA development during concomitant monitoring were enrolled as the control group. The purpose of our study was to investigate risk factors associated with IPA in febrile neutropenic patients with hematological malignancies by comparing the two groups in terms of demographic, clinical and laboratory findings.

Case selection

Inclusion criteria

Febrile neutropenic patients aged over 18, with hematological malignancy diagnosed at the Hematology Clinic and who had received high-dose chemotherapy or stem cell transplant were included in the study. MASCC (Multinational Association for Supportive Care in Cancer) scores were lower than 21 in all of the patients.

Exclusion criteria

Patients undergoing FEN attack during monitoring, who had not undergone high resolution computerized tomography (HRCT) aimed at diagnosis of IPA, and/or without galactomannan (GM) monitoring, and aged under 18 were excluded from the study.

Monitoring of febrile neutropenic patients

Our hospital's hematology clinic is located on the same floor as the ward for BMT patients. It contained 15 beds, three dormitory-type rooms (each capable of housing four patients), and three transplant rooms with HEPA filters. Only allogeneic BMT patients were followed in transplant rooms. The physical conditions were changed during construction and restoration works between June 2011 and March 2012. During the construction time, the hematology clinic remained in operation at the department opposite the area where the works were taking place, and the number of beds was increased to 16. However, patients scheduled for BMT were not admitted to the department. Once the construction and repair works were complete, the BMT unit and the hematology department began operating as two distinct units on the same floor. Ward patients transferred to the opposite ward during construction were placed in two-patient rooms. When the construction and repair works had ended, the ward patients continued to be monitored in the same unit. The number of beds in the BMT unit was increased to seven, and patients began being observed in single rooms with positive pressure. HEPA filters and generally improved physical conditions.

In the light of the EORTC/MSG recommendations, patients' serum GM is studied twice a week, while HRCT is performed on a regular basis. Patients with findings suggestive of IPA are evaluated in terms of bronchoalveolar lavage (BAL) and microbiological and histopathological investigation of specimens obtained from BAL is performed in suitable cases.

Data collection

Files from 200 patients diagnosed with hematological malignancies at the Internal Diseases department's hematology clinic and subsequently referred to the Infectious Diseases Department following development of FEN in the 3-year period between January 1, 2010 and December 31, 2012 were reviewed retrospectively. Forty-eight (48) patients meeting the exclusion criteria were excluded, and the study proceeded with the remaining 152 patients.

GM values, HRCT reports and microbiological and histopathological report records for patients undergoing BAL were obtained from patient files and the hospital automation system. Demographic and clinical characteristics of the cases were recorded on a "FEN patient with hematological malignancy data form" (Appendix 1).

Serological tests

GM antigen was studied over three years using the Sandwich-ELISA method (Platelia™ Aspergillus, Bio-Rad, France). If the index value was ≥ 0.5 in consecutive serum specimens or ≥ 0.7 in a single specimen, and when the GM index in BAL fluid was ≥ 1, the result was regarded as positive.[4,5]

Radiological tests

Presence of at least one nodule determined at HRCT, single or multiple nodules and a ground glass appearance due to hemorrhage around these nodules (halo sign), air crescent finding of cavitation suggestive of IPA was regarded as significant for IPA.[3,6]

Invasive tests

Patients with suspected IPA and regarded as clinically indicated for BAL collection from patient records and the hospital automation system were listed. Microbiological and histopathological assessments of specimens were recorded on the "Febrile neutropenic patient with hematological malignancy data form."

Patient definition

Host factors were defined as absolute neutrophil count (ANC) under 500/mm³ and duration of neutropenia exceeding 10 days.[3]

Positivity in serum and BAL values was adopted as a microbiological criterion, while clinical findings such as cough, hemoptysis and chest pain and/or presence of findings in favor of IPA at HRCT were evaluated as clinical criteria.[3]

Based on EORTC/MSG criteria, patients defined as probable or proven IPA were included in the study as the case group.

Statistical analysis

Risk factors for IPA were identified with single variable analysis, while the Chi-square test (χ^2) was used for qualitative data. For measurement data, Student's t-test was used for parametric variables and the Mann-Whitney U-test for nonparametric variables. Measurement variables were expressed as mean±standard deviation and descriptive data as number and percentage (%). Analysis results were expressed as p-value, predicted relative risk (odds ratio [OR]) and 95% confidence interval. Statistical significance was set at $p<0.05$. Finally logistic regression analysis applied for the variables with significant p-value. Statistical Package for the Social Sciences (SPSS) 13.01 software was used for all analyses.

Results

Fifty-five (55/36.2%) of the 152 patients in the study were female and 97 (63.8%) were male. Mean age of female patients was 46.3±13.5 and mean age of male patients 45.0±15.3. Patients' demographic characteristics, underlying diseases and the comparison of characteristics and risk factors of patients in the control and case groups are shown in Tables 1 and 2, respectively.

Fourteen (14/9.2%) of the 152 patients in the study received autologous BMT and 12 (7.8%) allogeneic BMT. IPA developed+ in only three (21.4%) patients receiving BMT, two allogeneic and one autologous. BMT did not increase the risk of IPA, the incidence of which was low in patients treated with BMT. Comparison of patients with or without BMT among themselves revealed that acute myeloid leukemia (AML) was the primary diagnosis in 23% of patients receiving BMT, that the level of accompanying bacterial infection in these patients was 15.3%, and that 15.5% used multiple antibiotics.

The number of patients receiving antifungal prophylaxis was 19 (29.2%) in the case group and 42 (48.2%) in the control. Fluconazole represented 23% of the agents used in antifungal prophylaxis and posaconazole represented 77%. The number of patients not receiving antifungal prophylaxis was 46 (70.8%) in the case group and 45 (51.7%) in the control group. This difference was sta-

TABLE 1 Demographic characteristics and underlying diseases in febrile neutropenic patients.

Patient characteristics	n=152	Percentage (%)
Female	55	36.2
Mean age±SD (min-max)	46.3±13.5 (18-78)	
Male	97	63.8
Mean age±SD (min-max)	45.0±15.3 (18-76)	
Underlying hematological malignancy		
Acute myeloid leukemia (AML)	81	53.3
Acute lymphoblastic leukemia (ALL)	26	17.1
Non-Hodgkin lymphoma (NHL)		
Multiple myeloma (MM)	26	17.1
Hodgkin lymphoma (HL)	9	5.9
Count of previous FEN attacks		
0	40	26.3
1	39	25.7
2	24	15.8
3 or more	49	32.2
Number of patients placed in hepa filtered rooms	12	7.8

FEN: febrile neutropenia.

TABLE 2 Comparison of characteristics and risk factors of patients in the case and control groups.

Risk factors	Case n=65 (%)	Control n=87 (%)	p
Age	44.8±16.4	60.2±17.1	0.633
Sex (male/female)	24/41	56/31	1.000
Underlying hematological malignancy			
AML	44 (67.7)	37 (42.5)	0.002
ALL	10 (15.4)	16 (18.4)	0.787
NHL	7 (10.8)	19 (21.8)	0.115
Other	4 (6.2)	15 (17.2)	0.072
Number of previous FEN attacks			
0	16 (24.6)	24 (27.5)	0.821
1	11 (16.9)	28 (32.1)	0.519
2	10 (15.3)	14 (16.1)	0.915
3 or more	38 (58.5)	35 (40.2)	0.026
Presence of relapse of primary disease	36 (55.4)	14 (16.1)	<0.001
Deep neutropenia			
MNS < 100/mm³	59 (90.8)	2 (2.3)	<0.001
Neutropenia of long duration > 3 weeks	60 (92.3)	43 (49.4)	<0.001
Presence of CMV infection	18 (27.7)	4 (4.6)	<0.001
Presence of bacterial infection	46 (70.8)	9 (10.3)	<0.001
Use of multiple antibiotics (> 3)	23 (35.4)	5 (5.8)	<0.001
Bone marrow transplant	3 (4.6)	23 (26.4	0.001
Steroid use	4 (6.2)	22 (25.3)	0.004
Non-administration of antifungal prophylaxis	46 (70.8)	45 (51.7)	0.027
Hospitalization during the construction works	18 (52.9)	16 (47.1)	0.244

FEN: febrile neutropenic; CMV: cytomegalovirus; MNS: ????; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma.

tistically significant (p=0.027) and not receiving antifungal prophylaxis increased the risk of IPA 3.53-fold.

During the construction works, IPA developed in 18 (52.9%) individuals in the case group and 16 (47.1%) in the control group (p=0.244). The construction works did not influence the incidence of IPA significantly.

Multivariate analysis was carried out for all of the factors identified as positive on univariate analysis. Presence of relapse of primary disease, neutropenia for more than three weeks, and presence of bacterial infections were identified as risk factors associated with IPA. On the other hand, the incidence of IPA was reduced by 80% with posaconazole prophylaxis (Table 3).

TABLE 3 Risk factors for invasive pulmonary aspergillosis (IPA) (logistic regression analysis).

Variables	p	Odds ratio	95% confidence interval
Presence of relapse of primary disease	0.036	3.22	1.07-9.67
Neutropenia of > 3 weeks	0.002	7.01	2.03-24.15
Presence of bacterial infection	0.000	11.50	3.77-35.03
Posaconazole prophylaxis	0.008	0.18	0.05-0.64

Discussion

Aspergillosis does not vary depending on age, sex or race.[1,2,7,8] In agreement with the literature, no statistically significant difference was observed between the two groups in terms of mean age or sex.

Several studies have shown that AML and myelodysplastic syndromes (MDS) are the hematological malignancies associated with the greatest risk of IPA.[8-10] AML was the most common primary disease in our study, followed by acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL) and other hematological malignancies. No statistically significant difference was determined in terms of risk of IPA among patients with ALL, NHL or other hematological malignancies. In terms of underlying diseases, our results are compatible with the literature.

While there are no previous studies elucidating the relation between number of previous neutropenic attacks and risk of developing IPA, some authors have reported

that the risk of IPA may rise as the number of FEN attacks increases.[11,12] No significant difference in terms of risk of IPA was determined in our study comparing patients with zero, one or two previous attacks. However, a statistically significant correlation was determined between a history of three or more previous attacks and IPA. These results were in agreement with those in the literature.

Presence of relapse of primary disease is associated with poor prognosis. More aggressive chemotherapies are applied in this patient group and length of hospitalization is greater. This patient group therefore represents a higher risk of development of IPA.[13-15] The number of patients with relapse in our case group was significantly higher than in the control group. Presence of relapse of primary disease increased the risk of IPA 3.22-fold. These results were again compatible with the literature.

Sufficient count and function of neutrophils in the circulation are known to be important to keep fungal infections under control.[1] Deep and prolonged neutropenia is one of the significant risk factors for development of IPA. Deep neutropenia is defined as lower than 100/mm³.[12,15,16] The number of deep neutropenic patients was significantly higher in our case group. This finding is compatible with the literature.

The risk of IPA increases in line with duration of neutropenia.[1] The frequency at which IPA develops increased by 1% every day in the first three weeks of neutropenia, rising to 4-5% after the 5th week.[17,18] In the literature, presence of neutropenia lasting more than three weeks has been shown to be the most significant risk factor in terms of development of IPA.[1,17,18] In our study, the number of patients with neutropenia exceeding three weeks was significantly higher in the case group compared to the control group. Neutropenia exceeding three weeks in length increased the risk of IPA 7.01-fold. These findings were compatible with the literature.

Several studies have reported that the risk of IPA increases in patients with cytomegalovius (CMV) infection.[16,19] The number of patients with CMV in our study was significantly higher in the case group than in the control group. On the other hand, CMV infections may also be due to long-term neutropenia in case group as mentioned in the literature.[20]

Some studies have reported that accompanying bacterial infection in patients with FEN and multiple antibiotic use can lead to the development of IPA by damaging microbial flora.[12,16,21] In our study, the number of patients with accompanying bacterial infection was higher in the case group than in the control group. Presence of bacterial infection increased the risk of IPA 11.50-fold. The number of patients using three or more antibiotics in our study was also significantly higher in the case group. These findings are compatible with the literature. In conclusion, the preparation of a treatment protocol with each center closely observing its own microorganism profile and the patients' antimicrobial treatment being adjusted in the light of that center's epidemiological data, as well as the prevalence and sensitivity profiles of the microorganisms isolated, represents the most rational approach.

Several recent studies have reported that the risk of IPA increases in the presence of chronic obstructive pulmonary disease (COPD). The most important factor predisposing patients with COPD to develop IPA is corticosteroid use. However, the doses and durations of corticosteroid use that constitute a risk are uncertain.[15,22] Although the number of patients with COPD in this study was higher in the case group than in the control group, the difference was not statistically significant. We attribute this finding to the low number of patients with COPD.

IPA is less common in subjects receiving autologous bone marrow transplant than in those receiving allogeneic bone marrow transplant. The prevalence of IPA in subjects receiving allogeneic bone marrow transplant varies depending on multiple factors such as donor-receiver compatibility.[19,23] IPA developed in only three of the 26 patients undergoing BMT in this study. Two of these received allogeneic transplant and one autologous. Although this appears to contradict the literature, when we compared our patients with or without BMT in terms of risk factors, the number of patients diagnosed with AML was low in the BMT group, and levels of accompanying bacterial infection and antibiotic use were also low. Moreover, the number of patients who received antifungal prophylaxis was much higher in the BMT group.

Several studies have reported that steroid use leads to the development of IPA. However, the dose and duration of corticosteroid use that would represent a risk are not clear. One meta-analysis investigated the findings of 71 controlled studies and determined that a daily prednisolone dose < 10 mg or cumulative dose < 700 mg did not increase the risk of infectious complication.[24] Another study reported that a steroid dose ≥ 1 mg/kg per day over ≥ 21 days increased the risk of IPA.[25] Dexamethasone at 40 mg/day for 4-6 days is used as a steroid in some chemotherapy regimens. Statistically significant difference was determined when the two groups were analyzed in terms of the effect of steroid use on risk of IPA.

The administration of prophylaxis in patients with hematological malignancies is controversial. Different practices can be seen from one hospital to another in the same country. Primary prophylaxis can be applied to patients at high risk (receiving AML, MDS or allogeneic BMT).[21] The use of posaconazole for IPA prophylaxis in high-risk AML and MDS patients is more effective than fluconazole or itraconazole, and appears as prophylaxis in the IDSA guideline.[26,27] Publications regarding posaconazole prophylaxis appear promising, and the number of centers applying posaconazole prophylaxis is increasing.[21,26-30] Antifungal prophylaxis can be given in selected BMT patients similar to solid organ recipients.[31,32] The application of antifungal prophylaxis in patients undergoing autologous BMT is still controversial, and antifungal prophylaxis is not recommended for this patient group in the IDSA guideline.[31] Further studies are needed to identify which patient group will in fact benefit from prophylaxis. Since most of our patients were autologous BMT, no antifungal prophylaxis was given to them, which is in accordance with current guidelines. Prophylaxis was administered to 40% of our patients, with posaconazole in 2/3 of these and fluconazole in the remaining 1/3. The number of patients not receiving antifungal prophylaxis was significantly higher in the case group compared to the control group, and not receiving antifungal prophylaxis increased the risk of IPA 3.53-fold. The incidence of IPA was reduced considerably through the posaconazole prophylaxis.

The presence of *Aspergillus* spores in hospital environment is an important risk factor for the development of IPA. There is actually a large number of nosocomial outbreaks reported in the literature during construction works.[14,33,34] There was ongoing construction works for a few months in the current study; however, this did not affect the incidence of IPA importantly.

Conclusion

It should be kept in mind that reduction of disease incidence may be possible with elimination of preventable risk factors. Due to difficulties in diagnosis, a significant proportion of patients with IPA are diagnosed late, and the disease is often fatal. It is therefore of great importance for patients with multiple risk factors for the development of IPA to be identified and closely monitored, and for diagnostic procedures in these patients to be performed without delay. Success can be improved by teams comprising hematology, infectious diseases and clinical microbiology, radiology and medical microbiology specialists collaborating within a multidisciplinary approach.

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Common mental disorders in medical students: A repeated cross-sectional study over six years

Edméa Fontes de Oliva Costa[1]*, Carlos Mauricio Cardeal Mendes[2], Tarcísio Matos de Andrade[3]

[1]MD, MSc, PhD, Adjunct Professor of Medicine at the Universidade Federal de Sergipe (UFS), PhD in the Program of Post-Graduate Medicine and Health at the Universidade Federal da Bahia (PPGMS/UFBA), and Fellow of Foundation for Advancement International of Medical Education and Research (FAIMER-Br), Aracaju, SE, Brazil
[2]MD, MSc, PhD, Biostatistic Professor at the PPGMS/UFBA, Salvador, BA, Brazil
[3]MD, MSc, PhD, Associate Professor of Medicine at the PPGMS/UFBA, Salvador, BA, Brazil

Summary

Introduction: Becoming a medical doctor is a very complex process. Factors related to the student's personality, the educational process and the daily experience with death contribute to peculiar psycho-emotional experiences, not always properly investigated during medical training.
Objective: To estimate the prevalence of common mental disorders (CMD) and associated factors, over six years of medical undergraduate course among all students of a class at a public university in Brazil.
Method: Cross-sectional study based on repeated surveys. All 40 students enrolled in 2006 in the first year of our medical school were included and evaluated annually until 2011 using the SRQ-20 and a structured questionnaire prepared by the authors on sociodemographic, personal and educational aspects. We performed logistic regression and correspondence analysis.
Results: The 40 freshmen in the first evaluation had a mean age of 20 years (SD=2.4), 57.5% were female, and 41% were approved after taking their third entrance exam. The prevalence of CMD increased over the years: from 12.5% in the first year to 43.2% in the fifth. The following variables were potentially associated with CMD: female sex (PR=1.38), originating from capital cities (PR=1.97), the program was less than they expected (PR=3.20), discomfort with program activities (PR=2.10), dissatisfaction with teaching strategies (PR=1.38), and feeling that the program is not a source of pleasure (PR=2.06), being R2=28.8% and AIC=60.04.
Conclusion: The factors potentially associated with the high prevalence of CMD were those related to medical training, showing that it is necessary to implement preventive measures and review the educational process in order to reduce the damages caused by the development of CMD.

Keywords: mental disorders, medical students, mental health, medical education, occupational health.

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***Correspondence:**
Address: Av. Pedro Calazans, 986
Aracaju, SE – Brazil
Postal code: 49055-520
edmeaolivacosta@gmail.com

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Introduction

Common mental disorders (CMD), also known as minor psychiatric disorders, are mild psychic troubles that may cause large biopsychic social impact over many years. CMD do not match the formal criteria for depression and/or anxiety diagnoses according to Diagnostic and Statistical Manual of Mental Disorders–Five Edition (DSM-V) and International Classification Disease–10th Revision (ICD-10), although they are an important public health problem given the limitations they cause, which range from impaired work performance to the potential development of more serious mental disorders. These limitations reflect the importance of identification and early intervention for CMD.[1] The prevalence of this disorder varies from 7 to 22% in the populations of industrialized countries and from 22 to 51.6% in Brazil.[2-6]

Becoming a medical doctor is a highly complex process. Factors related to the student's personality that motivate their professional choice, the educational process and daily experience with pain and death inherent to the craft contribute to peculiar psycho-emotional experiences that are not always adequately investigated

during medical training. Stress among medical students appears to be a serious problem, which increases the likelihood of a CMD.

An increased prevalence of mental disorders is noted early in medical students, as indicated by various works published in Brazil and in other countries. Unfortunately, only a limited number of longitudinal or follow-up studies are available.[7-11] Among Brazilian medical students, the prevalence of CMD varies from 31.7 to 44.7%.[9-15]

Permanent research on mental disorders among medical students and critical reflection by medical schools regarding their role in the promotion and prevention of these disorders will help train physicians to be healthier and emotionally better prepared to help diminish the health problems of the people they assist. Thus, our study aims to estimate the prevalence of CMD, associated factors, their changes and movements over the course of six years of the medical undergraduate course among students of a class at a public university in northeastern Brazil. This is a novelty because there are no previous studies including a population with these characteristics. It also aimed to propose preventive measures, if needed.

Method

Setting

Our study was conducted at a public university in northeastern Brazil. The program was offered to 40 students per semester in 2006. The students were selected through a difficult entry exam.

The program is based on a traditional teaching method of 12 semesters divided into three cycles: Basic Sciences (1st to 4th semesters), Introductory Clinical Cycle (5th to 9th semesters), and Internship (10th to 12th semesters).

Researched population

All 40 medical students enrolled in the first semester of 2006 (2006/1 class) were surveyed in this study.

Pilot study

We conducted a previous pilot study with the students enrolled in 2005 aiming to control the quality, train research assistants in data collection and refine the instruments to be applied after this study, particularly regarding language and the students' receptivity.

Study design and data collection

This is not a cohort study, since we chose not to identify the participants, consequently obtaining more true answers and improving respondent adherence.

The authors conducted a repeated inquiry cross-sectional study with all 40 medical students of the class of 2006/1. The students were annually researched through two instruments applied in the classroom from 2006 to 2011. The researchers asked the professors for permission to apply the questionnaires during class.

Therefore, we were not able to separate those already diagnosed with CMD in order to exclusively follow the healthy individuals.

We decided to collect data annually instead of semiannually to avoid information accuracy bias because the instruments we used tended to not detect the disorder when the respondent was annoyed by the repetition.

Research instruments

We used two self-administered questionnaires. One was created by the authors and tested in the pilot study conducted in 2005. The questionnaire contained 54 pre-coded closed questions on socialdemographic characteristics, the educational process and personal aspects related to career choice, and the psycho-emotional experiences of each respondent. The other assessment was the Self-Reporting Questionnaire (SRQ-20) by the World Health Organization (WHO) for the "screening" of CMD in populations during primary attention. This questionnaire contains a rating scale for the following symptoms: anxiety, depressive and somatoform.[16] It is a self-administered instrument validated for application in Brazil, with satisfactory levels of sensitivity (89%), specificity (81%), positive predictive value (81%), negative predictive value (82%) and misclassification (19%).[2]

The SRQ-20 comprises 20 questions with binary responses. For our study, we considered the last 30 days. Students with a score ≥ 6 points for men and ≥ 8 points for women were considered probable cases. The cut-off point in our research was determined based on the original work by Mari and Williams,[2] other studies on medical students in Brazil, and the pilot study cited above.[2,13,15]

The association of the dependent variable (CMD) with the explanatory variables was investigated by calculating the adjusted prevalence ratio (PR) for the fifth year, which is the period with the highest prevalence of CMD.

The students' privacy was assured during data collection by placing the students far from one another in the classroom after being informed about the study and introduced to a staff member to clarify doubts regarding the questionnaires.

Data analysis

First, we described the population using descriptive statistics, followed by a simple analysis and construction of

tables. Then, we performed the multiple analysis of correspondence with canonical normalization for the evaluation of the geometric relationships in the Chi-square distances of the studied variable contingencies in a multifactorial and multidimensional context. Next, we conducted a Poisson regression with a link "log" for the fifth year of the program applying the R program.[17,18] Since the entire population was the target of this study, we did not perform inferential statistics. Thus, given the non-probabilistic sampling plan, an estimate of robust variance based on the Sandwich estimative was not necessary.

We chose as inclusion criterion for the Poisson regression model to select only those variables that were most visually evident in the matching map – nearer to the outcome variable (CMD.yes): expectations regarding the program (ep), thoughts of dropping out of the university (dos), physical activities (pha), feelings about program activities (fa), steady partner (sp), emotional support (es), academic performance (ap), satisfaction with teaching strategies (ste), other occupation (occ), shares the burden of difficulties with someone (dd), place of origin (pr), sex (sx), religion (rel), medical program as a source of pleasure (mpsp). The criterion used to infer an association between CMD and these predictor variables was to consider only the variables that remained in the final regression model with adjusted OR>1.35.

Ethical considerations

This study was approved by our institutional ethics committee for human research (CAAE: 0018.0.107.000-06). The study participants signed a confidentiality agreement authorizing the disclosure of data but concealing their identity throughout the study period, including that involving the completion of questionnaires.

Results

Of the 40 students enrolled in the study (2006/1 class), one dropped out of the school, and another student failed the first year. In the subsequent years, some student losses were noted due to participation refusal. Of the participants, 17.9% entered in the first entry exam, 28.9% in the second exam, and 41% in the third exam, and 12.9% in the fourth or more exams.

The average age the students who joined the program was 20 years (standard deviation = 2.4). In addition, 57.5% of the students were female, and 67.5% were from the state capital (Table 1).

Although 51.3% of the students reported having a physician in the family, only 2.7% said that their career choice was influenced by family members. Regarding their motivation for choosing the medical school, 54.1% reported a desire to help others.

The prevalence of CMD throughout the program was: 12.5% in the first program year (n=40; data collected on the first day of school), 15.2% in the second year (n=33), 33.3% in the third year (n=36), 27% in the fourth year (n=37), 43.2% in the fifth year (n=37) and 24.32% in the sixth year (n=37). Mental disorder diagnosis by a psy-

TABLE 1 Distribution of students from the 1st and 6th year medicine program based on sociodemographic variables. Aracaju, SE, Brazil, 2011.

Variables	1st-Year N	6th-Year N
Total	40 (100%)	37 (100%)
Students mean age	20.0	24.3
Standard deviation	2.4	2.0
Sex		
Female	23(57.5%)	20 (54.1%)
Male	17 (42.5%)	17 (45.9%)
Religion		
Yes	29 (72.5%)	17 (45.9%)
No	11 (27.5%)	20 (54.1%)
Place of origin		
State capital	27 (67.5%)	30 (81.1%)
Hinterland	5 (12.5%)	5 (13.5%)
Other states	8 (20.0%)	2 (5.4%)
Living arrangements		
Relatives	35 (87.5%)	33 (89.2%)
Friends/colleagues	1 (2.5%)	2 (5.4%)
Alone	4 (10.0%)	2 (5.4%)
Family income (Minimum wage)		
1 to 5	6 (15.0%)	3 (8.1%)
6 to 10	9 (22.5%)	9 (24.3%)
11 to 15	7 (17.5%)	8 (21.6%)
16 to 20	7 (17.5%)	4 (10.8%)
Over 20	4 (10.0%)	6 (16.2%)
Do not know	7 (17.5%)	7 (18.9%)
Has another occupation?		
Yes	5 (12.5%)	5 (23.1%)
No	35 (87.5%)	*32* (76.9%)
Steady partner		
Yes	13 (32.5%)	28 (75.7%)
No	27 (67.5%)	9 (24.3%)
Presence of a physician in the family		
Yes	20 (51.3%)	18 (48.6%)
No	19 (48.7%)*	19 (51.4%)

*1 missing.

chiatrist reported by the students presented its highest frequency in the 5th year of the program (10.8%), followed by the 3rd and 6th years (8.3%).

Dissatisfaction with the profession choice was less frequently reported and only mentioned by one student in the 3rd and 4th program year and by two students in the 5th and 6th program year. From the 3rd program year on, over one third of the students reported considering the program was less than they expected; this number achieved its highest frequency in the 5th program year at 47.2% (Table 2).

The correspondence analysis maps display the variables potentially associated with CMD in each year of the program. Thus, in the first two years that correspond to the Basic Sciences cycle, the following associated variables were noted: a) in the 1st year, being female, having no steady partner, not practicing physical activities and not having emotional support (eigenvalue equal to 0.0128 and 0.005, with corresponding inertia of 37.9% and 15%, respectively, for the first and second dimensions); b) in the 2nd year, not having a steady partner, having low performance, feeling uncomfortable with the program activities, and not being satisfied with the teaching strategies (eigenvalues equal to 0.0116 and 0.006, with corresponding inertia of 32.2 and 17.8%, respectively, for the first and second dimensions).

From the Introductory Clinical Cycle onward, we identified the following variables: a) in the 3rd year, low performance, lack of emotional support, feeling uncomfortable about college activities, lack of physical activities, lack of a steady partner, thoughts of dropping out of the school, not feeling that the program is a source of pleasure

TABLE 2 Distribution of medical students from the 2nd program year according to variables related to professional choice and the educational process. Aracaju, SE – Brazil, 2011*.

Variables	2nd year	3rd year	4th year	5th year	6th year
	N	N	N	N	N
Total	33 (82.5%)	36 (90.0%)	37 (92.5%)	37 (92.5%)	37 (92.5%)
Satisfaction with career choice					
Yes	33 (100%)	34 (97.1%)	36 (97.3%)	35 (94.6%)	35 (94.6%)
No	–	01 (2.9%)	01 (2.7%)	02 (5.4%)	02 (5.4%)
Missing		01			
Expectations regarding the program					
As expected or more than expected	27 (81.8%)	19 (59.4%)	22 (61.1%)	19 (52.8%)	19 (55.9%)
Less than expected	06 (18.2%)	13 (40.6%)	14 (38.9%)	17 (47.2%)	17 (44.1%)
Missing			01	01	03
Thoughts of dropping out of the school?					
Yes	03 (9.1%)	13 (36.1%)	11 (29.7%)	12 (32.4%)	14 (37.8%)
No	30 (90.9%)	23 (63.9%)	26 (70.3%)	25 (67.6%)	23 (62.2%)
Academic performance					
Bad/not so good	11 (33.3%)	11 (30.6%)	09 (24.3%)	09 (24.3%)	09 (24.3%)
Good	22 (66.7%)	25 (69.4%)	28 (75.7%)	28 (75.7%)	28 (75.7%)
Acquisition of skills to become a good physician					
Yes	24 (72.7%)	25 (75.8%)	29 (82.9%)	25 (69.4%)	28 (77.8%)
No	09 (57.3%)	08 (24.2%)	06 (17.1%)	11 (30.6%)	08 (22.2%)
Missing		03	02	01	01
Satisfaction with teaching strategies					
Yes	11 (33.3%)	12 (33.3%)	11 (29.7%)	05 (13.5%)	11 (29.7%)
No	22 (66.7%)	24 (66.7%)	26 (70.3%)	32 (86.5%)	26 (70.3%)
Feelings about program activities					
Comfortable	28 (84.8%)	24 (68.6%)	21 (58.3%)	14 (38.9%)	18 (50.0%)
Uncomfortable	05 (15.2%)	11 (31.4%)	15 (41.7%)	22 (61.1%)	18 (50.0%)
Missing		01	01	01	01

*The students of the first program year were excluded from the analysis of educational process variables, given that responses to the questionnaire were obtained on the first day of class.

and dissatisfaction with the teaching strategies (eigenvalues equal to 0.0193 and 0.008, with corresponding inertia of 39.5 and 18.1%, respectively, for the first and second dimensions); b) In the 4th year, the following variables were identified: considering the program less than they expected, not feeling that the program is a source of pleasure, feeling uncomfortable with the program activities, not being satisfied with the teaching strategies and having no doctor in the family (eigenvalues equal to 0.0140 and 0.005, with inertia corresponding to 39.0 and 15.6%, respectively, for the first and second dimensions); c) The following were noted in the 5th year (assessed in the 9th semester), which involves the transition to the internship – being female, being from the capital, the program being less than they expected, feeling uncomfortable with the program activities, dissatisfaction with teaching strategies and the program being a source of pleasure (eigenvalues equal to 0.0355 and 0.007, with corresponding inertia of 58.0 and 12.9%, respectively, for the first and second dimensions) (Figure 1).

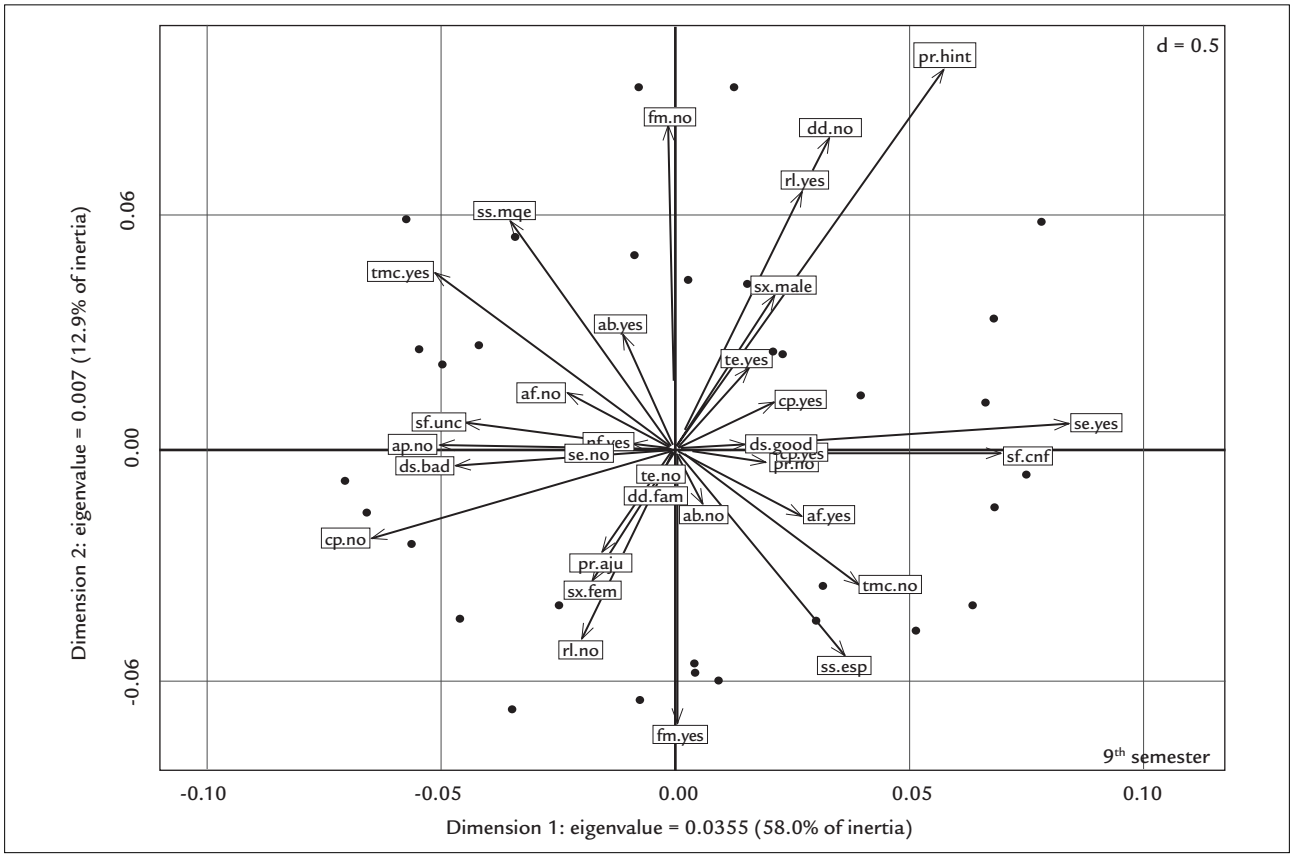

FIGURE 1 Correspondence analysis map: common mental disorders among medical students and associated factor in 5th program year (9th semester). Aracaju, SE – Brazil, 2011.

Outcome variable:
CMD (common mental disorders): yes/no
Variables related to sociodemographic aspects:
df (doctor in the family): yes/no
pr (place of origin): aju (Aracaju city)/hint (hinterland/others)
rel (religion): yes/no
sp (steady partner): yes/no
sx (sex): fem (female)/male (male)
Variables related to personal aspects:
dd (hares the burden of difficulties with someone): yes/no
es (emotional support):yes/no
fh (feels happy): yes/no
pha (physical activities): yes/no
Variables related to educational process:
ap (academic performance): bad/good
dos (thoughts of dropping out of the university): yes/no
ep (expectations regarding the program): le mqe (program less than they expected)/me (program more than or equal to the expected)
fa (feelings about program activities): uncom dcnf (uncomfortable)/ com cnf (comfortable)
mpsp (medical program as a source of pleasure): yes/no
occ (other occupation): yes/no
ste (satisfaction with teaching strategies): yes/no

During the internship (6th program year), the following variables were associated with CMD: low performance, feeling uncomfortable with the program activities, not being satisfied with the teaching strategies, and feeling that the program is not a source of pleasure (eigenvalues equal to 0.0213 and 0.005, with corresponding inertia of 48.9 and 13.6%, respectively, for the first and second dimensions) (Figure 1).

A Poisson regression (PR) analysis was performed in the 5th program year, specifically in the 9th semester (the data collection period that corresponds to the six months preceding the internship wherein an increased prevalence of CMD was noted). We intended to verify the associated size of the variables identified in the correspondence analysis map at that time. Thus, we described the adjusted PRs for each variable potentially associated with CMD: female sex (PR=1.38), originating from capital cities (PR=1.97), the program was less than they expected (PR=3.20), discomfort with program activities (PR=2.10), dissatisfaction with teaching strategies (PR=1.38) and feeling that the program is not a source of pleasure (PR=2.06) being R2=28.8% and AIC=60.04.

Discussion

The increased prevalence of CMD identified in our study is consistent with the results of other studies.[13,15,19]

CMD prevalence among the students at the beginning of their program was low and similar to that observed in the general population. This finding was expected because the students answered the questionnaire on the first day of school. However, in the second year, the prevalence of CMD increased. Another longitudinal study also identified this increase and considered the program itself a chronic stressor for the students because the depression rate increased disproportionately throughout the medical program in a non-episodic manner.[20]

Only a minority of the respondents succeeded in their first attempt to enter the medical school through a difficult entry exam. The remaining students repeated the entry exam for three or four years after intense studying to accomplish the long-awaited dream of getting into medical school. Thus, the lack of emotional support reported by freshmen and the social isolation demanded by this rhythm of study, in addition to the expectation of approval, may be responsible for greater physical illness in the first year.

As reported by other researchers, the vast majority of medical students at the beginning of the program "have expectations regarding medical practice and not academic work itself." Therefore, the students want to have contact with patients and to help the suffering people. However, these events do not occur in the first year of the program, when the subjects taught are primarily related to basic sciences, leading to a conflict of interest or even lack of motivation.[21]

In our study, an increase in CMD prevalence, mental disorder diagnoses made by a psychiatrist, emotional stress, dissatisfaction with the program choice, worsening of expectations for the future and thoughts of dropping out of the school, which were noted from the third program year onward, suggest that the process of medical education contributes to these results. Other researchers have demonstrated that the psychological intensity inherent to medical activities may be an important factor for emotional disorders in medical students, medical residents and doctors, who are predisposed or more vulnerable.[22,23]

In some studies assessing medical schools with a traditional curriculum such as ours, the final year appears as a potential stressor. However, other studies indicate that important moments in other phases or transitions in the program are also stressors: the first year, when students first handle a corpse, and the third year, when the Introductory Clinical Cycle begins and patient contact first occurs. In our study, an increased prevalence of CMD is noted in our institution during the fifth program year (semester 9); this period corresponds to the transition to the internship, which begins in the tenth semester.[13,24] We consider that the CMD prevalence falls in the 6th program year, maybe due to overcoming the internship transition stress as well as to the greater integration of knowledge acquired over the years.

Another study that has assessed throughout the last 21 years the assistance and psycho-educational support service for medical students at São Paulo University (USP) demonstrated that the following has been a good preventive measure to avoid more serious cases: the suicide rate among them diminished 8 times, reaching the same level of the local population.[25] We cannot compare these results with ours since this kind of service does not exist in our institution.

Based on the correspondence analysis maps and the logistic regression results, we identified that variables potentially associated with CMD occurred mainly in the third year of the medical program onward and were related to the educational process. Additionally, being female and/or the lack of a steady partner and/or not being engaged in physical activities were also identified as critical variables in various program years.

"Originating from the capital" appeared as one of the variables potentially associated with CMD in the fifth year; this finding has been confirmed in several studies

that characterize urban areas as more stressful due to violence, less solidarity and traffic problems that create difficulties in the fulfillment of schedules etc.[26-29]

Medical students learn from their professors the importance of physical activities and leisure in the prevention of diseases, particularly those related to mental health. However, excessive program loads and the resulting lack of time is the most common excuse for not taking the advice themselves. Instead, students adopt self-medication with psychoactive substances and ilicit drugs, which demand greater effort and time. These activities are more frequently reported among medical students, according to other studies.[30,31]

Our study is not characterized as a cohort study because we chose to use anonymous questionnaires, ensuring that the participants concealed their identities although we followed the group of students for six years with few losses and no new participants. Thus, we were not able to initially identify and exclude those with CMD with the aim of following only the healthy individuals; however, adherence and truthfulness were ensured by this design. It is likely that, if the students were identified, they would not offer authentic responses or may have refused to participate in the study.[32]

Our research has limitations primarily attributable to its design (repeated enquiry cross-sectional survey), since we cannot establish causality to the identified associations once they simultaneously analyze outcome and exposure. However, we proposed hypotheses and identified potential factors associated with the generation of the disorder that can contribute to the establishment of necessary preventive measures in this population and other similar academic communities.

Conclusion

CMD prevalence increased among respondents in the third year of medical school and increased non-linearly throughout the years. Students in the third and fifth program years were the most affected, and these periods correspond to moments of transition in the program, namely, the Introductory Clinical Cycle and Internship, respectively.

Factors potentially associated with CMD were primarily related to the educational process, which demonstrates that the medical school must reflect critically on their role in the promotion and prevention of these disorders in students.

Further studies in this and other institutions of similar profiles will contribute to the comparison and validation of our results.

Finally, the results show that preventive measures should be implemented, such as establishing psychoeducational support services for students and professors and revising the educational process to minimize the losses provoked by the development of CMD.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Transtorno mental comum em estudantes de medicina: Estudo transversal por inquéritos repetidos durante seis anos

Introdução: Tornar-se médico é um processo bastante complexo. Fatores relacionados a personalidade do aluno, processo educacional e experiência diária com dor e morte contribuem para vivências psicoemocionais peculiares, nem sempre devidamente investigadas durante a formação médica.
Objetivo: Estimar a prevalência de transtornos mentais comuns (TMC) e fatores associados durante os seis anos de graduação entre todos os estudantes de uma turma de medicina de uma universidade pública brasileira.
Método: Estudo transversal por inquéritos repetidos. Todos os 40 alunos admitidos em 2006 na escola médica pesquisada foram incluídos no estudo e avaliados anualmente até 2011 através do SRQ-20 e de um questionário estruturado elaborado pelos autores sobre aspectos sócio-demográficos, pessoais e educacionais. Realizadas regressão logística e análise de correspondência.
Resultados: Os 40 calouros na primeira avaliação tinham média de idade de 20 anos (DP=2,4), sendo 57,5% do sexo feminino e 41% aprovados no terceiro vestibular. A prevalência TMC aumentou ao longo do curso: de 12,5% no primeiro ano para 43,2% no quinto. As seguintes variáveis foram potencialmente associadas à TMC no quinto ano: sexo feminino (RP=1,38), originários de capitais (RP=1,97), achar o curso menos do que esperava (RP=3,20), ter desconforto com as atividades do curso (RP=2,10), estar insatisfeito com estratégias de ensino (RP=1,38) e sentir que o curso não é fonte de prazer (RP=2,06) sendo R2=28,8% e AIC=60,04.
Conclusão: Fatores potencialmente associados com alta prevalência de TMC foram relacionados à formação médica, mostrando que é necessário implementar medidas preventivas e revisão do processo educacional no intuito de reduzir os danos causados pelo desenvolvimento de TMC.

Palavras-chave: transtornos mentais, estudantes de medicina, saúde mental, educação médica, saúde ocupacional.

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The impact of anemia and body mass index (BMI) on neuromotor development of preschool children

Selen Ozakar Akca[1]*, Mehmet Ömer Bostanci[2]

[1]Health School, Hitit University, Çorum, Turkey
[2]Department of Physiology, Medical Faculty, Hitit University, Çorum, Turkey

Study conducted at Hitit University, Çorum, Turkey

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***Correspondence:**
Hitit University, Health School
Address: Çevre Yolu Bulvarı
Çorum – Turkey
Postal code: 19000
selenozakar@hitit.edu.tr

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Summary

Objective: According to data from the World Health Organization (WHO), anemia is a prevalent health problem that leads to increased morbidity and mortality, especially in preschool children. Anemia is recognized as a major health problem due to its negative effects on the mental and physical development during childhood. The aim of our study was to determine the levels of anemia of children in a kindergarten affiliated to the Directorate of National Education using a non-invasive method, and to investigate the effects of anemia on the physical, mental and neuromotor development of children.
Method: The levels of anemia was evaluated by using a non-invasive measurement device. Data collection was performed by means of a questionnaire to evaluate the children's physical development and set Denver Developmental Screening Test II scores.
Results: Our findings show that 21% of non-anemic and 15% of anemic children are in the suspected abnormal group according to their DDST II total score. Furthermore, it has been identified that mild anemia has a positive effect on neuromotor development, while overweight and obesity affect neuromotor development in a negative way.
Conclusion: According to the results obtained from the study, mild anemia may have a positive effect on the children's neuromotor development, while malnutrition could have a negative impact.

Keywords: anemia, Denver Developmental Screening Test II (DDST II), neuromotor development, obesity, child, preschool.

Introduction

Anemia is defined as a decrease in the amount of red blood cells or hemoglobin in the blood and results in a decline of oxygen-carrying capacity and the amount of oxygen that reaches the body's tissues. Normal hemoglobin, hematocrit and average erythrocyte volume values are different according to age and gender. Therefore, a separate assessment of each patient is made to diagnose anemia. Levels two standard deviations below the normal value are considered to be anemia.[1,2] Since anemia is a symptom of many diseases rather than a primary illness itself, it may often worsen the dysfunction of other organs.[3]

The World Health Organization (WHO) sees anemia as a common health problem that especially leads to increased mortality and morbidity in preschool children. Worldwide prevalence of anemia is between 22.9 and 26.7%.[4,5] The WHO has issued a social health problem rating according to anemia prevalence and as a result of this, it was reported that countries with a prevalence of anemia at 5% or less do not have a health problem, while prevalence at the 5-19% range is considered a mild problem, between 20-39% is considered a moderate one, and above 40% is seen as a major health issue.[6] The anemia rate above 40% seen in Turkey is regarded by WHO as a serious public health problem.[4]

Considering that 47.4% of preschool children and 25.4% school children have anemia in the world, it has been recognized a major health problem due to its negative impacts on mental and physical development during childhood.[3] Given that childhood is the fastest growth and

development period, anemia-related problems (growth retardation, motor and mental performance decline, behavior disorders etc.) are of great concern.[7]

Similarly to anemia, obesity is also regarded as an important public health problem.[8] Childhood obesity occurs especially in developed countries but increased prevalence is observed all over the world.[9] This increased prevalence of obesity is so serious that it could be described as an epidemic. Although prevalence varies from country to country, it has rapidly grown over the last 20 years. Comparing the results between the years 1988-1994 and 2003-2004 according to the National Health and Nutrition Examination Survey (NHANES) in the United States (US), the prevalence of overweight in the age range between 2 and 5 years has increased from 7.2 to 13.9%. At the same time, the frequency between 6 and 11 years old rose from 11 to 19%.[10] It is reported that the obesity prevalence in Turkey has increased in the last 20 years from 6-7% to 15-16%.[11]

Obesity causes many physical, emotional and psychosocial problems, leading to educational and social issues (e.g., economic burden) as well. Awareness is thus extremely important in winning the battle against obesity. Obesity not only leads to chronic diseases later in life, but also during childhood. These include many diseases that affect the neurological system.[12,13] In addition, obesity has a negative impact on children's education. Studies performed on this topic determined that overweight/obese children have lower reading skills and mathematic scores, poorer classroom performance, less success as students, less connection to schoolmates, greater desire to quit school, and they cannot proceed to further education in life with the same level of success as normal weight children.[12,14]

Considering the clinical and social impacts of anemia and obesity, taking necessary measures are not only important for the purpose of individual treatment but also in terms of public health. Having in mind that health checks are not a habit in our society, every child must be evaluated individually according to their growth/development.

After having reviewed the available literature, we did not find any studies showing the impact of anemia and obesity on 5-6 year-old children regarding physical, mental and neuromotor development. Our study aimed to determine the presence of anemia and obesity in children at a kindergarten facility affiliated with the Directorate of National Education of Corum using a non-invasive method, and to investigate the impact of anemia and obesity on the children's physical, mental and neuromotor development.

Method

Preparation

The study included all 5-6 year-old children enrolled in the kindergarten affiliated with the Directorate of National Education of Çorum. The research was done by means of a descriptive method and avoiding sample selection. All children (916) aged between 5 to 6 years who were present at the kindergarten during the study's dates (January – June 2015) and whose parents/guardians did not refuse the application of the Denver Developmental Screening Test II (DDST II) constituted the study sample. The DDST II was applied to all participating 5-6 year-old children. Additionally, hemoglobin values were measured using a non-invasive method, and body mass index (BMI) was determined.

Before initiating the study, approval was obtained from the Provincial Directorate of National Education (23.12.2014/6817100) and the Ankara Numune Education and Research Hospital ethics committee (19.02.2015/E-15-424). After receiving information pertaining the study's purpose and method, the parents/guardians of the children expected to participate signed a proper consent form. Furthermore, they were made aware that if anemia and/or obesity were detected, they would be informed and referred for treatment. DDST II was evaluated and performed by the screener.

Instruments

Research data was collected by interview using a questionnaire, the children's anemia and obesity status assessment form, and the DDST II screening test. The sociodemographic characteristics of the children were also investigated using the questionnaire.

The children's levels of anemia (hemoglobin value) assessment was performed using a non-invasive hemoglobin measurement device (Masimo, rainbow DCI-mini SC1000). This device was chosen due to its portability and capacity of proving fast results to determine anemia or blood loss in a non-invasive manner.[15,16] The purpose of hemoglobin measurement in children is to obtain a concrete feedback about their levels of anemia. In our study, the WHO hemoglobin cut-off values of anemia were taken as reference and, therefore, the lower limit for hemoglobin levels in children between the ages of 5 to 11 years was accepted as 11.5 g/dL. Children with hemoglobin levels lower than that were considered anemic.[3] Anemia is classified as mild, moderate or severe based on the concentrations of hemoglobin in the blood. In our study, hemoglobin concentration at 10.0 g/dL was accepted as the lower limit for mild anemia.[17]

To evaluate the children's BMI, we used the international standard indicators defined by the National Center for

Health Statistics (NCHS) and approved by the Center for Disease Control and Prevention (CDC) and the WHO. Percentage curves established for Turkish children yielded the BMI of the children evaluated.[18-20]

Height was measured using a standard stadiometer, with the children standing barefoot. During height measurement, researchers made sure that the most protruding point of the head, shoulders, hips and heels were in contact with the vertical plane and feet were adjacent to each other. Weight was obtained using a digital scale sensitive to 20 g variations, and the children were asked to remove their jackets before their weight was read. The remaining clothing was accepted as weighing approximately 1 kg, which was subtracted from the weight read from the digital scale. In order to compare the children's height and weight measurements in a healthy way, the same weight and height measurement device was used and the measurement was performed by the same person with the appropriate technique.

Body mass index was calculated by using the formula: Weight [kg]/height^2 [m^2]. The CDC defines the BMI percentage range 85-95% as overweight and over 95% as obese during childhood and adolescence.[19-21] In our study, the percentage curve defined for Turkish children was used, and the ones with BMI < 5 were accepted as underweight, 5-84 as normal, 85-95 as overweight and BMI > 95 as obese.

The evaluation of the neuromotor status of children was done based on the DDST II score. This test was developed by Frankenburg, Dodds, Fandal, Kazuk and Cohrs (1967) in order to help medical personnel detect developmental problems in children. The test was reviewed in 1990 and the Denver II was then created. The first standardization of the Denver Developmental Screening Test in Turkey was done in 1987 by Yalaz and Epir. The test-retest reliability of the Turkish version is 89%, while inter-rater liability is 95%.[22,23]

Denver II consists of 121 items and assesses four development areas, including the children's personal, social, fine and gross motor and language skills. There are five "Test Behavior" items at the end, which help the test screener assess how children use their behavior and skills. Each item is scored according to a combination of answers by the caregivers, the child's evaluation and observation. Children are assessed as a result of the performed test and in accordance with their total score by dividing them into four defining classes as normal, abnormal, suspect and untestable. While forming these groups, caution and delay of children's motor performance were taken into consideration. The caution concept in DDST II can be explained as follows: children who are to the left of the age line or on more than one item intersected by the age line in the area of 75-90% or refusing to perform those items get a caution point. The reason is that in the standardization sample more than 75% of the children were able to perform this task earlier than the surveyed child. A delay is indicated when a child fails or refuses an item that falls completely to the left of the age line or when a child refuses to fulfill that task. This indicates that the child has failed an item that 90% of children in the standardization sample passed at an earlier age. In light of this information, children who were included in the normal group in terms of his/her development have no delays and a maximum of one caution. On the other hand, children with one delay and/or two or more cautions have been included in the suspect group. Children with two or more delays were allocated into the abnormal development group. The age line of children is drawn in the test form from top to bottom. Age scales located on the top and bottom of the test scale show the ages from 15-day to 6 years. Every test item is shown with a horizontal rectangle on the test scale. If the child shows normal development in terms of behavior, he/she will pass. If abnormal development is detected, the child will fail, and if the child refuses to attempt the requested task, this will be evaluated as a refusal.[23]

The identification of children to be included in the study was done according to the following conditions: major congenital malformation absence, being a singleton, not having been born premature, dysmature and malnourished, lack of chronic illness, lack of metabolic disorders, not having been exposed to surgical intervention for any reason, and having considered to get the consent of families whose children have participated in the study. Furthermore, children who have refused to perform the test have not been included in the study. This study is limited to data obtained from 916 children who were at the kindergarten in Çorum, were available, and included in the study.

Statistical analysis

In the data evaluation, the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA; license, Hitit University) software was used. Hemoglobin and BMI values were presented to the neuromotor development groups as average±standard deviation (SD). The relation between neuromotor development groups and BMI, as well as hemoglobin levels, was investigated using Chi-square analysis. $p<0.05$ was accepted as a statistically significant level.

Results

Our study included 916 children, comprising 428 girls and 488 boys. DDST II has been analyzed in two sections by dividing it into a normal group and an abnormal-suspect group. Of the examined children, 19% were allocated into the suspect-abnormal group based on their DDST II scores for personal-social (4.6%), fine motor (5.9%), language (6.6%) and gross motor (9.1%) categories (Table 1).

While the hemoglobin average of 5-6 years old children who participated in the study was 11.94±0.84, 29.8% of children were found to be anemic (Table 1, Figure 1). Our study did not show any child with severe or moderate anemia. In Table 1, DDST II distribution results are given according to the hemoglobin value. When comparing the personal-social, fine motor, language and gross motor test results of DDST II separately with hemoglobin values, no statistically significant difference was seen ($p>0.05$). 21% of the children without anemia were allocated into the suspect-abnormal group, whereas 15% of the anemic children were also in the same group. Furthermore, it has been proven that total score of DDST II compared with hemoglobin values of the children shows a statistically significant difference according to the neuromotor development of children with and without anemia ($p<0.05$; Figure 1).

The average BMI of the surveyed children was 16.33±2.27, and it has been determined that 39.6% were normal, 8.2% were overweight, and 24.7% were obese. The distribution of DDST II results according to BMI is given in Table 2. Fourty-six (46) out of 252 underweight children, 63 out of 363 children with normal weight, 16 out of 75 overweight children and 49 out of 226 obese children were ranked in the suspect-abnormal group. Furthermore, it was seen that the total score of DDST II is statistically significant according to their BMI ($p<0.05$; Figure 2).

We have found a rate of underweight children of 27.5% in our study. Our study shows that 26.4% of suspect-abnormal children were underweight (Figure 2). However, being underweight did not prove to lead to significant changes in neuromotor development of children ($p>0.05$).

Discussion

The data which we have obtained from our study shows that obesity is affecting neuromotor development in a negative way according to the total score of DDST II, while mild anemia has a positive effect on neuromotor development.

Growth retardation is shown as one of the most common problems in children within the first 6 years of life, and there is a growth retardation rate of 12-16% during childhood.[24] As developmental disorders may pass unnoticed during regular inspections, especially in early childhood, it is necessary to perform a standard assessment in order to diagnose growth retardation. For this reason, developmental screening tests have to be used for the age group 0-6.[25-27] In light of these findings, the standardized DDST II, which provides information about a child's personal-social, fine motor, language and gross motor features, was used. In total, 19% of the 5-6 year-olds in our study were allocated into the suspect-abnormal group

TABLE 1 Distribution according to the hemoglobin values of DDST II results (N=916).

		n	%	X±SS	Median	Minimum	Maximum
Personal-social	Normal	874	95.4	11.93±0.83	12.00	8.60	15.70
	Suspect	20	2.2	12.11±0.92	12.30	10.00	13.50
	Abnormal	22	2.4	12.01±0.97	12.00	10.00	13.90
Fine motor-adaptive	Normal	862	94.1	11.94±0.84	12.00	8.60	15.70
	Suspect	47	5.1	12.01±0.69	12.00	10.10	13.40
	Abnormal	7	0.8	11.62±0.86	12.00	10.20	12.60
Language	Normal	855	93.3	11.93±0.84	12.00	8.60	15.70
	Suspect	47	5.1	12.05±0.76	12.10	10.10	13.70
	Abnormal	14	1.5	12.17±0.78	12.05	10.80	13.50
Gross motor	Normal	833	90.9	11.92±0.84	12.00	8.60	15.70
	Suspect	54	5.9	12.57±0.72	12.15	10.70	14.20
	Abnormal	29	3.2	12.10±0.88	12.10	10.00	12.50
Total	Normal	742	81	11.92±0.84	11.90	8.60	15.70
	Suspect	101	11	12.04±0.82	12.10	10.00	14.20
	Abnormal	73	8	12.02±0.86	12.00	10.00	13.90
	Total	916	100	11.94±0.84	12.00	8.60	15.70

due to their total DDST II score (Table 1). It was reported that in the study performed by Güven et al.,[26] 25.7% of the 0-6 age group of children were in the abnormal and suspect group. The study published by Doğan and Baykoç[27] shows that 19.45% of 5-6 year-old children were in the abnormal and suspect group, which is in line with our research findings. Our study included preschool children and comprised a large sample to represent all children in this age group. It is reported that early identification of developmental delays is kept equivalent with early treatment and is helping to reduce loss of function and secondary behavioral problems.[28] Children with identified developmental delays in our study were referred to the departments responsible for the provision of early treat-

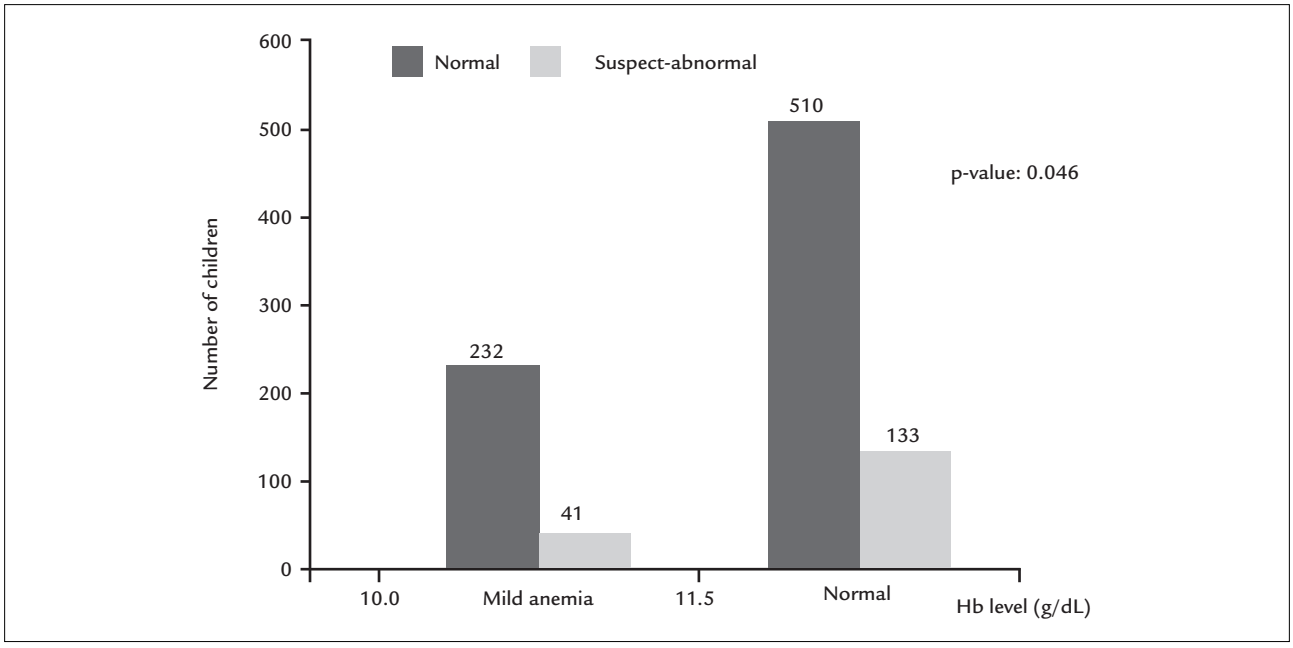

FIGURE 1 Comparison between total score of DDST II and hemoglobin levels (N=916).

TABLE 2 Distribution according to body mass index (BMI) of DDST II results (N=916).

		n	X±SS	Median	Minimum	Maximum
Personal-social	Normal	874	16.35±2.28	15.99	8.33	26.59
	Suspect	20	15.49±2,53	16.54	8.46	19.01
	Abnormal	22	16.47±1.74	16.15	13.55	20.14
Fine motor-adaptive	Normal	862	16.31±2.29	15.97	8.33	26.59
	Suspect	47	16.61±2.08	16.53	13.19	22.31
	Abnormal	7	16.57±2.16	16.74	14.05	19.44
Language	Normal	855	16.33±2.80	16.00	8.33	26.59
	Suspect	47	16.15±2.05	15.90	13.10	23.00
	Abnormal	14	16.75±3.00	16.67	12.31	23.97
Gross motor	Normal	833	16.30±2.28	15.94	8.33	26.59
	Suspect	54	17.20±2.02	16.97	13.22	23.58
	Abnormal	29	15.55±2.23	16.07	8.46	19.01
Total	Normal	742	16.32±2.30	15.94	8.33	26.56
	Suspect	101	16.40±2.14	16.16	12.40	23.58
	Abnormal	73	16.30±2.27	16.53	8.46	23.97
	Total	916	16.33±2.27	16.00	8.33	26.59

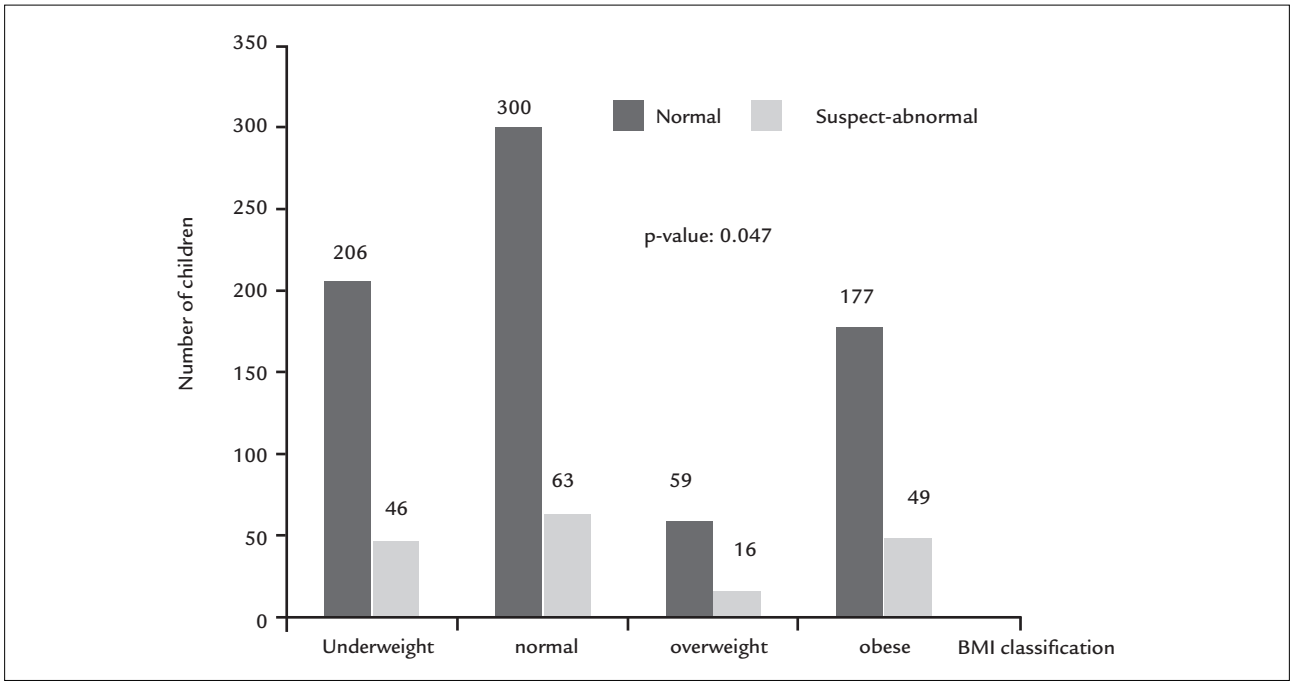

FIGURE 2 Comparison between total score of DDST II and body mass index (N=916).

ment, which shows the importance of our study in terms of social contribution.

Anemia is defined as having a hemoglobin value under -2 SD according to age group.[3] Anemia is commonly reported all over the world and should be monitored by screening programs due to more severe effects in infancy.[29]

Out of 2,872 4-6 year-old children, 3.4% surveyed by Karagün et al. were determined to be anemic.[30] In the retrospective study conducted in Balıkesir (Turkey), 563 children between the ages of 0 to 18 were investigated and the frequency of anemia among 5-7 year-old children was found at 13.6%.[31] In our study, 5-6 years old children have been taken into consideration and all of those with a value of 11.5 g/dL or lower were considered anemic. Based on the non-invasive evaluation, it was determined that the hemoglobin average of 916 children is 11.94±0.84 (Table 1). Furthermore, it was seen that 29.8% (n=273) of children who participated in the study have a hemoglobin value of ≤ 11.5 g/dL (Figure 1). The high incidence of anemia in our study reveals the importance of follow-up with anemia screening programs in the preschool period, and treatment support.

Anemia is a disease that has an impact on biochemical processes, cellular function, growth and development, mental and behavioral development, the immune system, physical capacity, thermoregulation and many hematologic and non-hematologic systems, such as the gastrointestinal tract.[30-33] According to conducted studies, the decrease of one unit in hemoglobin in a child increases the mild to moderate mental retardation risk 1.28 times. Even if these children get treated, their Bayley test scores (used for developmental follow-up) will still be low after ten years.[34] Furthermore, it is emphasized that early diagnosis and treatment of anemia is very important due to anemia's significant effects on children's growth, development and cognitive functions.[31] The relation of total DDST II score between anemic and non-anemic 5-6 year-old children was found to be statistically significant ($p<0.05$; Figure 1). Additionally, it was determined that 21% of non-anemic and 15% of the anemic children was in the suspect-abnormal group according to their DDST II scores. Considering that children who participated in our study did not show any severe or moderate anemia, our study's results show that the neuromotor development of children with mild anemia is better than that of children without anemia. While some published studies[35,36] support neurogenesis of physiological hypoxia (3% O_2), they reported that anoxia (< 1% O_2) and severe hypoxia (1% O_2) have negative effects. Data obtained by our study reveals that mild hypoxia may have positive effects on neuromotor development. In order to explain the mechanisms behind this, new studies must be conducted.

In terms of growth and development, the age range 3 to 6 years is an important period. As for body adiposity, the preschool period is of great importance. While

the amount of adipose tissue decreases after infancy until the age of 6-8 years, it than increases thereafter. This early adiposity increase poses a big risk with regard to obesity.[21] The BMI average of 916 children within our study was determined at 16.33±2.27 (Table 2); 8.2% of these were overweight and, 24.7% were obese (Figure 2). In addition to obesity, protein energy deficiency is a very common nutritional problem among pre-school children in our country. Nevertheless, our study revealed that being underweight does not have a significant impact on the children's neuromotor development. The relationship between the children's BMI and DDST II total scores was considered statistically significant, and we found that 26.4% of the suspect-abnormal children were underweight, 36.2% were normal, 9.2% were overweight and 28.2% were obese (Figure 2).

As a result, mild anemia seems to present a positive effect on neuromotor development, while malnutrition may have a negative impact on children's neuromotor development. To investigate the underlying causes of the relationship between neuromotor development and malnutrition, further studies are required. In addition, new studies also are needed to evaluate the effects of severe or moderate anemia on neuromotor development. Raising awareness in families regarding anemia, malnutrition and neuromotor development is expected to provide a positive contribution in terms of early diagnosis and treatment of diseases.

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Conflict of interest

The authors declare no conflict of interest.

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Bariatric surgery in the elderly: A narrative review

Everton Cazzo[1]*, Martinho Antonio Gestic[2], Murillo Pimentel Utrini[3], Felipe David Mendonça Chaim[2],

Francisco Callejas-Neto[4], José Carlos Pareja[1], Elinton Adami Chaim[1]

[1]MD, PhD, Full Professor, Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-Unicamp), Campinas, SP, Brazil
[2]MD, MSc, Assistant Physician, Department of Surgery, FCM-Unicamp, Campinas, SP, Brazil
[3]MD, Assistant Physician, Department of Surgery, FCM-Unicamp, Campinas, SP, Brazil
[4]MD, MSc, Full Professor, Department of Surgery, FCM-Unicamp, Campinas, SP, Brazil

Summary

Introduction: Due to population ageing, the elderly obese population is increasing. Bariatric surgery is the standard treatment option for morbid obesity nowadays, but there is some controversy regarding its routine indication in the elderly population.
Objetive: To review the current evidence about bariatric surgery in the elderly.
Method: On-line search in the electronic databases Medline and Lilacs and compilation of the most significant data. The most relevant studies in the area over the past 16 years have been considered for this review.
Results: There was significant methodological heterogeneity in the studies found in the literature. Historically, old age was associated with poorer outcomes after bariatric surgery, both in regards to early postoperative complications and less weight loss, and resolution of comorbidities. More recent studies have shown better results, with morbidity and mortality comparable to those observed in younger populations. More cautious patient selection and the evolution of the surgical technique appear to be the cause of such improvement. An extended multidisciplinary team including a geriatrician and a social worker may also help to improve the preoperative approach.
Conclusion: Bariatric surgery is a safe and effective therapeutic option in the elderly population, but careful patient selection and specific preoperative assessment are mandatory.

Keywords: obesity, aged, health of the elderly, geriatrics, digestive system surgical procedures.

Study conducted at the Department of Surgery, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-Unicamp), Campinas, SP, Brazil

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***Correspondence:**
Departamento de Cirurgia – Unicamp
Address: R. Alexander Fleming, s/n
Campinas, SP – Brazil
Postal code: 13083-887
notrevezzo@yahoo.com.br

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Introduction

Population ageing, that is, a significant increase in life expectancy, is a worldwide phenomenon that was first detected in developed countries as early as the late 1970s and 1980s, and has also been affecting underdeveloped countries in the last decades. In Brazil, the elderly – people aged 60 years old or older – represent a population of 23.5 million people, more than double of the estimates reported in 1991.[1]

The prevalence of obesity among the elderly has shown a steady and significant increase in the last years. In the United States of America, in individuals aged 60 to 69 years old, 42.5% of the women and 38.1% of the men are obese. Among those aged 70 to 79 years, 31.9% of the women and 28.9% of men are also obese.[2] In a Brazilian population, Silveira et al.[3] observed a 25.3% prevalence of obesity in elderly individuals, 30.8% among women and 17.4% among men. Several reasons are proposed for the higher prevalence of obesity among women, and the most significant are hormonal (mainly the menopause), occupational, and cultural factors, associated with a greater life expectancy.[4] The frequency of obesity among the elderly was higher than the 12% overall prevalence observed in the general population in a recent survey conducted by the Brazilian Census Bureau (IBGE).[4]

Since bariatric surgery has become the standard treatment for morbid obesity, the possibility of performing this surgical modality in the elderly has raised some con-

cerns. Historically, in Brazil, surgery was not warranted for individuals aged 65 years or older.[5] It was only in 2013 that the Federal Health Department authorized bariatric surgeries to be performed in individuals above this age limit. Currently, there is not an upper limit for age. The indications for surgery are equal to those in younger individuals: body mass index (BMI) equal or higher than 40 kg/m^2 or equal or higher than 35 kg/m^2 associated with obesity-related comorbidities. The same government ordinance that established that there would not be an upper age limit for surgery also states that any clinical condition that could enhance the surgical risk to prohibited levels must be considered prior to the procedure.[6]

Although surgery is currently the best treatment option for morbid obesity, the outcomes in the elderly were not so positive in the first published reports, leading to some controversy. Our study sought to review the past and current evidence on bariatric surgery in the elderly and evaluate a possible specific preoperative approach to this group.

Method

A review of the literature was conducted through an online search for the following Medical Subject Heading (MeSH) terms in English: bariatric surgery; aged; health of the elderly (Medline search via PubMed); and the following MeSH/DeCS terms in English, Portuguese, and Spanish: bariatric surgery/cirurgia bariátrica/cirugia bariátrica; aged/idoso/anciano; health of the elderly/saúde do idoso/salud del anciano (Lilacs search via Bireme). We included original studies that reported on population studies about the effects of several modalities of bariatric surgery on elderly individuals. All of the articles were screened based on title and abstract. Full-text articles were obtained from journals available from the Commission for Improvement of Higher Education Personnel (Comissão de Aperfeiçoamento de Pessoal de Nível Superior – CAPES) Foundation (Ministry of Education, Brazil) website. Articles that did not provide a full version were requested directly to the authors. Articles presenting potentially relevant studies were read and analyzed to assess the inclusion criteria. We excluded articles that consisted of in vitro or animal studies, articles in which the participants' characteristics did not match those mentioned above, poster session abstracts, narrative review articles and other types of publications (non-standard bariatric surgical techniques; studies without appropriate follow-up; or studies with critical methodological issues). Other papers were used for contextualization and discussion.

Results

Many articles were found in duplicity in both databases, leading to a final count of 13 studies eligible for our review. Table 1 summarizes the main studies selected for this review.

TABLE 1 Database search results for bariatric surgery on the elderly on October 10th, 2016.

Electronic databases	Search strategies	Results
Medline (PubMed)	(Bariatric surgery) AND ((Aged) OR (Health of the Elderly))	10 retrospective cohorts 3 systematic reviews
Lilacs (Bireme)	((Bariatric surgery) OR (Cirurgia Bariátrica) OR (Cirurgia bariátrica)) AND ((Aged) OR (Anciano) OR (Idoso)) OR ((Health of the Elderly) OR (Salud del Anciano) OR (Saúde do Idoso))	6 retrospective cohorts 3 systematic reviews

Discussion

A recurring problem in regards to the available evidence of bariatric surgery in the elderly is the lack of homogenous standardization and method. First, the age limit to consider an individual as aged is variable, with some articles stating ages as low as 50 years and others as high as 70 years. Furthermore, most studies were database analyses, which were not prospectively assessed and enrolled individuals who underwent several different techniques of bariatric surgery. Despite the overall poor quality, however, there was a large number of individuals enrolled in these studies, leading to statistical significance in spite of the methodological limitations.

Historically, population studies published in the 2000s about bariatric surgery in older individuals reported significantly worse outcomes in regards of morbidity and mortality compared with younger subjects. Sugerman et al.,[7] in a database analysis of 80 consecutive individuals aged 60 years or older who underwent varied bariatric surgical techniques, observed a higher prevalence of preoperative comorbities; the mean excess weight loss and resolution of comorbidities were lower than those observed in younger populations; there were no perioperative deaths. Flum et al.,[8] in a retrospective cohort study enrolling 16,155 individuals who underwent varied bariatric procedures, reported higher perioperative mortality in individuals aged 65 years or older (4.8% versus 1.7% in younger individuals), as well as higher one-year mortality (11.1% versus 3.9%, respectively), concluding that patients aged 65 years or

older had a substantially higher risk of death within the early postoperative period than younger patients. Dunkle-Blatter et al.,[9] in a single-center retrospective analysis enrolling 1,065 patients, reported that the 90-day operative mortality rate was 1.64% in the older group versus 0.53% for the younger group. Livingston et al.,[10] in a database analysis enrolling 1,067 consecutive individuals who underwent gastric bypass surgery, identified older age as a predictor of mortality, since they found that patients older than 55 years had a threefold higher mortality from surgery than younger patients, although the complication rate, 5.8%, was the same in both groups, suggesting that older patients lack the reserve to recover from complications when they occur. In a database analysis conducted by Varela et al.,[11] the authors observed that, compared with nonelderly patients, elderly patients who underwent bariatric surgery had more comorbidities, longer lengths of stay, more overall complications (18.9% vs. 10.9%), pulmonary complications (4.3% vs. 2.3%), hemorrhagic complications (2.5% vs. 1.5%) and wound complications (1.7% vs. 1.0%); the in-hospital mortality rate was also significantly higher in the elderly group (0.7% vs. 0.3%). A Brazilian retrospective study carried out by Pajecki et al.[12] revealed that surgical morbidity (26% vs. 37%, respectively) and mortality (0 vs. 12.5%, respectively) were higher in patients over 65 years, and this group had the same benefits observed in patients aged less than 65 years in regards to weight loss and comorbidity control.

More recently, studies are showing a trend toward improvement of the surgical outcomes of bariatric surgery in the elderly. Dorman et al.,[13] in a database analysis enrolling 48,378 individuals who underwent varied bariatric surgical techniques, observed that patients aged 65 years or older presented a non-statistically significant trend toward higher mortality and did not experience higher risk of major complications for either open or laparoscopic procedures; nonetheless, they were more likely to experience prolonged length of stay. Morgan and Ho,[14] in a retrospective cohort study enrolling 12,062 individuals who underwent bariatric surgery, observed that 18.1% of all the procedures were performed in patients ≥ 55 years old; older bariatric patients were statistically more likely to require longer hospital admissions, have more postoperative complications and require intensive care admissions compared to patients < 55 years old; however, 30-day (no deaths in the older cohort) and long-term mortality rates did not differ from those observed in younger individuals, suggesting that bariatric surgery may confer health benefits to carefully selected obese older patients who cannot achieve weight loss by other means. Batsis et al.,[15] in a retrospective population-based study that analyzed 40 consecutive individuals aged 60 years or older who underwent bariatric surgery, observed a perioperative mortality of 2.5%, along with considerable weight loss, improvement in cardiovascular risk factors, and decrease in prevalence of metabolic syndrome, considering it to be an effective treatment in this population. Gebhart et al.,[16] in a comparative database analysis, observed that the elderly represented 2.7% of all bariatric surgeries in the 1999-2005 period, with an increase to 10.1% in the 2009-2013 period; in-hospital mortality was 0.3% for the nonelderly and 0.7% for the elderly in 1999-2005, whereas in 2009-2013, in-hospital mortality had decreased to 0.1% for the nonelderly and 0.05% for the elderly, concluding that better patient selection and evolution of the surgical technique may explain this significant improvement. In a systematic review enrolling 1,206 individuals aged 55 years or older, Lynch and Belgaumkar[17] observed that the 30-day mortality rate was 0.3% and 0.18% for laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic adjustable gastric banding (LABG), respectively; meta-analyses of BMI reduction indicated sustained and clinically significant BMI reduction for both RYGB (mean percentage of excess weight loss at 1 year, 72.6%) and LAGB (mean percentage of excess weight loss at 1 year, 39.1%). Another systematic review conducted by Giordano and Victorzon,[18] encompassing 8,149 patients aged 60 years or older, observed a pooled mortality of 0.01% in the 30-day postoperative period and a pooled overall complication rate of 14.7%, concluding that outcomes and complication rates of bariatric surgery in patients older than 60 years are comparable to those in younger populations, despite the type of procedure performed. In both systematic reviews, the authors comment that the heterogeneity of the studies preclude further conclusions, but reveal a newer trend toward safety regarding bariatric surgery in the elderly, and proposing that a major factor related with these outcomes is a more efficient and careful preoperative selection of the individuals who are eligible for surgery. A systematic review carried out by Chow et al.[19] including 1,835 individuals who underwent RYGB found a mean excess weight loss of 66.2%, with mean 30-day mortality at 0.14 %, and mean total post-operative complication rate at 21.1%, with wound infections being the most common (7.58%) followed by cardiorespiratory complications (2.96%). The authors concluded that bariatric surgery is effective in producing marked weight loss in patients ≥ 65 years with an acceptable safety profile. Table 2 summarizes the main reported outcomes of the above cited studies and their respective levels of evidence according to the Oxford Centre for Evidence-based Medicine.[20] An important question addressed in all of the systematic reviews is that prospective controlled studies are necessary to lead to evidence of better quality.

TABLE 2 Main results of bariatric surgery in the elderly reported in the literature.

	Sugerman et al.[7]	Flum et al.[8]	Dunkle-Blatter et al.[9]	Livingston et al.[10]	Varela et al.[11]	Pajecki et al.[12]	Dorman et al.[13]	Morgan et al.[14]	Batsis et al.[15]	Gebhart et al.[16]	Lynch and Belgaumkar[17]	Giordano and Victorzon[18]	Chow et al.[19]
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Systematic review	Systematic review	Systematic review
Level of evidence	2b	2b	2b	2b	2b	2b	2b	2b	2b	2b	2a	2a	2a
N	Elderly: 80	Overall: 16,155 Elderly: 1,517	Overall: 1,065 Elderly: 76	Overall: 1,067 Elderly: 113	Overall: 49,275 Elderly: 1,339	Elderly: 46	Overall: 48,378 Elderly: 1,994	Overall: 12,062 Elderly: 2,179	Elderly: 40	Overall: 60,709 Elderly: 6,105	Elderly: 1,206	Elderly: 8,149	Elderly: 1,835
Surgical morbidity	Minor: NR Major: 8.7%	NR	Minor: 26.2% Major: 4.9%	Minor: NR Major: 5.8%	Overall: 18.9%	Overall: 30.4%	Minor: NR Major: 4.3%	Overall: 12%	NR	Major: RYGB: 1.54% SG: 1.29% LAGB: 0.66% Minor: NR	NR	Overall: 14.7%	Overall: 21.1%
Perioperative mortality	0	4.8%	1.6%	3.5%	0.7%	4.3%	0.4%	0	2.5%	RYGB: 0.14 SG: 0.12 LABG: 0	LRYGB: 0.3% LAGB: 0.18%	0.01%	0.14%

N: number of individuals; NR: not reported; LAGB: laparoscopic adjustable gastric banding; LRYGB: laparoscopia gastric bypass: SG: sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass.

In regard to the selection criteria for bariatric surgery in the elderly, there is no universal or standard protocol of preoperative evaluation. The standard general assessment may be insufficient for a population with specific needs and concerns, such as that of older individuals. Batsis and Dolkart[21] proposed an individualized approach to older candidates to bariatric surgery that encompasses and contemplates aspects and domains that are not so prominent in younger individuals. These authors propose that older candidates should be evaluated by an extended multidisciplinary team that would include a geriatrician and a social worker, and that the preoperative assessment must incorporate five specific topics for this population: 1) evaluation of functional status; 2) assessment of frailty; 3) cognitive assessment; 4) identification of depression; 5) social support and discharge planning. Their proposal is based on the fact that worse surgical outcomes are mostly related to impaired functional status, presence of frailty, delirium that occurs in previously cognitive impaired individuals, presence of depression and other psychiatric conditions that may be underestimated prior to surgery, and the unavailability of caretakers and ideal housing conditions for these individuals after surgery. Experienced geriatricians and social workers may help to achieve a more thorough preoperative assessment and to select only individuals eligible for surgery, reducing any avoidable risks. This group of individuals, due do specific characteristics and possible major risks, should undergo surgery in high-volume centers.

The evolution of surgical technique, especially the development of minimally invasive approaches, constitutes an important factor in the improvement of the surgical outcomes over time, along with cautious and careful patient selection and preoperative assessment.

Conclusion

Bariatric surgery has become a safe and effective therapeutic option for obesity in the older population; however, thorough patient selection and a specific preoperative assessment are key points to lead to satisfactory outcomes.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Cirurgia bariátrica no idoso: uma revisão narrativa

Introdução: Em virtude do envelhecimento populacional, a população obesa idosa também está aumentando. A cirurgia bariátrica é o tratamento padrão-ouro para obesidade mórbida atualmente, porém sua realização rotineira em idosos ainda é controversa.

Objetivo: Revisar a literatura atual sobre a cirurgia bariátrica em idosos.

Método: Revisão *on-line* das bases de dados eletrônicas Medline e Lilacs e compilação dos dados mais significativos. Os estudos mais relevantes na área nos últimos 16 anos foram considerados para esta revisão.

Resultados: Houve grande heterogeneidade metodológica nos estudos encontrados. Historicamente, a idade avançada estava associada a resultados inferiores após a cirurgia bariátrica, em relação tanto a complicações pós-operatórias quanto à perda de peso e resolução de comorbidades. Estudos mais recentes têm mostrado resultados melhores, com morbidade e mortalidade comparáveis às observadas em indivíduos mais jovens. A seleção criteriosa de pacientes e a evolução da técnica cirúrgica parecem estar ligadas a essa melhora. Uma equipe multidisciplinar expandida, com geriatra e assistente social, pode também colaborar para uma melhor abordagem pré-operatória.

Conclusão: A cirurgia bariátrica é uma opção terapêutica segura e efetiva na população idosa, mas uma seleção criteriosa de pacientes e avaliação pré-operatória específica precisam ser realizadas.

Palavras-chave: obesidade, idoso, saúde do idoso, geriatria, procedimenos cirúrgicos do sistema digestório.

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Ischemic left ventricle systolic dysfunction: An evidence-based approach in diagnostic tools and therapeutics

Eduardo Gomes Lima[1]*, Felipe Pereira Câmara de Carvalho[2], Jaime Paula Pessoa Linhares Filho[2], Fabio Grunspun Pitta[2], Carlos Vicente Serrano Jr[1]

[1]MD, PhD, Department of Atherosclerosis, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (InCor-HC-FMUSP), São Paulo, SP, Brazil
[2]MD, Department of Atherosclerosis, InCor-HC-FMUSP, São Paulo, SP, Brazil

Summary

Coronary artery disease (CAD) associated with left ventricular systolic dysfunction is a condition related to poor prognosis. There is a lack of robust evidence in many aspects related to this condition, from definition to treatment. Ischemic cardiomyopathy is a spectrum ranging from stunned myocardium associated with myocardial fibrosis to hibernating myocardium and repetitive episodes of ischemia. In clinical practice, relevance lies in identifying the myocardium that has the ability to recover its contractile reserve after revascularization. Methods to evaluate cellular integrity tend to have higher sensitivity, while the ones assessing contractile reserve have greater specificity, since a larger mass of viable myocytes is required in order to generate contractility change. Since there are many methods and different ways to detect viability, sensitivity and specificity vary widely. Dobutamine-cardiac magnetic resonance with late gadolinium enhancement has the best accuracy is this setting, giving important predictors of prognostic and revascularization benefit such as scar burden, contractile reserve and end-systolic volume index. The latter has shown differential benefit with revascularization in some recent trials. Finally, authors discuss interventional procedures in this population, focusing on coronary artery bypass grafting and evolution of evidence from CASS to post-STICH era.

Keywords: coronary artery disease, heart failure, coronary artery bypass graft.

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***Correspondence:**
Address: Av. Dr. Enéas de Carvalho Aguiar, 44, 2º andar, sala 2
São Paulo, SP – Brazil
Postal code: 05403-000
eduglima@yahoo.com.br

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Introduction

Approximately 5.1 million persons in the United States have clinically manifest heart failure (HF),[1] while the lifetime risk of developing HF is 20% for Americans ≥ 40 years of age.[2] Heart failure with reduced ejection fraction (HF-REF) and preserved ejection fraction each make up about half of the overall HF burden.[3] The most common etiology of HF-REF in the developed world is ischemic heart disease, which is associated with more than 60% of diagnoses.[4] Coronary artery disease (CAD) associated with left ventricular systolic dysfunction is a condition related to poor prognosis.[5,6] Despite the fact that this condition has been studied for over 30 years, there is a lack of robust evidence in many aspects related to this condition, from definition to treatment.

Definitions and concepts

Since the CASS trial,[7] we know that the left ventricle ejection fraction impacts on CAD prognosis and treatment. However, a correct definition for "ischemic myocardiopathy" has not been established in all these years. The concept that this condition is an association between significant coronary obstruction and systolic dysfunction of the left ventricle is too simplistic and disregards important pathophysiologic and causative mechanisms. Even LVEF cut-off values considered as dysfunctional vary among different trials[8] and need consensus.

For many authors, ischemic cardiomyopathy is a spectrum ranging from stunned myocardium associated with myocardial fibrosis to hibernating myocardium and repetitive episodes of ischemia. In clinical practice, relevance

lies in identifying the myocardium that has the ability to recover its contractile reserve after revascularization.

The concept of hibernating myocardium is often confused with viable myocardium. Currently, the term "viable myocardium" has a prospective aspect; it is the one that has potential recovery following re-established coronary flow. On the other hand, "hibernating myocardium" can only be used retrospectively, representing the myocardial contractile reserve that recovered after revascularization.[9]

Ventricular dysfunction in chronic coronary artery disease is known to be an important prognostic predictor. Discrepancy between loss of left ventricular function caused by an infarct (necrosis/fibrosis) and that resulting from potentially reversible chronic ischemic insult (hibernating myocardium) may have relevant clinical implications.

Several studies have shown contractile recovery after restored blood flow, in both the acute and chronic settings. Kim et al.,[10] using cardiac magnetic resonance imaging (MRI) before and after revascularization documented contractile recovery in dysfunctional myocardial segments in patients with chronic CAD.

Association between myocardial viability and favorable clinical outcomes has been suggested in several studies. In a meta-analysis of 24 studies, Allman et al.[1] demonstrated that the presence of viability is correlated with reduction in mortality when these patients underwent revascularization. While in the absence of viability, there was no difference regarding mortality depending on the treatment performed (revascularization or medical treatment).

There are several non-invasive methods of myocardial viability identification, which is based on three parameters: metabolism evaluation and cell integrity, presence of tissue non-viable by determining the extent of fibrosis and/or necrosis, and, finally, evaluation of contractile reserve after inotropic stimulation.[11]

Methods to evaluate cellular integrity tend to have higher sensitivity (single-photon emission computed tomography – SPECT, positron emission tomography – PET and myocardial contrast echocardiography – MCE), while those assessing contractile reserve (dobutamine stress echocardiography – DbE and dobutamine stress cardiac magnetic resonance – DbCMR) have greater specificity, since a larger mass of viable myocytes is required to generate a contractility change. Since there are many methods and different ways of viability detection, sensitivity and specificity vary widely (Table 1).

The use of complementary test examinations for viability assessment, therefore, may provide crucial information for the identification of patients who could possibly benefit from the indication of myocardial revascularization.

Diagnosis

SPECT

This method evaluates technetium-99 or thallium-201 radioisotope uptake by viable myocytes, which depends on cellular and mitochondrial integrity. Both protocols have good sensitivity to predict contractile recovery after revascularization (thallium-201, 87%, versus technetium-99, 83%). However, in both cases, specificity is

TABLE 1 Comparison of imaging techniques for viable myocardium assessment.[21]

Technique	N. of studies	N. of patients	Mean LVEF (%)	Sensitivity (%)	Specificity (%)
Dobutamine echocardiography – Total	41	1421	25-48	80	78
Low-dose DbE	33	1121	25-48	79	78
High-dose Dbe	8	290	29-38	83	79
MCE	10	268	29-38	87	50
Thallium scintigraphy – Total	40	1119	23-45	87	54
TI-201 rest-redistribution	28	776	23-45	87	56
TI-201 re-injection	12	343	31-49	87	50
Technetium scintigraphy – Total	25	721	23-54	83	65
Without nitrates	17	516	23-52	83	57
With nitrates	8	205	35-54	81	69
PET – Total	24	756	23-53	92	63
CMR – Total	14	450	24-53	80	70
Low-dose dobutamine	9	272	24-53	74	82
Late gadolinium-enhancement protocol	5	178	32-52	84	63

below other available methods (thallium-201, 54%, technetium-99, 65%).[12]

Although widespread and available in most centers, low spatial resolution and exposure to radiation can limit its usefulness.

PET

PET viability evaluation is becoming increasingly common in clinical practice. The combination of a tracer for evaluation of blood flow and fluorine-18 fluorodeoxyglucose (18F-FDG) to detect cellular metabolism proved to be a promising approach in viability assessment.

The method can provide four result patterns, and the three main ones related to ischemic cardiomyopathy are: low blood flow with preserved metabolism (mismatch compatible with hibernating myocardium), decrease in both blood flow and metabolism (match compatible with fibrosis/necrosis), flow and metabolism preserved (normal tissue).[12]

Studies have shown that the use of PET in viability assessment has good sensitivity, about 92%, but with moderate specificity of 63%.[13] It has better spatial resolution and less radiation exposure compared with SPECT, but is still an expensive test, little available and has limited utility in diabetic patients, especially in type 1, which depends on the sensitivity of the glucose transporters.

Echocardiography

The use of echocardiography in the myocardial viability approach is based on three parameters: wall thickness, contrast enhancement by myocytes, and contractile reserve with inotropic stimulation.

The decrease in ventricular wall thickness (end-diastolic wall thickness < 6 mm), since it is associated with loss of tissue due to fibrosis/necrosis, showed a high negative predictive value for contractile recovery after revascularization.[14]

In recent years, the use of contrast echocardiography (MCE) has increased. Contrast enhancement assesses myocardial perfusion and, subsequently, cellular integrity.

The evaluation of contractile reserve by dobutamine stress, however, was further studied. The dysfunctional segment at rest, after inotropic stimulation, presents contractile recovery. Low dose dobutamine (5-10 mcg/kg) is enough to assess the contractile reserve. After an initial improvement, contractility worsens at higher doses of dobutamine (20 mcg/kg), which is the so called "biphasic response," highly suggestive of viable myocardium.[15]

Despite presenting good sensitivity (80%) and specificity (78%), this method has limitations, such as poor acoustic window and being an operator-dependent technique.[13]

Cardiac MRI

Cardiac magnetic resonance has been gaining importance in ischemic myocardiopathy. Good spatial resolution, lack of exposure to radiation and acoustic window independence are advantages of resonance compared to other methods such as echocardiography and SPECT.[16]

Viability assessment by resonance is based on three main parameters: end-diastolic wall thickness (EDWT), low-dose dobutamine inotropic stimulation and late gadolinium enhancement (LGE) imaging.

The evaluation of EDWT constitutes the measure of maximum thickness of myocardial wall at rest. In comparison with PET (FDG uptake), Baer et al.[17] demonstrated that a measure ≥ 5.5 mm was associated with viability. In turn, thicknesses < 5.5 mm had low uptake in PET, representing low probability of viability.

The low-dose dobutamine stress resonance (≤ 10 mg/kg per minute) has proven a useful tool in clinical practice. The inotropic stimulation promotes an improvement of myocardial contractility in viable segments, which was associated with increased likelihood of contractile recovery after revascularization.[18]

The gold standard technique for viability assessment is LGE. It relies on a greater distribution of gadolinium in the extracellular space (i.e. in the areas of fibrosis/necrosis), resulting in delayed washout. The transmural extension of scars showed correlation with the potential contractile recovery, described by Kim et al.[10] Infarcted areas are < 50% more likely to functional improvement after revascularization, while those > 50% are associated with poorer outcomes.[19]

In a meta-analysis of 24 studies, Romero et al. compared these three techniques. The use of dobutamine stress showed better specificity and positive predictive value, while LGE was associated with better sensitivity and negative predictive value.[20]As a result, the best approach to select patients eligible for revascularization might be the use of two techniques combined. Some authors propose the initial realization of LGE, and areas of infarction between 50-75% would then be evaluated with inotropic dobutamine stress. Improved contractile function would help in predicting viable areas. Scars < 50% and > 75% have a high and low probability of functional recovery, respectively.[21]

Although many studies point to the benefit of resonance and described tests in the management of ischemic cardiomyopathy, the lack of randomized controlled trials with hard clinical endpoints has not yet established the routine use of these methods in clinical practice.

Until recently, viability evaluation recommendations in ischemic cardiomyopathy were based on retrospective

and observational studies. However, prospective trials were conducted in this scenario. Despite yielding neutral results, these studies have several critical and methodological limitations that lead to more controversy in this regard.[22,23]

Treatment

The importance of treatment lies on the fact that patients with ischemic causes of left ventricular systolic dysfunction have significantly higher mortality rates than those with non-ischemic etiologies.[24]

The treatment of ischemic HF-REF can be didactically divided into medical and interventional therapies, the main goals being relief of symptoms and prognostic improvement.

Medical therapy is the cornerstone of patient management and is associated with significant improvement in survival and quality of life. In terms of interventional procedures, the most important is coronary artery bypass graft surgery (CABG), sometimes combined with surgical ventricular reconstruction (SVR) or surgery mitral valve repair. Other intervention procedures that can be used include insertion of implantable cardioverted-defibrillators (ICD), cardiac resynchronization therapy (CRT) among those with left bundle branch block, and orthotropic heart transplantation and ventricular assist devices in highly selected patients with advanced disease. Percutaneous coronary intervention (PCI) has been somewhat less studied.[25,26]

Medical therapy

Medical therapy is a priority in the management of CAD with systolic dysfunction, mainly because it is the only treatment directed to the disease itself, not only the lesion, acting on fundamental pathophysiologic pathways and improving outcomes.

The main classes of drugs include aspirin, statins, aldosterone inhibitors, beta-blockers, angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB).[25,26] However, it is important to emphasize that the utility and outcome benefits of these drugs are different.

Beta-blockers are very useful for the relief of angina in CAD patients. However, among those with left ventricle dysfunction this class of drug has prognostic implications. Treatment with beta-blockers was evaluated in the CIBIS-II (The Cardiac Insufficiency Bisoprolol Study II)[27] and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure)[28] trials, which showed that bisoprolol and metoprolol therapy had survival benefits among stable heart failure patients. In these two trials, 65% (n=2,606) and 50% (n=1,316) of patients had ischemic HF, respectively.

Similar to therapy with beta-blockers, ACEI are recommended for patients with CAD and HF-REF. The SOLVD trial[29] showed reduced mortality and hospitalization in patients with heart failure using enalapril. Among the patients, 70% were ischemic. As for ARB, candesartan was generally well tolerated and significantly reduced cardiovascular deaths and hospital admissions due to heart failure. Ejection fraction or treatment at baseline did not alter these effects.[30]

Aldosterone is important in the pathophysiology of heart failure. It is well known that blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with severe heart failure.[31] In addition, eplerenone reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.[32]

Surgical revascularization

The most important thing in CAD and HF-REF is to select patients that would benefit from revascularization procedures in terms of prognosis.

The first observational studies comparing survival in patients treated surgically versus medically suggested that CABG improves survival in patients with HF-REF and CAD. Reductions in mortality with surgery compared with medical therapy ranged from 10 to > 50%. However, most of these studies were conducted before the advent of beta-blockers and inhibitors of the renin-angiotensin-aldosterone system, or failed to provide sufficient details to determine if medical management would be optimal by current standards.[33-35]

One of the first randomized clinical trials, the Coronary Artery Surgery Study (CASS),[7] allocated 780 patients to an initial strategy of coronary surgery or medical therapy. In a subgroup analysis, patients with an ejection fraction of less than 0.50 exhibited better survival with initial surgery treatment (medical, 61% vs. surgical, 79%; p=0.01). Conversely, patients with an ejection fraction greater than or equal to 0.50 exhibited a higher proportion of individuals free of death and myocardial infarction with initial medical therapy (medical, 75% vs. surgical, 68%; p=0.04), even though long-term survival remained unaffected (medical, 84% vs. surgical, 83%; p=0.75). It should be noted that the CASS was randomized in the 1970s, when more than half of the patients did not use beta-blockers. The number of arterial grafts in the study was only 16%. LVEF < 35% and/or New York Heart Association functional classes III to IV were excluded.

Most trials comparing medical therapy with CABG for the treatment of stable angina ruled out patients

with severe LV dysfunction. The MASS-II (Medicine, Angioplasty or Surgery Study)[36] and the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)[37] excluded patients with severe LV dysfunction. The BARI 2D trial (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes)[38] included patients with LV dysfunction but only enrolled 17.5% with LVEF < 50%.

The STICH trial (Surgical Treatment of Ischemic Heart failure)[39] is the only prospective, randomized, controlled trial to specifically investigate the role of CABG in patients with LVEF < 35% who were also receiving OMT. Between 2002 and 2007, a total of 1,212 patients with an ejection fraction of 35% or less and CAD amenable to CABG were randomly assigned to medical therapy alone (602 patients) or medical therapy plus CABG (610 patients). Primary outcome was the rate of death from any cause. The first publication, comprising a 5-year follow-up, did not show significant difference between medical therapy alone and medical therapy plus CABG with respect to the primary end point of death from any cause. Patients assigned to CABG, as compared with those assigned to medical therapy alone, had lower rates of death from cardiovascular causes and death from any cause or hospitalization for cardiovascular causes.

Additional analyses of the STICH trial have been performed to identify subsets of patients with CAD and severe LV dysfunction most likely to benefit from revascularization.

In a post-hoc analysis, the Extent of Coronary and Myocardial Disease and Benefit From Surgical Revascularization in LV Dysfunction,[40] all 1,212 patients in the STICH surgical revascularization trial were included. This study focused on three prognostic factors: presence of 3-vessel CAD, EF below the median (27%) and end-systolic volume index (ESVI) above the median (79 mL/m^2). Patients were categorized as having 0 to 1 or 2 to 3 of these factors. Although 30-day risk with CABG was higher, a net beneficial effect of CABG compared with OMT was observed at > 2 years in patients with 2 to 3 factors (HR: 0.53; 95CI: 0.37 to 0.75; p<0,001), but not in those with 0 to 1 factor (HR: 0.88; 95CI: 0.59 to 1.31; p=0.535). Patients with more advanced ischemic cardiomyopathy achieve greater benefit with CABG. This supports the indication for surgical revascularization in patients with more extensive CAD and poorer myocardial dysfunction and remodeling.

However, more recently, the 10-year follow-up of the STICH trial has been published and the rates of death from any cause, death from cardiovascular causes and death from any cause or hospitalization for cardiovascular causes were over 10 years lower among patients who underwent CABG in addition to receiving medical therapy compared to those who received medical therapy alone.[41] These results are not included in any guideline, but will certainly change our current practice in the management of ischemic cardiomyopathy.

Percutaneous coronary intervention (PCI)

There is little evidence available regarding percutaneous treatment in patients with CAD and HF-REF. Two large trials that included patients with LV dysfunction were the BARI (Bypass Angioplasty Revascularization Investigation),[42] in which 22% of patients had LVEF < 50%, and the AWESOME[43] (Angina With Extremely Serious Operative Mortality Evaluation), in which 21% had LVEF < 35%. Subgroup analyses in patients with LV dysfunction from these trials suggest no difference in outcomes between PCI and CABG. However, these analyses involved less than 500 patients and included PCI with both balloon angioplasty and bare-metal stents.[44,45]

Bangalore et al.[46] have recently published a registry-based study from New York registries including 4,616 subjects with LVEF ≤ 35% and multivessel CABG that underwent to CABG or everolimus eluting stent. They observed a comparable long-term survival (median 2.9 years), but a higher risk of myocardial infarction (HR 2.16; 95CI 1.42-3.28; p=0.0003), a lower risk of stroke (HR 0.57; 95CI 0.33-0.97; p=0.04) and a higher risk of repeat revascularization (HR 2.54; 95CI 1.88-3.44; p<0.0001) associated to PCI. These data must be interpreted with caution, mainly because of the design of this study (observational, registry-based), the population studied and the device used (only everolimus-eluting stents).

Conclusion

CAD combined with left ventricle dysfunction is associated with poor prognosis, which is worse in the absence of myocardial viability. Diagnostic methods are useful to establish prognosis and to select specific populations with potential benefit with revascularization procedures. The best predictor of prognostic benefit after revascularization is a matter of debate. However, evidence suggest that patients with more advanced disease (angiographically, and involving left ventricular function/remodeling) would benefit from revascularization. A suggestion of algorithm based on most recent evidence is in Figure 1.

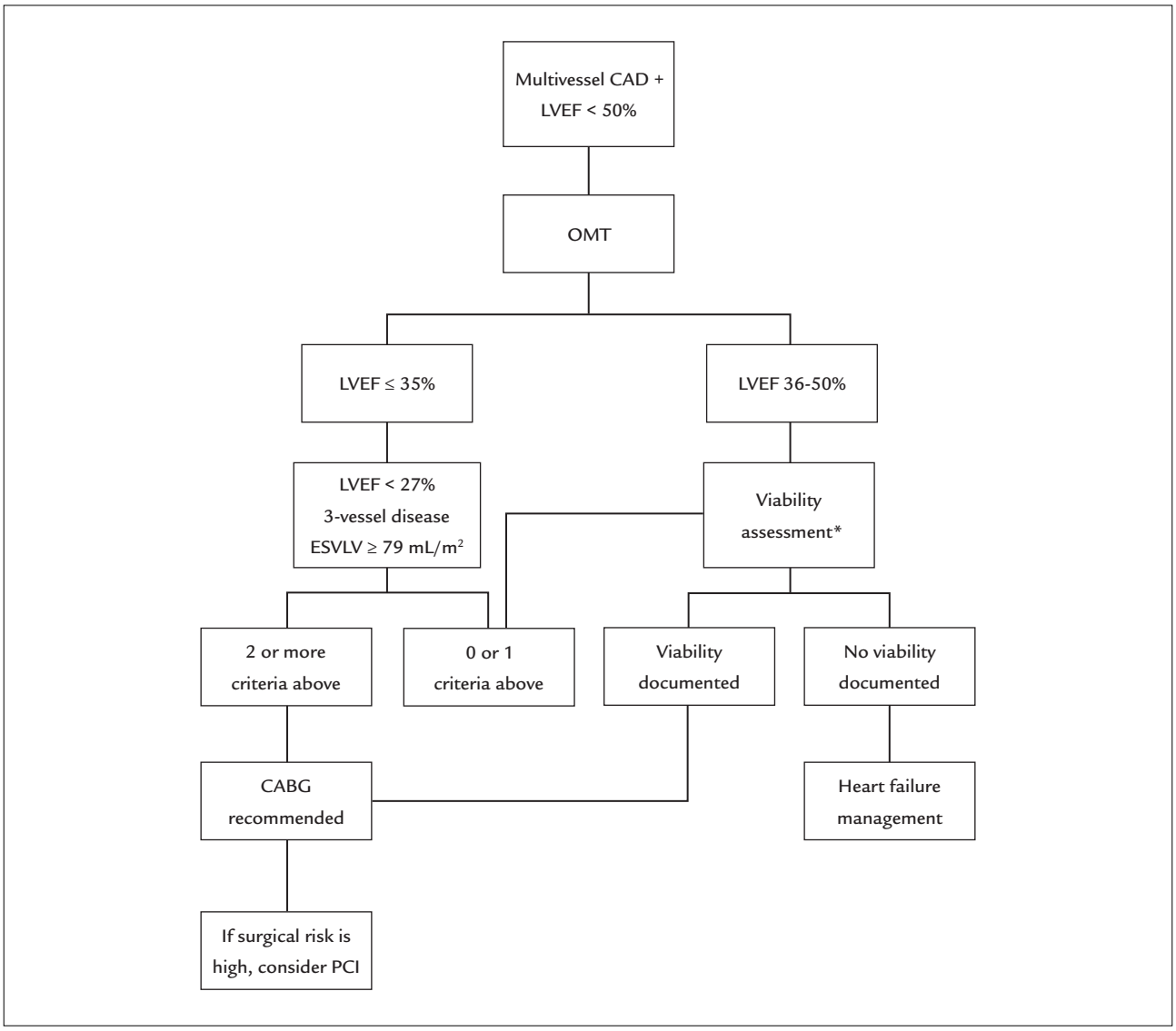

FIGURE 1 Suggested algorithm based on the most recent evidence in the post-STICH era.
*In the presence of akinetic segments.

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Miocardiopatia isquêmica: uma abordagem diagnóstica e terapêutica baseada em evidências

A doença arterial coronariana (DAC) associada à disfunção sistólica do ventrículo esquerdo é uma condição relacionada a mau prognóstico. Há uma falta de evidência robusta em muitos aspectos relacionados a essa condição, desde a definição ao tratamento. A cardiomiopatia isquêmica é um espectro que varia de miocárdio atordoado por fibrose miocárdica, passando por miocárdio hibernante, a episódios repetitivos de isquemia. Na prática clínica, a importância do problema é identificar o miocárdio que tem a capacidade de recuperar sua reserva contrátil após revascularização. Métodos para avaliar a integridade celular tendem a ter maior sensibilidade, enquanto os que avaliam a reserva contrátil têm maior especificidade, uma vez que uma maior massa de

miócitos viáveis para gerar uma mudança de contratilidade é necessária. Tendo em vista que existem muitos métodos e diferentes formas de detecção de viabilidade, a sensibilidade e a especificidade variam amplamente. O uso da ressonância magnética cardíaca com detecção de realce tardio associada a estresse com dobutamina tem a melhor acurácia na avaliação de viabilidade, além de fornecer importantes preditores de benefício prognóstico com a revascularização, tais como carga de cicatriz, reserva contrátil e índice de volume sistólico final. Finalmente, os autores discutem sobre procedimentos intervencionistas nessa população, com foco na revascularização cirúrgica do miocárdio e na evolução da evidência desde o estudo CASS até os *trials* da era pós-STICH.

Palavras-chave: doença arterial coronariana, insuficiência cardíaca, revascularização do miocárdio.

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Vitamin B12, bone mineral density and fracture risk in adults: A systematic review

Luciana Leal Gomes de Macêdo[1]*, Cecilia Maria Resende Gonçalves de Carvalho[2], Janaína Costa Cavalcanti[3], Betania de Jesus e Silva de Almendra Freitas[4]

[1]MSc Student, Food and Nutrition Graduate Program, Universidade Federal do Piauí (PPGAN-UFPI), Teresina, PI, Brazil
[2]Postdoctoral Degree in Nutrition and Public Health from Faculdade de Saúde Pública da Universidade de São Paulo (FSP/USP). Full Professor of Nutrition, UFPI, Teresina, PI, Brazil
[3]MD, Geriatrician, Hospital Universitário da Universidade Federal do Piauí (HU-UFPI). Internal Medicine Residency Training Program at Hospital Regional da Asa Norte (HRAN) and Geriatric Medicine Residency Program at Hospital Universitário da Universidade de Brasília (HU-UnB), Teresina, PI, Brazil
[4]PhD in Medical Sciences from Universidade Estadual de Campinas (Unicamp). Associate Professor I of Nutrition, UFPI, Teresina, PI, Brazil

Summary

Objective: To consolidate information available on the effect of vitamin B12 on bone mineral density and fracture risk, with emphasis on clinical trials, observational and longitudinal data conducted in humans.
Method: A systematic review of the literature of the past decade on the role of vitamin B12 in bone mineral density and fracture risk in subjects of all ages and both sexes was performed by means of a PubMed, Science Direct, Medline and SciELO database search. Articles included in this review were identified using the search terms: B12 Vitamin and Bone Mineral Density and Vitamin B12 and Risk of Fractures. Evidence quality of the included articles was evaluated by GRADE system.
Results: A total of 25 original studies were identified. After reviewing the titles and abstracts of articles, only 17 articles met the inclusion criteria. The present review provides evidence that the role of vitamin B12 on bone mineral density or fracture risk should be further elucidated. Controversies are explained by heterogeneity of methodologies used for the diagnosis of vitamin B12 and also by differences among populations investigated on the studies.
Conclusion: A real effect of vitamin B12 deficiency in bone health and the mechanisms associated with bone metabolism is not well established yet. It is extremely important to carry out more clarifying studies about this theme, especially with vulnerable groups such as postmenopausal and elderly women, as is well-known that they are greatly affected by deficiency of this vitamin.

Keywords: bone health vitamin, B12 vitamin supplementation, fracture risk.

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***Correspondence:**
Department of Nutrition
Address: Campus Ministro Petrônio Portella, s/n
Teresina, PI – Brazil
Postal code: 64049-550
luhlealmacedo@gmail.com

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Introduction

Osteoporosis is an important public health issue that can worsen over the years and increase financial spending within the context of a worldwide trend of increased life expectancy. This is a chronic, multifactorial disease, characterized by a decrease in bone mineral density and deterioration of the skeletal structure microarchitecture, leading to fragility and increased susceptibility to fractures.[1]

Several factors are associated with the etiology of bone mass loss, some of them having a nutritional origin. It is well established that preventive strategies such as calcium and vitamin D supplementation associated with regular physical activity decrease the incidence of fractures and increase bone mineral density.[2]

It is thus very important to identify risk factors for osteoporosis and to adopt interventions that may reduce the likelihood of fracture, assisting individuals who may benefit from faster screening for osteoporosis, thereby avoiding its negative repercussions regarding health and quality of life.

Some studies on the promotion of bone health have demonstrated the involvement of vitamin B12 in the quality of bone structure in humans.[3-5] The mechanism of action of this vitamin in the microarchitecture of bones is not yet

well characterized, but it seems to modulate the formation of collagen or alter the metabolism of osteoblasts, always in a dose-dependent manner.[6,7] Low levels of vitamin B12 increase the risk of reduced bone mineral density and fractures[8,9] in these individuals. However, the results are not yet conclusive and the actual impact of vitamin B12 deficiency on bone health and the mechanisms associated with bone metabolism is not well established.

Recent research has shown an association between vitamin B12 deficiency and increased risk of low bone mineral density, while other studies do not present consistent results.[7-9]

In this context, our main objective in this review is to consolidate the available information about the effects of vitamin B12 on bone mineral density and fracture risk, obtained mainly from clinical trials, observational data and longitudinal studies conducted in humans.

Method

Our study consists of a systematic review of literature, with search for articles in the following electronic databases: National Library of Medicine (PubMed), Science Direct, Medical Literature Analysis and Retrieval System Online (Medline) and Scielo. The bibliographic search was carried out between May and July, 2016. As a data search strategy, we included descriptors restricted to the "title," "summary" and "article descriptors" (mesh terms) fields: B12 Vitamin and Bone Mineral Density and B12 Vitamin and Risk of Fractures.

We included articles from the past ten years, written in English, Spanish and Portuguese, which evaluated the role of vitamin B12 on bone mineral density in populations of all ages and both sexes, including original articles/research that made the full version of the article available. Editorials, letters to the reader, review articles, articles that did not offer access to complete content, and those that were published in other foreign languages were excluded, as well as those assessing the role of vitamin B12 in other disorders such as dementia, myasthenia, and more.

Aiming at the adequate methodological quality of the systematic review, the selection was performed by three independent evaluators, strictly following the inclusion and exclusion criteria. The articles were evaluated first by title and then by abstract, and disagreements were resolved by consensus among researchers. The reference list of the articles identified in the electronic search was also reviewed in order to find studies that could contribute significantly to our review of the literature.

To grade the quality of the evidence and the strength of the recommendations found in the results of the articles included in our review, we used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, adopted by the Cochrane Collaboration. In the GRADE system, the quality of evidence is classified into four levels: high, moderate, low and very low.[10]

Results

In all, 2,529 articles were identified through search in electronic databases; 1,612 were excluded based on the initial criteria (publications written in the past 10 years in English, Spanish or Portuguese, with full text available). Of the remaining 917 articles, 892 were eliminated, as they did not include longitudinal or observational studies, or case-control studies performed in humans. Thus, 25 full texts were examined and 17 were included in our review. Of these, eight studies were excluded: one was a systematic review with meta-analysis; another study evaluated only markers of bone remodeling; and in six studies the bone mineral density and/or risk of fractures of the individuals was not investigated (Figure 1).

Overall, six longitudinal studies, nine cross-sectional studies and two randomized, double-blind, placebo-controlled clinical trials evaluating BMD and/or fracture risk in adult humans were found. Chart 1 shows the main results and the quality of the evidence presented by the included studies.

Discussion

The association between bone health and vitamin B12 alone or with other B vitamins has been extensively studied in the most diverse populations, as shown in Chart 1. Our review provides evidence that the role of vitamin B12 in bone mineral density or fracture risk needs to be better elucidated.

Among the 17 studies analyzed in our systematic review, only three found an association between vitamin B12 and fracture risk and/or bone mineral density. Fourteen studies did not find such an association. The controversies are supported by the heterogeneity of the methods used to diagnose B12 hypovitaminosis, such as: investigation of dietary intake of vitamin B12, plasma or serum vitamin levels and analysis of methylmalonic acid. The populations participating in the studies analyzed also differed: Dutch, Brazilians, Americans, Norwegians, Britons, Danes, Turks, Germans, Croats and Chinese.

The first studies that related vitamin B12 to bone problems, such as BMD reduction and fractures, were performed in individuals with pernicious anemia. An increased risk of fractures was found among the study participants.[11,12]

Of the nine cross-sectional studies included in the present review, two found an association between vitamin B12 and BMD. Clarke et al.[9] were the first to study the association between B vitamins (dietary intake and serum levels) and BMD in patients with celiac disease aged over 20 years. A significant association was found only between serum levels of vitamin B12 and BMD in the hip and neck of the femur among men. No significant association between serum levels of vitamin B12 (or any other biomarker of B-complex vitamins) and BMD was observed in women. Based on the findings of this study, the authors highlight the protective role of vitamin B12 in bone health, especially in individuals with celiac disease. However, since the study was done exclusively in patients with celiac disease, it would not be possible to extrapolate these findings to a healthy population.

In a recent work by Bailey et al.,[13] serum levels of vitamin B12 were not directly associated with BMD, but the main functional indicator of this vitamin, methylmalonic acid, as well as serum homocysteine levels, were significantly associated with the risk of developing osteoporosis.

Holstein et al.[14] concluded that only markers of bone formation (osteocalcin) were increased in individuals who had higher serum levels of B-complex vitamins, including B12. However, in the same study, no significant differences were found in the trabecular thickness of individuals with high and low serum levels of vitamin B12, thus questioning the true role of vitamin B12 in the turnover of bone biomarkers. It should be noted that this study involved patients diagnosed with osteoarthritis. The bone properties of those suffering from this disease may differ from those of the healthy population.

In a study by Bozcurt et al.,[15] postmenopausal women with low BMD in the femoral neck and in the vertebrae had significantly lower serum levels of vitamin B12. Also, homocysteine levels were higher in women diagnosed with osteoporosis than in normal or osteopenic patients.

Baines et al.[16] stated that the risk of osteoporosis in postmenopausal women was associated with a reduced folate concentration and increased homocysteine concentration in the blood. Although there was no significant association between vitamin B12 and BMD in this study, reduced serum levels of vitamin B12, B6 and folate were associated with an increase in plasma homocysteine concentrations and adverse effects on bone health. Rumbak et al.,[17] in turn, stated that among healthy women, regardless of menopausal status, aged 45-65 years, there was insufficient evidence that vitamin B12, homocysteine or folate levels were related to BMD.

Physiologically, in humans, vitamin B12 acts as an essential cofactor for two enzymes: methionine synthase and L-methylmalonyl-CoA mutase, both directly and

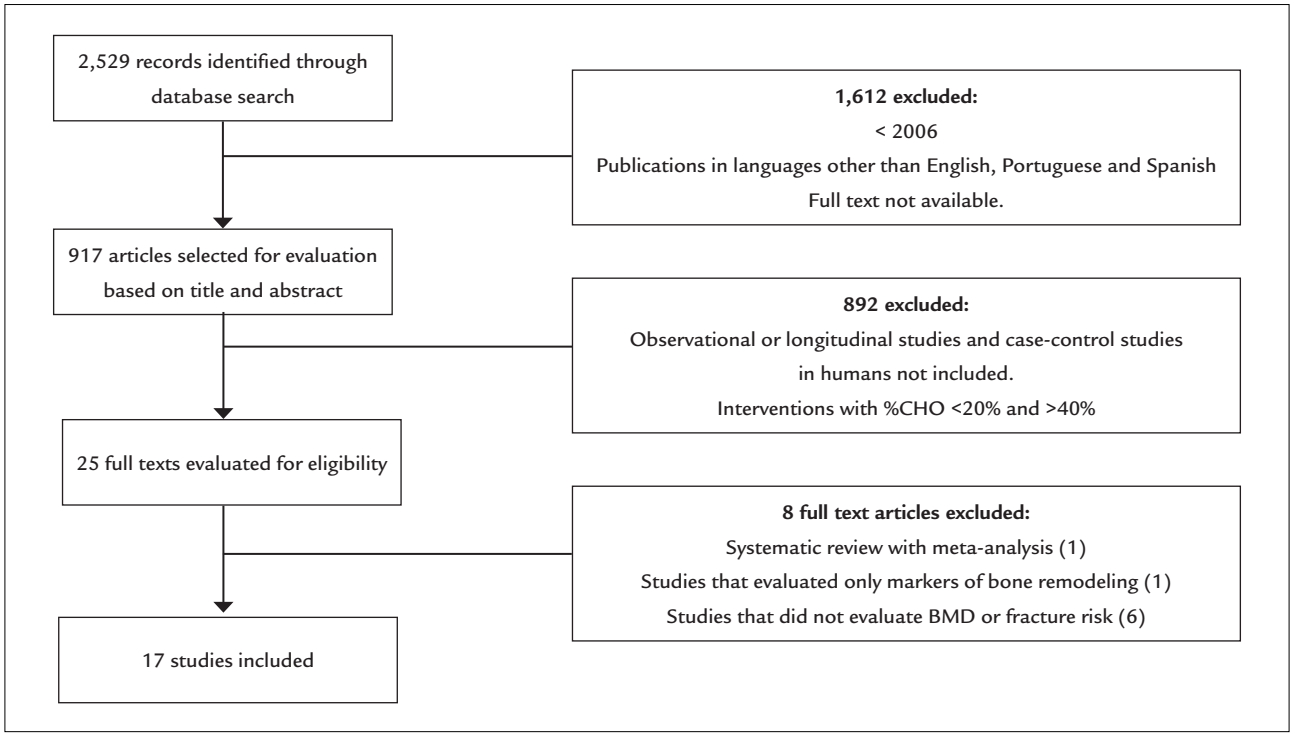

FIGURE 1 Flowchart of the studies evaluated for eligibility and included in the review.

CHART 1 Summary of all studies included in the final sample and their main results.

Authors and year	Design and participants	Variables	Intervention	Results Main	Quality of evidence (GRADE)
Epidemiological studies					
Baines et al., 2007[10]	Cross-sectional observational study 328 postmenopausal British women	Plasma homocysteine, serum levels of vitamins B6, B9 and B12, genotype of the MTHFR enzyme, and BMD	–	Folate levels were significantly associated with BMD (p=0.02), but vitamin B6 and B12 were not (p=0.91 and p=0.82, respectively)	Moderate
Gjesdal, et al., 2007[16]	Prospective longitudinal observational study 4,766 elderly Norwegian men and women, aged 65-67 years, for 13 years	Plasma levels of homocysteine, vitamins B9 and B12, polymorphism of genotypes 677C → T and 1298A → C MTHFR, and risk of fractures	–	Vitamin B12 and the MTHFR genotype were not associated with hip fractures Homocysteine increased the risk of fracture in both genders. Only among women there was an inverse association between folate levels and fracture risk	High
Yazdanpanah et al., 2007[18]	Prospective longitudinal observational study 5304 Dutch men and women aged 55 or over for 6 to 7 years	Association of dietary intake of vitamins B2, B6, B9 and B12 with BMD and risk of fractures	–	There was no association of vitamins B9 and B12 with BMD and the risk of fractures Positive association of vitamins B6 and B2 with BMD (β=0.09, p=1 × 10^{-8} β=0.06, p=0.002, respectively) Pyridoxine intake was inversely correlated with fracture risk	Low
Cagnacci et al., 2008[19]	Prospective longitudinal observational study 117 postmenopausal women, aged 54 years on average, for 5 years	Association between serum levels of vitamins B9 and B12, homocysteine and BMD	–	There was no association of vitamin B12 and homocysteine with BMD The rate of BMD variation over the 5 years correlated positively with serum folate levels (p=0.011)	Low
McLean et al., 2008[3]	Longitudinal observational study 1002 men and women with mean age of 75 years for 4 years	Plasma concentrations of vitamins B6, B9 and B12, and homocysteine with bone loss and risk of hip fracture in elderly men and women	–	Low concentrations of vitamins B12 and B6 were associated with increased risk of hip fracture. Lower plasma concentration of vitamin B6 was associated with greater bone loss	Moderate
Rejnmark et al., 2008[20]	Prospective longitudinal observational study 1,869 Danish women in perimenopause, aged between 43 and 58 years, for 10 years	Association of dietary intake and supplementation of vitamins B2, B9 and B12 with BMD and fracture risk		There was no positive association between B12, B9, B2 and BMD or fracture risk. At 5 years, cross-sectional analyzes indicated that folic acid intake correlated significantly with BMD	Low

(*continues*)

CHART 1 (Cont.) Summary of all studies included in the final sample and their main results.

Authors and year	Design and participants	Variables	Intervention	Results Main	Quality of evidence (GRADE)
Bozkurt et al., 2009[21]	Cross-sectional observational study 178 postmenopausal Turkish women	Relation of serum levels of homocysteine, vitamins B9 and B12 with BMD		Serum levels of vitamin B12, but not those of B9, were associated with osteoporosis in the lumbar spine and neck of the femur Homocysteine levels were found to be higher in women with osteoporosis compared to normal women or those with osteopenia	Moderate
Holstein et al., 2009[15]	Cross-sectional observational study 94 German women and men treated with hip arthroplasty	Association of serum levels of homocysteine, vitamins B6, B9 and B12 with OC (bone formation marker), TRAP (bone resorption marker), BMD and trabecular thickness	–	There was no positive association between vitamin B12, as well as the other vitamins analyzed, and BMD or homocysteine OC levels are lower in individuals with low levels of B-complex vitamins. Trabecular thickness is lower in individuals with low B9 concentrations.	Moderate
Halıloglu et al., 2010[14]	Cross-sectional observational study 120 postmenopausal women	Relation of serum levels of homocysteine, vitamins B9 and B12 with BMD and markers of bone remodeling (BAP and CTx)		There was no positive association of vitamins B12 and B9 with BMD and markers of bone remodeling. Homocysteine levels were higher in osteoporotic women but were not related to BMD	Moderate
Kakehasi et al., 2012[1]	Cross-sectional observational study 70 postmenopausal Brazilian women (50 to 79 years)	Plasma levels of vitamin B12 and BMD	–	There was no association between plasma levels of vitamin B12 and BMD (p=0.93)	Low
Rumbak et al., 2012[22]	Cross-sectional observational study 131 Croatian women aged between 45 and 65 years	Relation of serum levels of vitamin B12, plasma levels of homocysteine and red blood cells and serum levels of vitamin B9 to BMD	–	There was no association of vitamins B12 and B9 and homocysteine with BMD	Low
Dai et al., 2013[17]	Prospective longitudinal observational study 63154 Chinese women and men, aged between 45 and 74 years, for 13.8 years	Association of dietary intake of vitamins B1, B2, B3, B6, B9 and B12 with the risk of hip fractures		Inverse relationship between dietary intake of vitamin B6 and risk of hip fracture in older women but not in men There was no association between the dietary intake of B12 and the other B vitamins and the risk of fractures	Moderate

(*continues*)

CHART 1 (Cont.) Summary of all studies included in the final sample and their main results.

Authors and year	Design and participants	Variables	Intervention	Results Main	Quality of evidence (GRADE)
Bailey et al., 2015[23]	Cross-sectional observational study 2806 American women aged ≥ 50 years	Association of homocysteine and vitamin B12 with BMD and risk of osteoporosis	–	High levels of homocysteine and methyl malonic acid were associated with increased risk of osteoporosis in the lumbar spine. Vitamin B12 was not directly associated with BMD	High
Clarke at al, 2015[9]	Cross-sectional observational study 110 women and men over the age of 20 under treatment for celiac disease	Association of nutritional status of vitamins B2, B6, B9 and B12 with BMD	–	Only serum levels of vitamin B12 were significantly determining for femoral and hip BMD in men but not in women	Low
Bahtiri et al., 2015[13]	Cross-sectional observational study 139 postmenopausal women	Association of serum levels of homocysteine and vitamin B12 with BMD		Serum homocysteine levels were significantly higher in osteoporotic women than in the other groups and inversely correlated with lumbar spine and femoral neck BMD. Serum vitamin B12 levels were not associated with BMD	Low
Clinical trials					
Gommans et al., 2013[24]	Randomized, double-blind, placebo-controlled clinical trial 8,164 patients of both sexes with recent episodes and cerebrovascular events	Supplementation of B-complex vitamins would decrease the incidence of fractures in patients with cerebrovascular disease	Control: N=4075 Placebo treatment: N=4089, B complex vitamins: (folic acid: 2 mg, vitamin B6: 25 mg, vitamin B12 500 µg	Homocysteine levels were lower in the treatment group There was no association between treatment with B vitamins and fracture risk	High
van Wijngaarden et al., 2014[25]	Randomized, double-blind, placebo-controlled clinical trial. 2,919 Dutch male and female participants, aged ≥ 65 years and high concentrations of homocysteine (12-50 µmol/L), for 2 years	Combined vitamin B9 and B12 supplementation to prevent osteoporotic fractures	Control: daily doses of placebo + 600 IU of vitamin D3 Treatment: daily doses of 500 µg of vitamin B12 and 400 µg of vitamin B9 + 600 IU of vitamin D3	There was no significant reduction in the risk of fractures between groups In the treatment subgroup there was a reduction in fractures among participants over 80 years of age Homocysteine levels decreased significantly in the treatment group	High

BMD: Bone Mineral Density; MTHFR: Methylene Tetrahydrofolate Reductase; OC: Osteocyclin; TRAP – Tartrate Resistant Acid Phosphatase; BAP: Specific Bone Alkaline Phosphatase; CTx: Carboxyterminal Telopeptide Crosslinking.

indirectly involved in the metabolism of homocysteine (Hcy) and methyl malonic acid (MMA), two functional biomarkers of vitamin B12 deficiency.[26] Methylmalonic acid is a sensitive marker for vitamin B12 deficiency.[27]

Low levels of vitamin B12 in conjunction with folate and vitamin B6 deficiency are closely related to the metabolism of homocysteine (Hcy). Hyperhomocysteinemia is associated with increased markers of bone remodeling and, consequently, increased risk of fracture. Thus, hyperhomocysteinemia caused by deficiency of vitamin B12 as well as folate may be considered as new risk factors for osteoporosis related to the deficiency of these micronutrients.[18,28]

During perimenopause, there is an increase in the rate of remodeling and loss of bone mass at each cycle of remodeling, caused by the decrease in circulating levels of estrogen.[29] In addition, homocysteine levels, also linked to osteoporosis and fractures,[13,16,18] are higher in postmenopausal women,[30,31] and are inversely related to folate levels and possibly vitamin B12, two essential cofactors for remethylation to methionine. The other cross-sectional studies with postmenopausal women in our review found no association between serum or plasma levels of vitamin B12 and BMD.[1,22,24]

Six longitudinal studies with large population cohorts were included. Of these, only one found association of vitamin B12 with BMD. McLean et al.[3] concluded that low concentrations of vitamins B12 and B6 were associated with increased risk of hip fracture and the risk remained high even after adjusting for homocysteine and BMD. In that same study, individuals who were grouped as vitamin B12 deficient had a greater tendency to lose bone mass compared to the group of individuals who had higher vitamin B12 concentrations.

In agreement with these findings, the Framignham Osteoporosis study, developed with the participation of 2,576 American men and women, found a positive relation between serum vitamin B12 levels (< 148 pg/mL) and hip BMD in men and vertebral BMD in women. These results corroborate the information that vitamin B12 is a modifiable risk factor for the prevention of osteoporosis.[32] Morris et al.[33] also found evidence in which vitamin B12 status indicators (serum levels and methylmalonic acid) and serum homocysteine levels were associated with BMD in American men and women (n=1,550) over 55 years of age.

Neither Yazdanpanah et al.,[19] Rejnamark et al.[21] or Dai et al.[23] found any association between dietary intake of vitamin B12 and bone mineral density and/or risk of fractures. It should be noted that cobalamin levels were verified through food surveys (food frequency questionnaires and food registry). There was no analysis of serum levels of B vitamins to assess the actual nutritional status of vitamin B12. It is noteworthy that such a result of the dietary intake of this vitamin could be biased because it is self-reported.

A study by Gjesdal et al.[18] with a high level of evidence according to the GRADE score showed no association between plasma levels of vitamin B12 and the risk of hip fractures.

None of the two randomized, double-blind, placebo-controlled trials in our review found evidence of a positive effect of vitamin B12 (and other B-complex vitamins) supplementation on the risk or incidence of osteoporotic fractures. In both studies, serum homocysteine levels were lower in the groups receiving B complex supplementation (Chart 1), but there was no reduction in fracture risk between the control and treatment groups.[25,34]

The experimental trials are also contradictory regarding the action of vitamin B12 on bone tissue. The direct action of vitamin B12 on osteoblasts was observed, based on the functional and dose-dependent proliferative response found when two osteosarcoma cell lines were stimulated with cyanocobalamin.[6] While investigating the impact of vitamin B12 and folate deficiency on the healing of fractures in mice, although hyperhomocysteinemia was detected in this group, there were no changes in bone repair in the context of this nutritional alteration.[35] Taken together, the experimental data from these studies are of potential clinical relevance, despite using different experimental models.

In the randomized study of B-Probe intervention (2,919 participants ≥ 65 years) who underwent exploratory subgroup analyzes involving people over 80 years of age, combined vitamin B12 and folic acid supplementation had a beneficial effect in preventing osteoporotic fractures. However, another outcome found in this study was the association of treatment with the increased incidence of cancer, recommending caution regarding the supplementation of these vitamins in the elderly.[34]

Conclusion

The association between vitamin B12 levels, low bone mineral density and risk of fractures has been described in the literature, but the studies are quite heterogeneous and the results are contradictory. So far, the actual impact of vitamin B12 deficiency on bone health and the mechanisms associated with bone metabolism are not well established. Further studies are of paramount importance, especially in vulnerable groups such as postmenopausal women and elderly individuals, both greatly affected by vitamin deficiency. This also reinforces the relevance of

identifying individuals who may benefit from appropriate therapy intervention in time to reduce morbidity and mortality associated with decreased bone mineral density.

Resumo

Vitamina B12, densidade mineral óssea e risco de fraturas em adultos: uma revisão sistemática

Objetivo: Consolidar as informações disponíveis acerca dos efeitos da vitamina B12 sobre a densidade mineral óssea e o risco de fraturas, com destaque para ensaios clínicos, dados observacionais e longitudinais realizados com humanos.
Método: Foi realizada uma revisão sistemática da literatura dos últimos dez anos sobre o papel da vitamina B12 na densidade mineral óssea e no risco de fraturas em populações de todas as idades e para ambos os sexos, com busca de artigos nos bancos de dados eletrônicos: PubMed, Science Direct, Medline e SciELO. Como estratégia de busca de dados incluíram-se os descritores: B12 Vitamin and Bone Mineral Density e B12 Vitamin and Risk of Fractures. A qualidade das evidências dos artigos incluídos foi avaliada pelo sistema GRADE.
Resultados: Após a análise dos títulos e dos resumos dos artigos, a estratégia de busca resultou em 25 referências, das quais 17 artigos preencheram os critérios de elegibilidade. Esta revisão fornece evidências de que o papel da vitamina B12 sobre a densidade mineral óssea ou o risco de fraturas ainda precisa ser mais bem elucidado. As controvérsias encontram respaldo na heterogeneidade das metodologias utilizadas para o diagnóstico da vitamina B12 e também na variedade de populações presentes entre os estudos.
Conclusão: Ainda não está bem estabelecido o real impacto da deficiência de vitamina B12 na saúde dos ossos e sobre os mecanismos associados ao metabolismo ósseo. É de suma importância a realização de mais estudos esclarecedores, principalmente em grupos vulneráveis como as mulheres pós-menopausa e os idosos, grupos estes bastante afetados pela deficiência dessa vitamina.

Palavras-chave: saúde óssea, suplementação de vitamina B12, risco de fratura.

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CD20 role in pathophysiology of Hodgkin's disease

Marcelo Antônio Oliveira Santos[1]*, Marinus de Moraes Lima[2]

[1]Medical Student, Centro Universitário Maurício de Nassau and Scientific Director of the Epidemiology and Cardiology Research Group, Universidade Federal de Pernambuco, Recife, PE, Brazil
[2]MD Hematologist, Hospital do Câncer de Pernambuco, and Associated Professor of Medicine (Hematology), Centro Universitário Maurício de Nassau, Recife, CE. MSc in Pharmacology from Universidade Federal do Ceará, Fortaleza, CE, Brazil

Study conducted at Centro Universitário Maurício de Nassau, Recife, PE, Brazil

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***Correspondence:**
Centro Universitário Maurício de Nassau
Address: Rua Jonathas de Vasconcelos, 316, Boa Viagem
Recife, PE – Brazil
Postal code: 51021-140
marcelosantos.med@gmail.com

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Summary

Hodgkin's lymphoma (HL) is a tumor comprising non-malignant and malignant B-cells. Classical HL expresses CD15+ and CD30+ antigens, and 20 to 40% of patients are CD20+. This antigen is a ligand free protein present in B lymphocyte cells and its function is not well known. Some studies suggest that expression of CD20 may play a major role in Hodgkin's disease pathophysiology and may affect the patients' treatment prognosis, as well as relapse and refractory response. In the past few years, development of monoclonal anti-CD20 antibodies changed drastically the treatment for non-Hodgkin lymphomas in which CD20 is expressed. HL treatment is essentially composed of radiotherapy and chemotherapy; however, monoclonal anti-CD20 antibodies applicability is not well delimitated due to lack of information about clinical outcomes with anti-CD20 monotherapy or combined drug therapy using a classic regimen, as well as about CD20 pathophysiology mechanisms in B-cells tumors. The objective of our review is to discuss CD20 function in Hodgkin's lymphoma development, its influence on disease evolution and outcomes, as well as its effects on therapeutics and patients' prognostic.

Keywords: Hodgkin's disease, CD20 antigen, pathophysiology, rituximab, review.

Overview

Hodgkin's lymphoma (HL) is a tumor derived from B-cells composed by Hodgkin and Reed-Sternberg (RS) cells, which represent, respectively, mononucleated and multinucleated subtypes. In addition to these malignant cells, HL infiltrates comprise T cells, neutrophils, eosinophils, macrophages, fibroblast, plasma cells and mast cells.[1,2]

The malignant cells are referred to as giant cells, also denominated Hodgkin Reed-Sternberg (HRS) cells, and their origin remains controversial.[1] Some theories point to either a fusion of B and non-B cells or mutation in germinal-center cells and loss of B cell receptor expression.[1,3,4] HRS cells seem to be dependent on both extracellular signals and endogenous signals derived from its own genome mutation. Macrophages may play a role in tumor support.[2]

In all classical HL, tumor cells correlation with Epstein-Barr virus (EBV) infection occurs in about 20 to 40% of cases, but its role in pathophysiology is poorly understood.[4-6] Immunohistochemistry and gene expression profiling suggest that EBV influences the B-cell microenvironment.[2]

The classical presentation of HL is painless lymphadenopathy, usually cervical and/or supraclavicular. B symptoms as fever, unintentional loss of more than 10% of bodyweight over 6 months and fatigue are present in 25% of patients and have prognostic value.[5]

Histological subtypes of classical HL include nodular sclerosis, mixed cellularity, lymphocyte depletion and lymphocyte-rich lymphoma. Typical immunophenotype for HRS in classical HL expresses CD15, CD30 and CD20 (in about 20% of patients).[3,4] There is still another subtype of non-classical HL know as lymphocyte-predominant HL (LPHL), which is characterized by presence of histiocytic cells, expression of CD20, and lack of expression of CD15 and CD30, unlike the classical presentation of HL.[6]

First line of treatment for classical HL includes chemotherapy and radiotherapy. The most common drug therapy regimen is adriamycin/doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD).[7] Most patients with classical HL have full remission after initial treatment; however, about 34% of patients with advanced disease and 15% of those with early disease experience a relapse after treatment.[8]

CD20 expression and function

The CD20 antigen is a transmembrane highly hydrophobic glycosylated phosphoprotein of ~35 kd encoded in humans by the MS4A1 gene.[9] Its structure is showed in Figure 1. CD20 is found in healthy mature B cells as early as in the pro-B phase, as well as in chronic lymphocytic leukemia, LPHL and in some cases of classical HL.[4,10] It has a specific role in the regulation of differentiation and growth of B cells through cell activation from a resting state (G0) on to G1, as well as regulation of the cell cycle from the S phase to mitosis, step-by-step.[9] It is part of a cell-surface complex that regulates calcium transport and is able to initiate an intracellular signaling pathway through calcium influx.[10-12] Nevertheless, disruption of calcium channel gene encoding does not demonstrate critical effects either on B-cell development or immune response implementation.[12]

The presence of CD20 expression in lymphocyte-predominant HL and some presentations of classical HL support the hypothesis that HRS cells derive from germinal-center B cells at the centroblast stage. Genetic studies with mRNA and DNA demonstrate rearrangement of immunoglobulin genes and presence of mutations in variable regions of immunoglobulin heavy chain. Also, HRS cells present hypermutation in variable regions of the immunoglobulin heavy chain gene.[7] Other mechanisms involved are deregulated expression of B cell molecules, down-regulation of B cell transcription factors and epigenetic silencing of B cell genes. EBV has potential to express LMP1 and LMP2A, which mimic key signals of growth and survival of B cells.[13] These evidences could connect both hypothesis of origin of HRB cells and EBV role in HL pathophysiology.

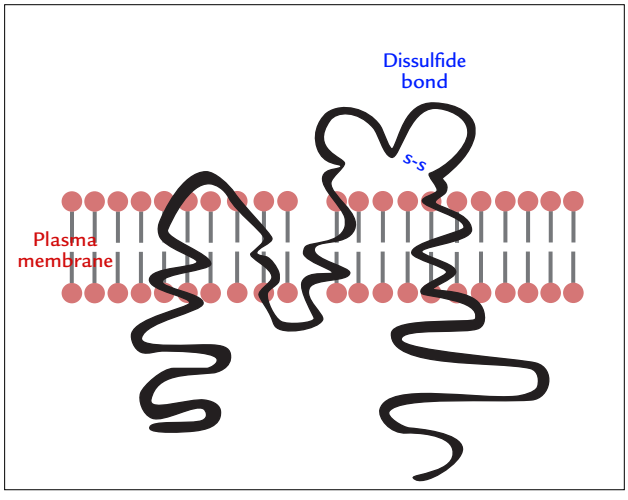

FIGURE 1 CD20 antigen structure. The disulfide bond is essential as binding site for rituximab, which is an anti-CD20 monoclonal antibody.

Anti-CD20 therapy

Anti-CD20 chemotherapy is vastly used in the treatment of non-Hodgkin tumors with a high expression of CD20 antigen. The most common drugs used as anti-CD20 agents are rituximab and obinutuzumab. These are monoclonal antibodies (mAb) that bind to the antigen ligand portion of the plasma membrane causing death of tumor cells by activation of the C1q cascade, leading to complement molecules deposition on cellular surface and apoptosis by complement-dependent cytotoxicity.[12]

Since in classical HL it is possible to find some cells expressing CD20 antigen, studies have associated gold standard chemotherapy, ABVD and anti-CD20 mAb to evaluate if this could improve treatment efficacy. In these studies, the point was not targeting the malignant HRS cells, but the clonotypic stem cell or the B cell harbored in the microenvironment, which is called "HRS cells off-targeting".[13,14] As a result, it could help to slow down solid infiltrated tumor growth, but it would not induce regression. In the other hand, there is some evidence suggesting that B lymphocytes may inhibit Th1-mediated anti-tumor responses.[13] Furthermore, evidences suggest that depleting normal B cells enhances antitumor response due to decreased interleukin-10 (IL-10) production by these cells.[14] All the pathways in which anti-CD20 mAb may perform direct or indirect control over the tumor population are represented in Figure 2.

Since LPHL expresses CD20, mAb could be used as a therapy option even as monotherapy. A group at Stanford University performed a clinical trial with rituximab that resulted in an overall response rate of 100% with limited toxicity effects. Association between chemotherapy and anti-CD20 as combined therapy is highly recommended for LPHL treatment[6] and for advanced classical HL or relapsed or refractory classical HL.[14]

CD20 relation to prognostic and clinical outcome

The role of CD20 as a prognostic factor remains controversial. CD20 has no known function that could imply in resistance to chemotherapy; however, it interferes in failure-free survival at 5 years, according to its expression.[11]

Greaves et al. demonstrated that no prognostic significance was found for CD20 expression, but nonfollicular CD20 expression influenced survival. Using 1,700 cells/mm^3 as a cut-off point, patients with high nonfollicular CD20 expression had overall survival improved (p=0.003) at 5 years (87% versus 70%), at 10 years (84% versus 52%) and at 20 years (76% versus 43%).[2]

Tzankov et al., in a study with 119 patients with classical HL followed for 12 years demonstrated that immunopheno-

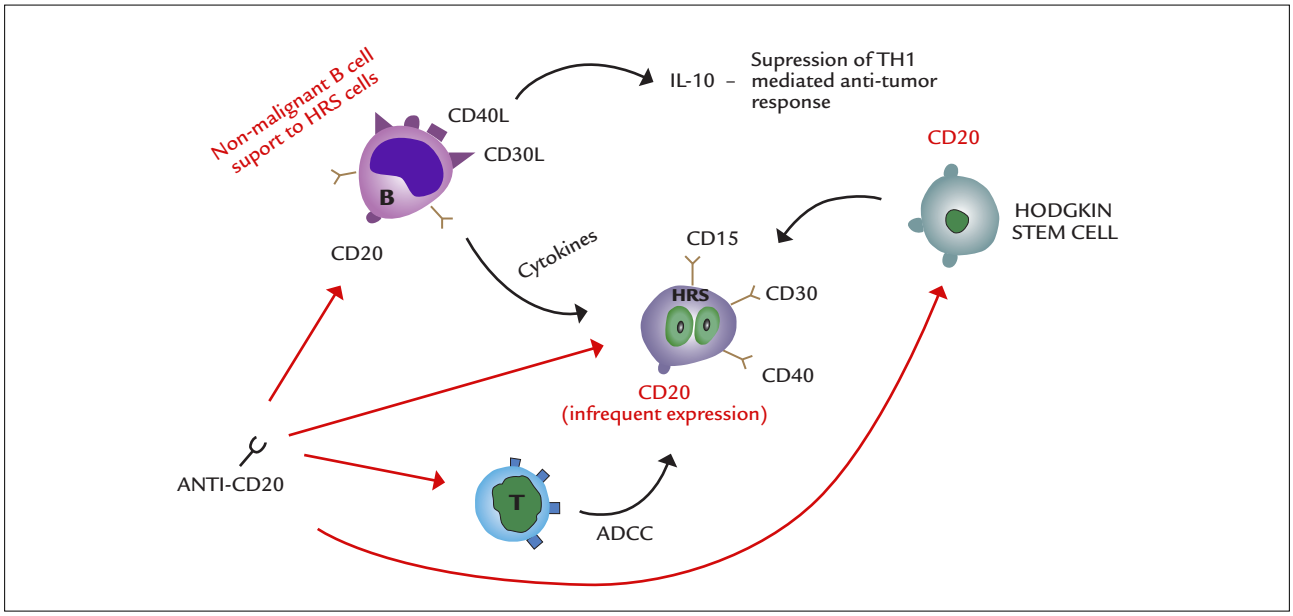

FIGURE 2 Main pathways where monoclonal anti-CD20 antibodies exert their function on Hodgkin's disease: a) inhibit Hodgkin stem cell proliferation directly, depleting new HRS cell formation; b) inhibit HBRS differentiation by binding CD20 ligand; c) activation of complement cascade through ADCC response mediated by T cells; d) depletion of support non-malignant B cells, which signals to RBS cells via cytokines and inhibit Th1 tumoral response by production of IL-10.

type CD30+/CD15±/CD20+ is associated with a favorable clinical outcome and CD20 was an independent positive prognostic factor (p=0.035). Failure-free survival was higher in CD20+ patients (286 months versus 202 months; p=0.022).[15]

Horvat et al. established a cut-off level of 25,000 molecules of equivalent soluble fluorochrome (MESF) of CD20 expression to determinate a predictive significance of better outcome with rituximab treatment. They found that patients with CD20 expression above the cut-off level had a significantly longer overall survival than those with lower levels (p=0.0383).[16]

Conclusion

CD20 antigen is a membrane protein without any known physiological ligand. The specific role it plays is not clear, but it has an essential function as regulator of B lymphocyte and germ-cell cell cycle, as well as on cellular growth and differentiation.

In Hodgkin's lymphoma, CD20 seems to be a marker for HRS cell origin and has a key importance in: suppression of Th1 antitumoral immune responses through IL-10 production; stimulation of non-malignant B lymphocytes through cytokine liberation, which supports HRS cell survival; proliferation of HRS cells by direct stimuli on Hodgkin stem cells.

Anti-CD20 therapy is a great modality of treatment, because of its potential to inhibit different stages in the physiopathogenesis of Hodgkin's disease. However, combined AVBD and rituximab (or another anti-CD20 mAb) seems to have a better result in advanced or relapsed/refractory classical HL. In early stages, gold standard therapies (chemo and radiotherapy), not combined with mAb, yield good results, except for LPHL, in which massive CD20 expression has a powerful response to mAb drugs even as monotherapy.

As a prognostic factor, CD20 expression is still controversial, but most studies have pointed out evidence that it could positively affect disease outcomes, and association between classic chemotherapy regimen and mAb drugs, especially rituximab, may improve overall survival and failure-free survival.

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Conflict of interest

The authors declare no conflict of interest.

Resumo

O papel do CD20 na fisiopatologia da doença de Hodgkin

O linfoma de Hodgkin (LH) é um tumor composto por células B não malignas e malignas. O LH clássico expressa antígenos CD15+ e CD30+, mas apenas cerca de 20 a 40% dos pacientes expressa também antígeno CD20. Este antígeno é uma proteína sem ligante presente nas células de linfócitos B cuja função não é bem conhecida. Alguns estudos sugerem que a expressão de CD20 pode ter um papel importante na fisiopatologia da doença de Hodgkin e pode afetar o prognóstico dos pacientes ao tratamento, bem como recaída e refratariedade. Nos últimos anos, o desenvolvimento de anticorpos monoclonais anti-CD20 mudou drasticamente o tratamento para linfomas não Hodgkin em que o CD20 é expresso. O tratamento do LH é composto essencialmente de radio e quimioterapia; no entanto, o espaço dos anticorpos monoclonais anti-CD20 não está bem delimitado em decorrência de: falta de informação sobre o desfecho clínico, seja na monoterapia com anti-CD20, seja na terapêutica combinada com o regime clássico; falta de informação sobre os mecanismos de fisiopatologia CD20 em tumores de células B. O objetivo desta revisão é discutir sobre a função do CD20 no desenvolvimento do linfoma de Hodgkin, sua influência na evolução da doença e os resultados, bem como os efeitos sobre terapêutica e prognóstico dos pacientes.

Palavras-chave: doença de Hodgkin, antígeno CD20, fisiopatologia, rituximab, revisão.

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Treatment of advanced melanoma – A changing landscape

Adriana Hepner[1], Alessandra Salgues[1], Carlos A. dos Anjos[1], Marina Sahade[1,2], Veridiana P. Camargo[1,2], Bernardo Garicochea[1], Alexander N. Shoushtari[3,4], Michael A. Postow[3,4], Gustavo S. Fernandes[1], Rodrigo R. Munhoz[1,2]*

[1]Oncology Center, Hospital Sírio-Libanês, São Paulo, SP, Brazil
[2]Medical Oncology Service, Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, SP, Brazil
[3]Melanoma and Immunotherapeutics Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[4]Weill Cornell Medical College, New York, NY, USA

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***Correspondence:**
Address: Rua Dona Adma Jafet, 91,
bloco A, 2° andar
São Paulo, SP – Brazil
Postal code: 01308-050
munhozrs@gmail.com

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Summary

Following decades of relative ostracism, advances in the treatment of melanoma have brought a new reality for patients, physicians and researchers. While antibodies targeting molecules involved in the modulation of the interaction between melanoma and immune cells changed the meaning of the term "cancer immunotherapy," a better characterization of the molecular aberrations involved in melanoma carcinogenesis prompted the development of inhibitors of the mitogen-activated protein kinase pathway (MAPK) that also led to significant improvements both in response rates and survival. As a result, new drugs have been approved for clinical use in the United States and Europe, including the immune-checkpoint blockers ipilmumab, pembrolizumab and nivolumab, the oncolytic herpesvirus talimogene laherparepvec, and the targeted-agents vemurafenib, dabrafenib, cobimetinib and trametinib. In this article, we review the results of studies that brought new approaches to the bedside and discuss how these developments are being incorporated into the care of patients in Brazil.

Keywords: melanoma, anti-PD1, anti-CTLA4, BRAF, MEK.

Introduction

Although it represents only 1% of all cutaneous malignancies, melanoma is still a challenge to public health due to its high metastatic potential and mortality.[1] Over the past decades, the number of cases of melanoma has increased dramatically, faster than any other type of cancer.[2] In the United States, 76,380 new cases and more than 10,000 deaths related to melanoma are expected in 2016, accounting for the vast majority of skin cancer deaths.[1] In Latin America, data regarding the incidence and prevalence of this disease are scarce,[3] and 5,670 new cases are estimated in Brazil in 2016 according to the Instituto Nacional do Câncer (Inca).[4]

While patients with early diagnosis have 5-year survival rates around 90%, historically, this number decreases to 10% in patients with advanced melanoma, with a median survival of 6 to 12 months.[1,2]

Even though surgery and radiotherapy may have a role in the management of metastatic disease in selected situations, systemic therapy is the mainstay of treatment for most patients.[5] For over three decades, dacarbazine was the most commonly used cytotoxic agent, resulting in objective responses in approximately 10% of the cases and with an arguable impact on overall survival, with approximately 20-25% of the patients alive at 12 months.[2,5] Other agents, such as vinblastine, cisplatin/carboplatin and taxanes, either used in combinations or in monotherapy, showed only short-lived benefits.[5] Non-selective forms of immunotherapy, including high dose interleukin-2 (IL-2) or biochemotherapy, had their widespread use hampered by significant toxicity and objective (albeit durable and potentially curative) responses limited to a small proportion of individuals, despite serving as a proof-of-concept that melanoma cells could be controlled or eradicated by the immune system.[6]

In the past decades, however, progress has been made in the understanding of both melanoma pathogenesis and the interaction between cancer and immune cells. The demonstration of aberrant activation of the mitogen-activated protein kinase pathway (MAPK) paved the way for the development of so-called targeted therapies,[7] including the currently available V-Raf Murine Sarcoma

Viral Oncogene Homolog B (BRAF) and mitogen-activated protein kinases enzyme (MEK) inhibitors (Figure 1).[8,9] In parallel, the manipulation of the immune system by blocking ligands and receptors that act as regulators of the T cell activation, the so-called immune checkpoints, exemplified by the cytotoxic T lymphocyte associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD1) and its ligand (PD-L1) have become important strategies to control advanced tumors (Figure 2). As a result, objective responses can be seen in more than 50% of the cases and the 25-35% probability of a patient being alive has transitioned from 12 months in the era of conventional chemotherapy to 48-60 months.[10]

While survival of patients with advanced melanoma has been considerably improved over a relatively short interval (Figure 3), the near future probably holds even more consistent advances. In this article, we will review the results of studies that led to a change in the management of patients with advanced melanoma and discuss how these new agents are being incorporated into treatment algorithms.

Manipulating signaling pathways in melanoma – The use of BRAF and MEK inhibitors

Activating mutations of the BRAF gene, which is an upstream component of the growth-promoting MAPK pathway (Figure 1), are found in approximately 40 to 60% of patients with metastatic melanoma.[7,9] In about 75 to 80% of the cases, the mutation occurs in the region that encodes the kinase domain and consists of the substitution of glutamic acid for valine at amino acid 600 (the V600E muta-

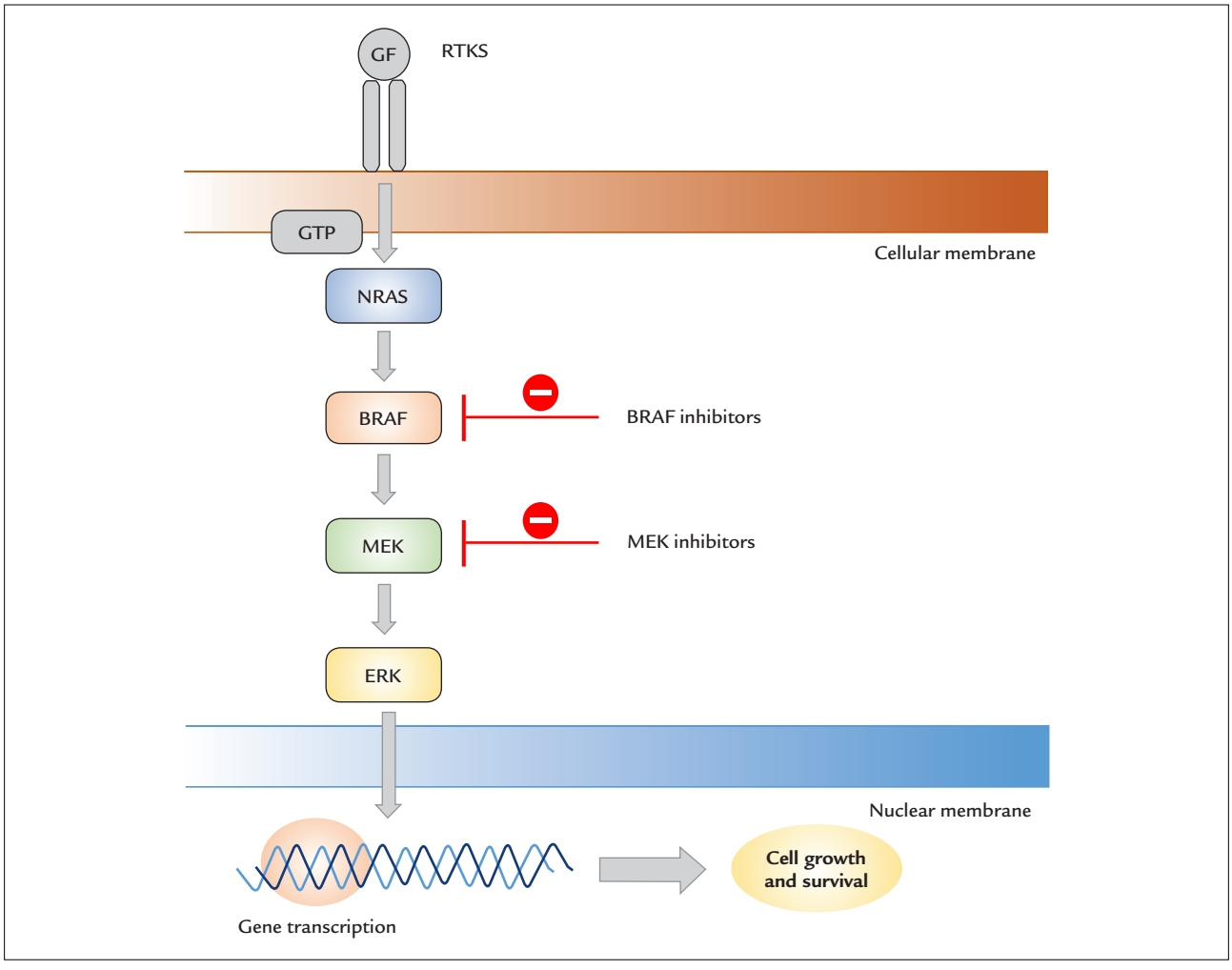

FIGURE 1 The MAPK pathway and the role of BRAF and MEK inhibitors.

RTKS: receptor tyrosine kinases; GF: growth factor; GTP: guanosine triphosphate; NRAS: neuroblastoma RAS viral oncogene homolog; BRAF: V-Raf murine sarcoma viral oncogene homolog B; MEK: mitogen-activated protein kinases enzyme; ERK: extracellular signal-regulated kinase.

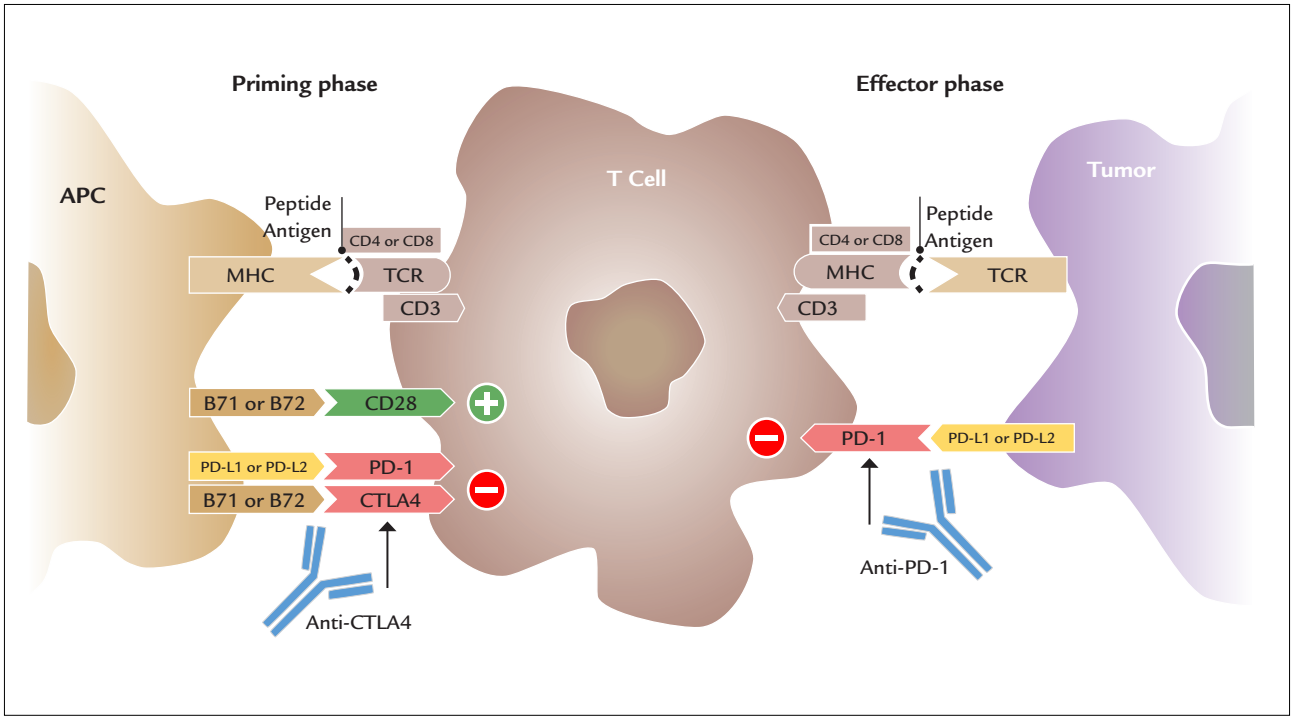

FIGURE 2 CTLA-4 and PD-1/PD-L1 in the immune synapse.

MHC: major histocompatibility complex; TCR: T cell receptor; CD: cluster of differentiation; B7.1 and B7.2 proteins; CTLA4: cytotoxic T lymphocyte associated antigen 4; PD1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PD-L2: programmed death-ligand 2.

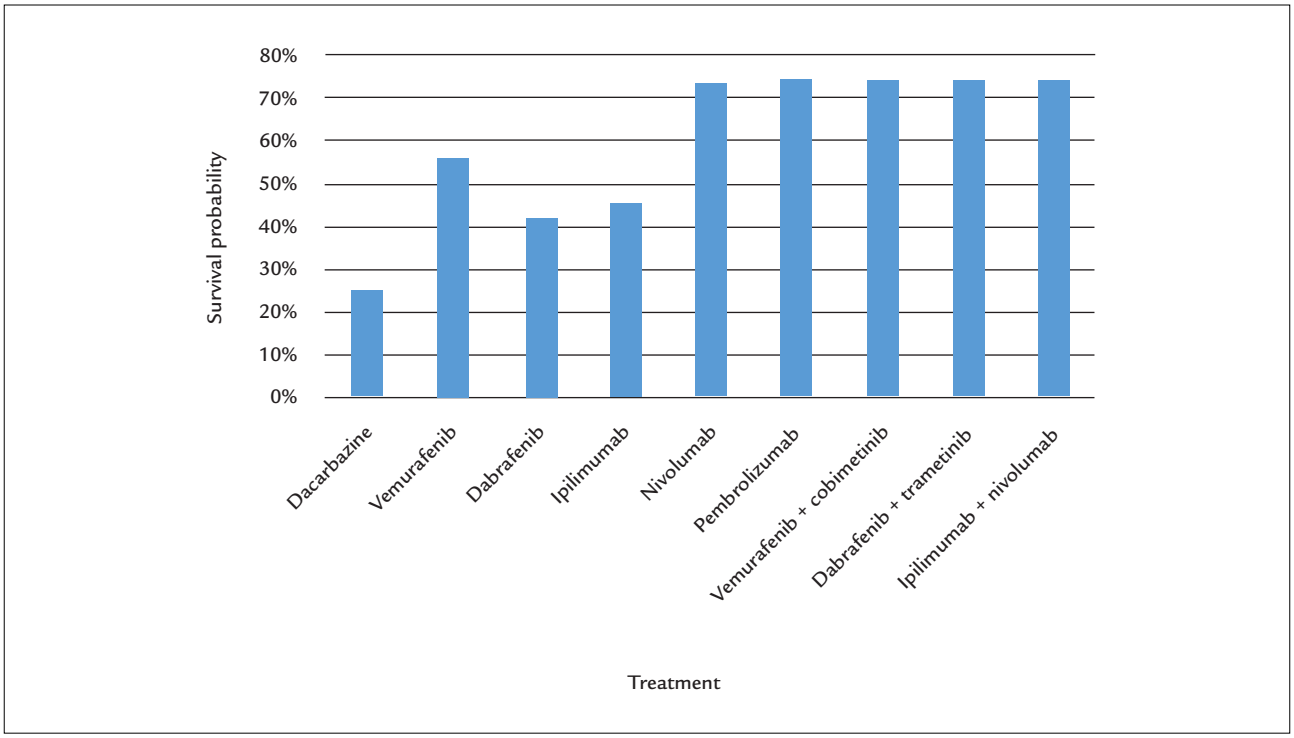

FIGURE 3 12-month overall survival rates across different studies.

tion).[11] In another 20% of the tumors harboring a BRAF mutation, an alternate substitution of lysine for valine occurs (the V600K mutation).[9,11] Therapeutic manipulation of the aberrantly activated MAPK pathway as a result of those specific mutations has been proven to be an important approach for the treatment of advanced melanoma patients.

The first investigated anti-BRAF agent was the multikinase inhibitor sorafenib, which failed to show meaningful clinical activity as a single agent or in combination with chemotherapy.[12] Since then, vemurafenib and dabrafenib, more potent and selective BRAF inhibitors (BRAFi), were developed. The clinical efficacy of orally-administered BRAF inhibitor vemurafenib in patients with BRAF V600-mutated melanoma has been established in the phase 3 BRIM-3 trial, in which 675 patients with metastatic/unresectable disease were randomly assigned to either vemurafenib (960 mg twice daily) or dacarbazine (1,000 mg/m^2 given intravenously every three weeks). The updated objective response rate (ORR) confirmed by an independent review was 47% among patients treated with vemurafenib compared to 9% in the dacarbazine arm.[13] After a median follow-up of 12.5 months, vemurafenib resulted in a statistically significant improvement in overall survival (OS) (13.6 vs. 9.7 months; HR 0.70, 95CI 0.57-0.87; p=0.0008), with 56% of the patients alive at 12 months. Progression-free survival (PFS) was also significantly prolonged (6.9 vs. 1.6 months; HR 0.38, 95CI 0.32-0.46; p<0.0001).[13]

Dabrafenib also demonstrated significant activity in advanced melanoma and has been approved for clinical use. In a phase 3 trial, dabrafenib (150 mg taken orally twice daily) was compared to dacarbazine (1,000 mg/m^2 given intravenously every three weeks) in 250 patients with unresectable stage III or stage IV melanoma harboring a BRAF V600E mutation. Dabrafenib significantly prolonged the median PFS (which was the primary endpoint of the study) (5.1 vs. 2.7 months; HR 0.33; 95CI 0.20-0.54; p<0.0001), resulting in an ORR of 50% versus 6%.[14] OS was updated following a median follow-up of 13 to 15 months; while the difference in survival was not statistically significant, crossover was permitted between the two groups and occurred in 57 % of the patients initially treated with dacarbazine.[15]

The most frequent toxicities associated with BRAF inhibition were dermatologic (rash, photosensitivity and hyperkeratosis), arthralgia, fatigue, nausea and diarrhea, although differences in the toxicity profile of dabrafenib and vemurafenib occur. Cutaneous squamous cell carcinomas (SCC) or keratoacanthoma may develop in up to 25% of patients treated with vemurafenib.[13] Conversely, febrile reactions/pyrexia and severe hyperglycemia are more frequent with dabrafenib and require attention.[14,15]

Nevertheless, despite initial response, secondary resistance often limits the benefit of single-agent BRAF inhibitors, and underlying mechanisms involve reactivation of the MAPK pathway in almost 70% of the cases.[16] Hence, blockade of an immediate downstream signaling component in the MAPK pathway, MEK, could potentially result in significant antitumor effect. Initially tested as single agent for patients who had not received prior treatment with a BRAFi, trametinib, a selective blocker of MEK1 and MEK2, was approved based on a survival advantage in the phase 3 METRIC study (6-month survival rate 81% vs. 67%; 95CI 0.32-0.92; p=0.01). Objective responses, despite comparing favorably to dacarbazine (ORR 8%), occurred in only 22% of the patients.[17] The rationale for the development of trials addressing dual MAPK pathway blockade was based on the possibility of minimizing the toxicity associated with paradoxical activation of the MAPK pathway in the setting of BRAF inhibition, delaying treatment resistance and enhancing the antitumor effect. Based on early evidence that simultaneous, rather than sequential administration, could represent the optimal approach, subsequent phase 3 studies evaluated BRAFi (vemurafenib or dabrafenib) given concurrently with MEKi (cobimetinib or trametinib).[18,19]

The combination dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) was compared to single-agent dabrafenib or vemurafenib in the COMBI-d and COMBI-v trials, respectively.[18,20,21] Both studies have consistently shown increased response rates, and gains in PFS and OS favoring the use of the combination (Table 1), with updated 3-year survival rates of 44 and 45%.[22,23] In addition, the two trials confirmed that the incidences of cutaneous squamous cell carcinoma and keratoacanthoma were significantly decreased with the combination treatment by almost one third.[18,20,21] In the coBRIM trial, another BRAFi/MEKi association was studied in 495 patients with previously untreated, BRAF-mutated, advanced melanoma. In this phase 3 trial, patients were randomly assigned to vemurafenib (960 mg given twice daily continuously, on days 1 to 28) plus cobimetinib (60 mg daily on days 1 to 21, followed by a 7-day interval) in 28-day cycles, or to vemurafenib plus placebo. Median PFS, the primary endpoint of the study, was significantly prolonged in the combination group (median PFS 12.3 vs. 7.2 months, HR 0.58; 95CI 0.46-0.72; p<0.0001). More importantly, combined blockade resulted in gains in overall survival (22.3 vs. 17.4 months, HR 0.70; 95CI 0.55-0.90; p=0.005) and ORR (70% vs. 50%).[19] These results have led to regulatory approvals of the aforementioned combinations.

TABLE 1 Selected published clinical trials.*

Study	Author, year	Phase	N	Intervention	ORR (%)	mPFS (months)	Survival data
Immune-checkpoint blockade							
-	Hodi, 2010	3	676	Ipilimumab 3 mg/kg vs. Ipilimumab 3 mg/kg+gp 100 vs. gp100	10.9 x 5.7 x 1.5	2.86 x 2.76 x 2.76	mOS 10.1 mo x 10.0 mo x 6.4 mo
-	Robert, 2011	3	502	Ipilimumab 10 mg/kg+DTIC vs. DTIC	15.2 x 10.6	Not available	5y OS 18.2% x 8.8%
KEYNOTE 001	Ribas, 2016	1	655	Pembrolizumab	33	5,2	mOS 23 mo
KEYNOTE 002	Ribas, 2015	3	540	Pembrolizumab 2 mg/kg vs. Pembrolizumab 10 mg/kg vs. CT	38 x 46 x 8	4.2 x 5.6 x 2.6	NR
KEYNOTE 006	Robert, 2015	3	834	Pembrolizumab q 14d x Pembrolizumab q 21d x Ipilimumab	33.7 x 32.9 x 11.9	5.5 x 4.1 x 2.8	2y OS 55% x 55% x43%
-	Topalian, 2014	1	107	Nivolumab	31	3,7	mOS 16.8 mo
CheckMate 037	Weber, 2015	3	405	Nivolumab vs. CT	32 x 5	4.7 x 4.2	NR
CheckMate 066	Robert, 2015	3	418	Nivolumab vs. Dacarbazine	40 x 13.9	5.1 x 2.2	NR x 10.8 mo
CheckMate 069	Postow, 2015	2	142	Ipilimumab/Nivolumab vs. Ipilimumab	61 x 11	NR x 4.4	NR
CheckMate 067	Larkin, 2015	3	945	Ipilimumab/Nivolumab vs. Nivolumab vs. Ipilimumab	57.6 x 43.7 x 19	11.5 x 6.9 x 2.9	NR
MAPK pathway blockade							
BRIM 3	McArthur, 2014	3	675	Vemurafenib vs. Dacarbazine	48 x 5	6.9 x 1.6	mOS 13.6 mo x 9.7 mo
BREAK 3	Hauschild, 2012	3	250	Dabrafenib vs. Dacarbazine	50 x 6	5.1 x 2.7	NR
METRIC	Flaherty, 2012	3	322	Trametinib vs. CT	22 x 8	4.8 x 1.5	6 mo OS 81% x 67%
coBRIM	Ascierto, 2016	3	495	Vemurafenib + Cobimetinib vs. Vemurafenib	70 x 50	12.3 x 7.2	mOS 22.3 mo x 17.4 mo
COMBI-v	Robert, 2015	3	704	Dabrafenib + Trametinib vs. Vemurafenib	64 x 51	11.4 x 7.3	mOS 25.6 mo x 18.3 mo
COMBI-d	Long, 2015	3	423	Dabrafenib + Trametinib vs. Dabrafenib	69 x 53	11.0 x 8.8	mOS 25.1 mo x 18.7 mo

*Data extracted from published manuscripts.
mo: months; N: number of patients enrolled; ORR: objective response rate; mPFS: median progression-free survival; OS: overall survival data; CT: chemotherapy; DTIC: dacarbazine; NR: not reached.

Besides alterations involving BRAF, other melanoma gene mutations have been identified, which can also offer significant therapeutic insights. NRAS, an upstream effector of the MAP and PI3K pathways, is mutated in about 20% of the cases.[9,24] Other less common mutations occur in NF1 and c-KIT.[7,9] Initial results of a phase 3 trial comparing binimetinib, a MEKi, to dacarbazine in patients with advanced NRAS mutation tumors, showed an increase in PFS (median PFS 2.8 vs. 1.5 months; HR 0.62; 95CI 0.47-0.80; p<0.001). In this trial, there was no significant difference in overall survival (11 vs. 10 months), although survival data were still immature.[24] Although infrequent, c-KIT mutations can be found in acral and mucosal melanomas; in several case reports, a rapid, but transient response was achieved with imatinib mesylate, a small molecule inhibitor of KIT and other tyrosine kinases.[25,26] These observations were confirmed in subsequent prospective, non-comparative phase 2 studies, in which imatinib resulted in response rates of approximately 20%, despite relatively short PFS intervals ranging from 2.8 to 3.7 months.[27,28] Taken together, although the benefit of targeted approaches in patients with melanoma

harboring non-BRAF mutations has been limited, these results serve as a proof of concept for future molecularly-driven treatment strategies.

Using the immune system to fight melanoma – The growing field of immunotherapy

Using the immune system to fight cancer has evolved from a "future perspective" to one of the most practice-changing breakthroughs in oncology in recent years, yielding the possibility of long-term clinical benefit and prolonged survival. Indeed, the development of monoclonal antibodies targeting co-receptors involved in escape mechanisms has shown exceptional results for the treatment of advanced melanoma.

The immune system can be divided into innate and adaptive immunity. The innate immune system is the initial defense against foreign antigens, which includes dendritic cells (DC), macrophages, neutrophils, basophils, eosinophils, natural killer cells (NK) and mast cells. These cells, once activated, release stimulatory cytokines that recruit additional elements of the immune response. The adaptive immune system is an antigen-specific response, dependent mainly on the antigen presenting cells (APCs), which process antigens and present them via mixed histocompatibility complex (MHC) class I and II molecules, to T cells through the T-cell receptor (TCR). Activated T cells, then differentiate into distinct functional phenotypes (exemplified per Th1, Th2 and Tregs), release cytokines and recruit effector cells, producing the T-cell-mediated response.[29]

Recently, ligands and co-receptors expressed on T cells, APC and tumor cells have been identified as potential targets for immunotherapy, due to their critical role as immune suppressors at the tumor microenvironment. These ligands and receptors, because of their function as regulators of the T cell activation and tolerance, have been termed "immune checkpoints" (Figure 2). Monoclonal antibodies directed against CTLA-4 and PD-1 and its ligand (PD-L1) illustrate successful approaches for the treatment of advanced melanoma.[30]

In the priming phase or early phase of immune activation, the CTLA-4 receptor is induced on T lymphocytes as negative regulator of T cell response, competing with CD28 for binding to B7 molecule on the antigen presenting cells.[30] Ipilimumab, a monoclonal antibody that targets CTL4, was the first checkpoint inhibitor approved for clinical use in metastatic melanoma patients in 2011, based on survival gains in both first and second-line settings and response rates of 10-15%.[31] In the largest combined analysis of 1,861 patients treated with ipilimumab in phase 2 and 3 trials, a plateau seen in the survival curve confirmed the possibility of sustained benefits, with 21% of those patients surviving beyond three years.[32] Of note, a recently-presented randomized trial comparing ipilimumab at 3 mg/kg versus 10 mg/kg demonstrated an improvement in overall survival in the group of patients treated with higher doses (mOS 15.7 m vs. 11.5 m; HR 0.84; 95CI 0.70-0.99; p=0.04), accompanied by an increase in the rates of grade 3-5 treatment-related toxicities (34.3% vs. 18.5%).[33]

Despite this initial success with CTLA-4 blockade, even more compelling results were seen with anti-PD1 agents pembrolizumab and nivolumab. The PD-1 receptor is expressed by activated T cells and binds to its ligands PD-L1 and PD-L2, resulting in abrogation of T cell-mediated responses and preventing the recognition and killing by cytotoxic cells.[30]

In phase 1 trials, ORR around 30% and median OS of 23 months and 16.8 months were seen with pembrolizumab and nivolumab, respectively.[34,35] These agents were initially approved for patients following progression on ipilimumab (and a BRAF inhibitor, in patients with melanoma harboring a BRAF mutation) based on the results of trials that demonstrated both favorable efficacy in comparison to cytotoxic chemotherapy. In the KEYNOTE 002 randomized phase 2 trial, 540 patients with ipilimumab-refractory disease were randomly assigned to pembrolizumab (2 mg/kg every three weeks), pembrolizumab (10 mg/kg every three weeks) or chemotherapy. The six-month progression-free rate, the primary endpoint of the study, was 34, 38, and 16%, respectively (pembrolizumab 2 mg/kg versus chemotherapy; HR 0.57; 95CI 0.45-0.73; p<0.0001; and pembrolizumab 10 mg/kg versus chemotherapy HR 0.50, 95CI 0.39-0.64; p<0.0001), with objective responses occurring in 21-26% of the cases.[36] Similarly, in the phase 3 CheckMate 037 study, 405 previously treated patients received either nivolumab or investigator's choice of chemotherapy. Objective responses were reported in 31.7% in the nivolumab group vs. 10.6% in the chemotherapy group, and less toxic effects were seen with nivolumab (rate of grade 3-4 adverse events: 9% vs. 32%).[37]

In the first-line setting, both pembrolizumab and nivolumab showed superiority in terms of efficacy and tolerability when compared to ipilimumab, and were rapidly incorporated into clinical practice for treatment-naïve patients. In the phase III KEYNOTE-006 trial, 834 patients received either pembrolizumab 10 mg/kg every two weeks, pembrolizumab 10 mg/kg every three weeks until disease progression or ipilimumab 3 mg/kg every three weeks for four doses. The trial demonstrated sig-

nificant improvement in 2-year survival rates for both pembrolizumab regimens versus ipilimumab (55% in both pembrolizumab arms vs. 43%; HR 0.68; 95CI 0.53-0.87; p=0.0008 and HR 0.68; 95CI 0.53-0.87; p=0.0008 for 2 week and 3 week schedules compared to ipilimumab, respectively). The 6-month PFS rate, a co-primary endpoint, was 47.3; 46.4 and 26.5% respectively, with a HR for disease progression for pembrolizumab versus ipilimumab of 0.58; p<0.001 for both 2 and 3-week regimens. ORR were 37, 36 and 13% for the same treatment arms.[38,39]

The longest follow-up data of melanoma patients on treatment with anti-PD1 therapy comes from the phase 1/2 dose escalation expansion cohort of nivolumab in 107 heavily pretreated advanced melanoma patients. The median overall survival was 17 months, but treated patients achieved an impressive 5-year survival rate of 34%.[35]

The combined administration of an anti-CTLA-4 and anti-PD1 antibodies was tested in a randomized phase 2 trial that accrued 142 treatment-naïve patients, with approximately 75% of BRAF "wild-type" (wt) tumors. Despite the increased incidence of grade 3 or 4 adverse events (54% vs. 24%), the combination of nivolumab and ipilimumab resulted in higher ORR in the BRAFwt population when compared to ipilimumab monotherapy, which was the primary endpoint (ORR in BRAFwt patients: 60% vs. 11%).[40,41] The hypothesis that combined immune-checkpoint blockade could result in improved outcomes was further tested in the CheckMate 067 phase 3 trial. In this study, 945 patients were randomized to receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg for four doses followed by nivolumab, nivolumab 3 mg/kg plus placebo or ipilimumab 3 mg/kg plus placebo. PFS and overall survival were the co-primary endpoints of the trial and the results were updated after a median follow-up of 18 months. The ORR was 19% for ipilimumab monotherapy compared with 57.6% for nivolumab plus ipilimumab (p<0.001) and 43.7% for nivolumab alone (p<0.001). The combination therapy was associated with a 58% relative reduction in the risk of disease progression when compared to ipilimumab alone (HR 0.42; 99.5CI 0.31-0.57; p<0.001); similarly, nivolumab monotherapy resulted in a relative risk reduction of 45% also compared with ipilimumab alone (HR 0.55; 99.5CI 0.43-0.76; p<0.001).[41] Although the study was not powered for the direct comparison of nivolumab plus ipilimumab vs. nivolumab, an exploratory analysis showed that combination therapy reduced the risk for progression by 24% compared with nivolumab monotherapy (HR 0.76; 95CI 0.60-0.92).[41,42] Grade 3 and 4 adverse events for the combination, nivolumab alone, and ipilimumab alone were 55, 16, and 27%, respectively and treatment discontinuation due to treatment toxicities were more frequent in the combination arm.[42] Longer follow-up and mature overall survival data are expected. Due to the high incidence of immune-mediated adverse events demonstrated in the setting of combined blockade, alternative treatment regimens are being investigated in an attempt to enhance the tolerability. As an example, the phase 1 KEYNOTE-029 trial combined "low dose" ipilimumab (1 mg/kg given every 3 weeks for 4 doses) with a standard dose of pembrolizumab (2 mg/kg given every 3 weeks); ORR in this study was 57%, and grade 3-4 toxicities occurred in 42% of the cases.[43]

While PD-1 blockers, either in monotherapy or in combination with ipilimumab, became the standard of care for patients with BRAFwt tumors, the best treatment to be given upfront remains to be determined for those with tumors harboring a BRAF mutation, and results of ongoing studies looking at the best sequence and combinations of BRAF/MEK inhibition and immune-checkpoint blockade are eagerly awaited, as discussed below.[44]

Future perspectives

The increasing understanding of the underlying immunologic mechanisms of tumorigenesis and tumor evasion has prompted the evaluation of additional receptors involved in the T cell response. Studies of agonist antibodies targeting the immune-stimulatory receptors OX40, CD27, CD137 and GITR are awaited. Similarly, promising results have been suggested by early-phase clinical trials investigating molecules targeting the inhibitory co-receptors LAG-3 and TIM-3, as well as indeoleamine 2,3-dioxygenase (IDO) inhibition, a tryptophan-metabolizing enzyme involved in immunosuppressive mechanisms.[45]

Another promising approach already approved for clinical use in the USA and Europe is talimogene laherparepvec (T-VEC), an oncolytic attenuated herpes virus designed to selectively replicate and lyse tumor cells and overexpress granulocyte macrophage colony-stimulating factor (GM-CSF), resulting in induction of tumor-specific T cell response. In a phase 3 trial with patients with stage IIIB-IV melanoma, intratumoral injections of T-VEC produced an improved durable response rate compared to intratumoral GM-CSF alone (16.3% vs. 2.1%; OR 8.9; p<0.001), leading to its approval by regulatory agencies.[46] Phase 1b studies tested combinations of T-VEC with systemic immunotherapies, revealing a safe profile and interesting results. T-VEC in association with ipilimumab produced an ORR of 50%, with 44% of the patients having durable responses of at least 6 months; the 18-month overall survival was 67%.[47] The combination of TVEC with

pembrolizumab achieved an ORR of 57.1%, with 23.8% having confirmed complete responses. This strategy is now being further evaluated in an ongoing phase 3 clinical trial (MASTERKEY265; NCT02263508).[48]

Another attractive approach involves combining anti-PD1/PDL-1 molecules with BRAF/MEK inhibitors. In a phase 1 dose-escalation study, patients received atezolizumab, an anti-PD-L1 agent, in association with vemurafenib. The trial demonstrated a manageable toxicity profile and promising antitumor activity, with an ORR of 76% and a median PFS of 10.9 months.[49] The triplet combination of pembrolizumab, dabrafenib and trametinib has also been shown to be feasible: although 67% of the patients experienced grade 3-4 adverse events, leading to discontinuation of treatment in 33% of the cases, this combination resulted in an ORR of 60%.[50]

Current treatment options for patients with advanced melanoma in Brazil – Same disease, different perspectives

Advances in the past 5 years have widened the treatment possibilities for advanced melanoma patients, with an undeniable impact on overall survival (Figure 3 and Table 1). In the USA and Europe, those with BRAF-mutated tumors can be treated, in the first line setting, with the anti-BRAF/MEK combinations vemurafenib/cobimetinib or dabrafenib/trametinib. Also, as mentioned before, immunotherapy with nivolumab, pembrolizumab, ipilimumab/nivolumab, ipilimumab or T-VEC is approved and available.

In Brazil, while nivolumab and pembrolizumab have been approved in 2016, the combination of ipilimumab and nivolumab has not been incorporated to date, and ipilimumab has been approved only for patients who have failed a first-line therapy. Similarly, for molecularly-selected patients, additional options include dabrafenib used as single-agent, vemurafenib as single agent or the combination of vemurafenib and cobimetinib. Quite concerning, however, is the fact that none of the mentioned approved therapies is available in the public health system, in which treatment still relies on standard cytotoxic chemotherapies.

If it is true that predictive and prognostic biomarkers can help in a better patient selection in a setting of skyrocketing costs associated with cancer care and often limiting toxicities, the only validated biomarker ready for unrestricted clinical use and that can direct treatment decisions is the assessment of the BRAF status. Factors involved in the antitumor immune response could potentially identify the best candidates for immune-checkpoint blockade, and many are being extensively investigated: total tumor mutational load, tumor peptidome, expression of PD-L1, clonality of the TCR, density and quality of immune infiltrates, gene expression profiles associated with an "inflamed" phenotype, genomic determinants of antitumor immunity and even the characterization of commensal bacteria that could potentially modulate cell-mediated responses. A better characterization of the mechanisms involved in primary and secondary resistance to either immunotherapy or targeted therapy is also mandatory for a rational development of future treatment strategies and compounds.

Conclusion

Therapies for patients with advanced melanoma have rapidly evolved over the past few years, improving quality of life and life expectancy. Checkpoint inhibition with antibodies directed against PD-1, nivolumab and pembrolizumab, alone or in combination with the anti-CTLA4 agent ipilimumab, has become the preferred approach for patients with advanced melanoma not harboring BRAF mutations. Molecularly-targeted therapies directed against the MAPK pathway also provide additional options for those with a BRAF V600 mutation, and the association of MEK inhibitors to BRAF inhibitors produced increased response rates, progression free survival and overall survival, and rational ways to combine and sequence this armamentarium will most likely allow for an even greater impact on survival for these patients. Although directed therapies have not been approved for non-BRAF molecular aberrations, including KIT and NRAS mutations, high expectations for the coming years are justifiable by both ongoing pre-clinical and clinical development. Translational research and future clinical trials are warranted to address the large body of questions that remain to be answered, and strategies to bring this reality to in a cost-effective manner to countries with significant cost contingency issues are mandatory.

Conflict of interest

The authors have the following conflicts of interest (COI) to disclose:

- A.H. – No COI to disclose
- A.S. – No COI to disclose
- C.A.A – Honoraria (BMS, MSD, Roche); travel expenses (MSD, Novartis, Roche); advisory role (BMS, MSD)
- M.S. – Honoraria (MSD); advisory role (MSD, Roche); travel expenses (BMS, MSD, Roche)
- V.P.C. – Honoraria (BMS, MSD, Novartis)
- B.G. – Honoraria (BMS, Janssen, MSD); advisory role (BMS, Janssen, MSD)

- M.A.P. – Honoraria (BMS, Merck); advisory role (BMS, Amgen); research funding (BMS)
- G.S.F. – Honoraria (Novartis, Mundipharma, Roche); advisory role (Mundipharma, Roche, Servier); travel expenses (Bayer, Mundipharma, Novartis, Roche, Servier); research involvement (BMS, MSD)
- R.R.M. – Honoraria (AstraZeneca, BMS, MSD, Roche, Novartis); advisory role (Roche, MSD); travel expenses (AstraZeneca, BMS, MSD, Roche, TEVA, Novartis); research involvement (Lilly, Roche)

Resumo

Tratamento de melanoma avançado – Um panorama em transformação

Após décadas de ostracismo, os recentes avanços no tratamento do melanoma trouxeram uma nova realidade para pacientes, médicos e pesquisadores. Enquanto anticorpos monoclonais voltados a moléculas envolvidas na modulação da interação entre células do melanoma e do sistema imune consolidaram o uso da "imunoterapia", um melhor conhecimento acerca das aberrações genômicas envolvidas na carcinogênese do melanoma viabilizaram o desenvolvimento de inibidores da via *mitogen-activated protein kinase pathway* (MAPK), o que também resultou em ganhos significativos em taxas de resposta e sobrevida. Consequentemente, novas modalidades de tratamento foram aprovadas para uso clínico nos Estados Unidos e na Europa, incluindo os bloqueadores de correceptores imunes ipilimumabe, nivolumabe e pembrolizumabe, o herpesvírus oncolítico talimogene laherparepvec (T-VEC), e os agentes-alvo vemurafenibe, dabrafenibe, cobimetinibe e trametinibe. Nesse artigo, revisamos os resultados que trouxeram novas alternativas para a prática clínica e discutimos a incorporação desses avanços ao cuidado de pacientes no Brasil.

Palavras-chave: melanoma, anti-PD1, anti-CTLA-4, BRAF, MEK.

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