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SUMMARY

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SECTIONS

ORIGINAL ARTICLES

REVIEW ARTICLES

Breast cancer and hormonal contraception: Should we rethink our concepts?

Câncer de mama e contracepção hormonal: devemos rever nossos conceitos?

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The emergence and development of hormonal contraception was an achievement for the emancipation of women at the family, psychological and sexual levels, as well as social and professional, having reached great proportions in the 1960s with regard to the role of women in society, with multiple repercussions as it initiated and integrated the sexual revolution of the 1960s in the United States. Although its use has initially provoked some controversy in various areas of society, what is certain is that its utilization rate has been increasing steadily over these almost 60 years. To illustrate, oral contraceptives have a very high efficacy and more than 100,150,000 users worldwide.[1]

Currently, the goal is to offer women an increasingly safe and effective hormonal contraception. It is important to keep in mind that this type of drug does not only have a contraceptive effect. There are many inherent non-contraceptive benefits, such as protection against dysmenorrhea and menorrhagia, menstrual cycle irregularities, iron deficiency anemia, ectopic pregnancy, pelvic inflammatory disease, ovarian cysts, benign breast disease, and tumors of endometrium and ovary. But its great benefit is the decrease in the number of unwanted pregnancies and, particularly in Brazil, the reduction of unprotected abortion and its harmful consequences, including death.

Hormonal contraception can be administered by several routes, the most frequent being the oral route, but there are also injectable products, implants, vaginal rings, intrauterine progesterone devices and skin adhesives. Contraceptives may include combined estrogen and progesterone, progesterone alone, or different doses of ethinyl estradiol. The current trend is to gradually decrease the amount of estrogen in the pill. The first pills contained 150 µg and we currently have pills with 15 µg.[2]

The association between use of hormonal contraception and breast cancer has been discussed for several years with results that are not always clear and conclusive.

In 2002, the CARE study, which compared 4,575 patients with oral contraceptives versus 4,682 patients in the control group, showed no difference in the risk of breast cancer.[3]

In 2008, the Wecare Study Group also failed to demonstrate any increase in breast cancer with the use of oral contraceptives.[4]

In 2006, an important meta-analysis that included 34 studies of premenopausal women conducted after 1980 and evaluated combined oral contraceptives (COCs) versus increased risk of premenopausal breast cancer showed a small risk for current COC use, increased risk for use before the first term pregnancy, and decreased risk for use after first term pregnancy.[5]

Another large study conducted in 2007 by the Royal College correlating COC and cancer risk (from 1968 to 2014) in a cohort of 23,796 COC users compared to 23,377 non-users found RR for breast cancer of 0.98 (95CI 0.98-1.10).[6]

Studies conducted in the last 10-15 years have failed to demonstrate increased breast cancer with the use of progestogen-treated intrauterine devices (IUDs).[7,8]

To date, no increased risk of breast cancer has been demonstrated with the use of hormonal contraception in patients with altered BRCA1 and BRCA2 genes.[9]

Regarding early breast cancer (women < 40 years), in a case-control study conducted in the USA, Canada, and Australia (n = 1,073) in 2005, COC risk after 1975 yielded an odds ratio of 0.74 for non-carriers of mutation, OR 0.18 for BRCA1 and OR 0.92 for patients with BRCA2. Therefore, there was no evidence that the use of low-dose COCs increases the risk of early onset of breast cancer in patients with a

mutation (there may even be a reduced risk for BRCA1 mutation carriers) and should not be contraindicated for a woman with germline mutation in BRCA1 or BRCA2.[10]

More recent studies also suggest that the associations between COC use and ovarian and breast cancer among women who carry BRCA1 or BRCA2 mutation are similar to those reported for the general population.[11]

Hannaford, in 2010, published a mortality risk assessment among women who used oral contraceptives compared to "never" users. The author observed that the absolute risk was 1/500 in users under 35 years, increasing 24% in current users, 16% 4 years after use, 7% after 5 years, and not significant after 10 years. The conclusion was that oral contraception was not associated with an increased risk of long-term death in this large UK cohort. According to the study, however, balance of risks and benefits may vary globally, depending on the patterns of oral contraception and risk of the disease.[12]

Another point of view is to evaluate the survival after breast cancer among previous users of COC. Women with invasive breast cancer participated in the Women's Contraceptive and Reproductive Experiences (CARE) study, cited above, a population-based case-control study (4,565 women aged 35-64 years), and the California Teachers Study (CTS) cohort with 3,929 women aged 28-91 years followed throughout life. There were 1,064 women who died in the CARE trial (mean follow-up, 8.6 years), while 523 died in the CTS (mean follow-up, 6.1 years). The authors concluded that the use of COC in the past is not associated with specific mortality from invasive breast cancer. These two independent studies demonstrated the non-association between COC use and survival among women with breast cancer.[13]

The recent result of the Royal College of General Practitioners Study on oral contraception with 44 years of follow-up was also positive. The longest study of the health effects of oral contraception in the world, published in 2017, aimed to examine the long-term risks or benefits of cancer associated with combined oral contraceptives, including overall survival. 46,022 women were recruited for up to 44 years. Rates of pathologies for users of combined oral contraceptives categorized as "EVER" (past users) and "NEVER" were calculated, along with standardized data for age, parity, social class and smoking. In total, 4,661 users (ever) were found with at least one cancer during 884,895 women-years of observation, and 2,341 non-users (never) with at least one cancer during 388,505 women-years of observation. The increased risk of breast and cervical cancer that has been observed in recent or current users appeared to be lost after approximately five years of interruption of the oral contraceptive with no evidence of recurrent cancer or increased risk in "ever" users over time. On the other hand, oral contraceptive use was associated with reduction in colorectal (incidence rate, 0.81), endometrial (incidence rate, 0.66) and ovarian cancer (incidence rate, 0.67), as well as lymphatic and hematopoietic (incidence rate, 0.74) cancer. There was no evidence of risk of developing a new cancer later in life for women who had used oral contraceptives. Thus, the overall calculation of cancer risk among past users of oral contraceptives was balanced, with the increased risk being offset by the benefits that persist for at least 30 years in relation to endometrial, ovarian and colorectal cancers. This leads to the conclusion that the majority of women who choose to use oral contraceptives do not expose themselves to a higher risk of cancer in the long run; on the contrary, with some types of cancer, many women benefit from significant risk reductions that persist for many years after discontinuation.

It should be kept in mind that contraceptives are used more often at younger ages and that breast cancer usually occurs much later, also considering that the associated risk for breast cancer is for recent or current user, disappearing after five years of discontinuation of the pill.[14]

However, different findings were also published in 2017 in a study that evaluated the associations between hormonal contraceptive use and the risk of invasive breast cancer in a nationwide prospective cohort including all women in Denmark aged 15-49 years age who had no cancer or venous thromboembolism and who did not receive treatment for infertility. There were 11,517 cases of breast cancer in a total of 1.8 million women who were followed on average for 10.9 years (a total of 19.6 million person-years). Compared with women who have never used hormonal contraception, the relative risk of breast cancer among all current and recent users of hormonal contraception was 1.20 (95CI 1.14-1.26). This risk increased from 1.09 (95CI 0.96-1.23) with less than one year of use to 1.38 (95CI 1.26-1.51) after more than 10 years of use (p=0.002).

And after discontinuing hormonal contraception, the risk of breast cancer was still higher among women who used hormonal contraceptives for five years or more compared to those who did not. Risk estimates associated with current or recent use of various oral contraceptives (estrogen-progestogen) ranged from 1.0 to 1.6.

The authors also concluded that women who currently or recently used a progestogen intrauterine device also had a higher risk of breast cancer compared to women who had never used hormonal contraceptives (RR 1.21; 95CI 1.11-1.33).

The absolute increase in breast cancer diagnosed among current and recent users of any hormonal contraceptive was 13 cases (10 to 16 cases), with 95CI, per 100,000 people, or approximately one extra case of breast cancer per 7,690 women using hormonal contraception for one year.[15]

Commenting on this study, I now make the observations of Febrasgo and its National Commission on Mastology. There is an increase in risk (1.3 new cases per 100,000 women), a risk that increased with time of use, and no increase in risk for users with less than 5 years. And for women under 35 years of age, who represent the vast majority of users of hormonal contraceptives, the study showed an increase of 0.2 cases of breast cancer in every 10,000 women per year. Remember that these data should be brought to light in view of the great benefit of hormonal contraception in the female reproductive context.

If we analyze the greatest increase in risk in the group of women aged over 35 or 40 years, this can be misinterpreted in view of the natural history of breast cancer, which has a higher incidence in this age group, although the comparative analysis against the non-hormonal contraceptive users has shown a relative increase in risk.

The increased risk for breast cancer among users of combined hormonal contraceptives has disappeared after discontinuation of the contraceptive, and this finding may demonstrate the non-influence of contraceptives on the genesis of breast cancer. If so, the risk would remain high all the time after discontinuation. Thus, there is no evidence of a causal relationship between contraceptive use and risk of breast cancer.

It should be considered that this study did not evaluate breast cancer mortality in users of hormonal contraceptives and therefore it is not possible to infer from the data presented that the increased risk described has the potential to aggravate the prognosis of breast cancer associated with use of hormonal contraceptives. These women are usually kept under increased surveillance and, as with hormone therapy users, the disease-specific mortality may be even lower when stratified by staging at diagnosis. Because breast cancer is a multifactorial disease, the sum of risks is more important than the increased risk conferred by any individual factor, that is, obesity, nulliparity, sedentary lifestyle, history of previous proliferative disease and family history.

Finally, it should be remembered that hormonal contraceptives represent a long-studied pharmacological class and are associated with high safety. The risk-benefit analysis should be individualized, and the final clinical decision should be elaborated after discussion based on the WHO eligibility criteria for the use of contraceptives.

Again, it is necessary to particularize the cases and the discussion with each patient to substantiate the indication of hormonal contraception, always considering the enormous known benefits. In addition to the drastic reduction of unwanted pregnancies, there is a decreased risk of ovarian, endometrial and rectal cancer and the treatment of numerous hormonal dysfunctions and abnormal bleeding.

Conflict of interest

The authors declare no conflict of interest.

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Osteoporotic vertebral compression fracture – Treatment with kyphoplasty and vertebroplasty

Fratura vertebral osteoporótica – Tratamento com cifoplastia ou vertebroplastia

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

Evidence collection method

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

We used the structured mode of formulating questions synthesized by the acronym PICO, where P stands for patients with osteoporotic vertebral fracture, I refers to intervention using kyphoplasty, C stands for comparison with vertebroplasty and O stands for the outcomes of efficacy and adverse events.

By raising a relevant question related to the proposed topic, we identified, based on the structured question, the keywords that formed the basis of the search for evidence in the databases: Medline-Pubmed, Embase Cochrane Library. The studies had their abstracts reviewed and after applying the eligibility criteria (inclusion and exclusion), 15 articles were selected in order to answer the clinical doubt (Annex I).

Clinical question

Does kyphoplasty bring any benefit to patients presenting osteoporotic vertebral compression fractures compared to vertebroplasty?

Grades of recommendation and levels of evidence

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

Objective

The purpose of this evaluation is to estimate the benefit and risk of kyphoplasty compared to vertebroplasty in the treatment of patients with osteoporotic vertebral compression fractures.

Introduction

The incidence of vertebral fragility fractures increases with age. Vertebral fractures lead to pain, functional disability and decreased quality of life, which can last for several years and can also affect mortality. A patient with acute fracture should be examined for diagnosis using radiology. In case of a low energy fracture, osteoporosis should be suspected and investigated. If the pain treatment fails, vertebroplasty or kyphoplasty may be considered. In the rare case of neurological impairment or unstable fractures, surgical treatment should be considered. After vertebral fragility fractures, the risk of new fractures is high and secondary preventive measures should be used. The best evidence for secondary prevention is currently the medical treatment of osteoporosis.

Vertebroplasty is usually performed through a special needle that slowly injects bone cement percutaneously through each side of the pedicle into the vertebral body.

Kyphoplasty uses two small incisions and a probe placed in the vertebral space at the fracture site. The bone is drilled and a balloon is inserted on each side. The balloons are inflated with contrast (to facilitate X-ray image orientation) and expanded to the desired height, and then removed. The spaces created by the balloons are filled with bone cement.

The results of both forms of treatment are usually measured in relation to quality of life, pain level and recurrence of fractures.

Data extraction

In 100 adult patients with pain and confirmed diagnosis of osteoporosis and thoraco-lumbar vertebral compression fractures, balloon kyphoplasty (50) was compared to percutaneous needle vertebroplasty (50). Operating time (44 ± 4.4 minutes vs. 46.2 ± 4.5 minutes) and volume of bone cement (4.91 ± 0.65 mL vs. 5.56 ± 0.62 mL) were significantly lower in patients treated with kyphoplasty. However, the pain (VAS) score was similar between the two treatment modalities at the 3-day and 6-month follow-up.[1,2] (**B**)

In 404 adult patients with osteoporotic vertebral fractures (T5 to L5), and clinical (1 to 3 points of acute pain) and imaging (radiography, tomography or resonance) signs of compression, balloon kyphoplasty (199) was compared with percutaneous vertebroplasty (205). Follow-up lasted 3 to 24 months. There are no significant differences between the two treatment modalities regarding the outcomes of quality of life (SF-36 and EQ-5D), low back pain, dysfunction score and new fractures. There was only less extravasation of bone cement in the kyphoplasty procedure compared to vertebroplasty (73% vs. 82%, respectively).[3] (**B**)

Recommendation

In patients with osteoporotic vertebral compression (symptomatic) fractures, the use of kyphoplasty compared to vertebroplasty after 3 to 24 months produces a slight reduction in surgical time and volume of bone cement. However, it does not determine any difference in the risk of recurrence of fractures, pain level, quality of life and level of dysfunction (evidence with a high risk of bias – **B**).

Conflict of interest

The authors state that there is no conflict of interest regarding this review.

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Annex I

Structured question

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

- **P** – Osteoporotic vertebral fracture
- **I** – Kyphoplasty
- **C** – Vertebroplasty
- **O** – Efficacy and adverse events

Search strategy

The scientific databases consulted were PubMed-Medline and Cochrane. A manual search was performed based on references of the reviews (narrative or systematic), as well as the selected studies.

PubMed-Medline

- (Osteoporosis OR Osteoporoses) AND (Vertebroplasty OR Kyphoplasty) AND Random*

Articles retrieved

- In all, 148 articles were retrieved from Medline. Of these, 13 were selected based on title and abstract.
- After analysis of the full texts and abstracts, three RCTs were included for assessment.[1-3]
- The main reasons for excluding 10 articles[4-13] were: RCT that did not compare vertebroplasty with kyphoplasty, as well as study protocols.
- The results of the RCTs included will be displayed individually first.

Inclusion criteria for selected studies

The selection of the studies, the evaluation of the titles and abstracts obtained after applying the search strategy in the consulted databases was conducted by two researchers in an independent and blinded manner, strictly following the inclusion and exclusion criteria, so that only potentially relevant articles would be retrieved. If title and abstract were not clear enough, the article was read in full.

Study design

Randomized controlled trials with no limit applied for year of publication.

Language

We included studies available in Portuguese, English, French or Spanish.

According to publication

Only full-text studies were considered for critical assessment.

Evidence selected based on critical assessment

The strength of the evidence from the RCTs was defined taking into account the study design and corresponding bias risks (randomization, blinding, loss, prognostic characteristics, outcomes, intention-to-treat analysis, sample calculation), the results of the analysis (magnitude and precision), relevance and applicability (Oxford/GRADE).[14,15]

Data analysis and extraction

Results obtained from included studies presented as means and standard deviations were: pain improvement, operative time, cement volume and extravasation, quality of life scores and dysfunction score. The results expressed in absolute numbers (absolute risk and NNT) were related to fracture risk. The confidence level was 5%.

All results are available as tables in Annex II.

Description of evidence

The available evidence will follow a sequence to be displayed:

- According to results of study retrieval and selection.
- According to the description of the characteristics and results of the individual studies included.
- The results comprise the number of patients, outcome, magnitude (mean difference or NNT), and precision (standard deviation and 95CI).

Recommendation

The global evidence summary will be elaborated considering the evidence described:

- The strength (Oxford/GRADE)[14,15] will be estimated as 1b or 1c (grade A) or strong, and 2a, 2b or 2c (grade B) or moderate, weak or very weak.
- The strongest evidence will be considered.

Annex II – Results from the studies included for assessment

TABLE 1 Description of study characteristics.

Studies	Population (N)	Intervention (N)	Comparison (N)	Outcome	Follow-up time
Liu et al.[2] Liu et al.[1]	Patients with pain and diagnosis of osteoporosis and vertebral compression fractures (VCFs) at the thoracolumbar (T-L) junction (T12-L1) (N=100)	Balloon kyphoplasty (N=50)	Percutaneous needle vertebroplasty (N=50)	Pain – VAS Score Operating time Volume of bone cement	60 months
Dohm et al.[3]	Participants included had osteoporosis and 1 to 3 points of acute pain due to VCFs in T5 to L5 vertebrae. Patients with more than 3 acute fractures, with VCFs for more than 6 months, were excluded (N=404)	Balloon kyphoplasty (N=199)	Percutaneous vertebroplasty with direct injection of bone cement into the site of fracture without the aid of a balloon (N=205)	Lumbar pain, quality of life (SF-36, EQ-5D), dysfunction (ODI score), extravasation of bone cement	3, 12 and 24 months

VCFs: vertebral compression fractures.

TABLE 2 Description of study biases.

Study	Question	Randomization	Allocation	Blinding	Losses	Prognosis	Outcomes	ITT Analysis	Sample calculation
Liu et al.[2]	Yes	Yes	No	No	No	Yes	No	No	Yes
Dohm et al.[3]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes

ITT: intention to treat.

TABLE 3 Description of study results.[1,2]

Outcomes	Kyphoplasty	Vertebroplasty	Significance
Operating time	44.0±4.4 minutes	46.2±4.5 minutes	p≤0.05
Volume of bone cement (PMMA)	4.91±0.65 mL	5.56±0.62 mL	p≤0.05
Pain – VAS Score, 6 months	2.6±0.6	2.6±0.6	NS
Pain – VAS Score, 3 days	2.6±0.6	2.3±0.5	NS

PMMA: polymethyl methacrylate; VAS: Visual Analogue Scale; NS: not significant.

TABLE 4 Description of results for study 3.

Outcome	Kyphoplasty	Vertebroplasty	Significance
SF-36 Physical Component Summary	3 m: 8.0 (6.3, 9.7) 12 m: 8.1 (6.4, 9.9) 24 m: 7.6 (5.4, 9.8)	3 m: 8.3 (6.41, 10.1) 12 m: 9.6 (7.6, 11.6) 24 m: 7.5 (5.3, 9.8)	NS
EQ-5D, quality of life	3 m: 0.29 (0.25, 0.33) 12 m: 0.30 (0.25, 0.35) 24 m: 0.28 (0.22, 0.34)	3 m: 0.32 (0.27, 0.36) 12 m: 0.32 (0.28, 0.37) 24 m: 0.31 (0.26, 0.31)	NS
Back pain	3 m: -4.5 (-5.0, -4.0) 12 m: -4.5 (-5.0, -4.0) 24 m: -4.0 (-4.7, -3.3)	3 m: -4.6 (-5.1, -4.1) 12 m: -4.3 (-4.9, -3.7) 24 m: -4.0 (-4.7, -3.4)	NS
ODI score	3 m: -28.4 (-31.5, -25.3) 12 m: -28.8 (-32.2, -25.4) 24 m: -26.9 (-30.9, -22.8)	3 m: -25.2 (-28.5, -22.0) 12 m: -28.0 (-31.6, -24.5) 24 m: -25.9 (-30.2, -21.6)	NS
Bone cement extravasation, CT	73%	82%	p≤0.05

Fulminant liver failure in a street runner: Effects of heat stroke

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Summary

We present a clinical case of liver failure induced by heat stroke.

Keywords: Hepatic Insufficiency. Heat Stroke. Fever.

Introduction

Running is one of the most democratic sports, requiring few resources for its practice. In recent years, the number of participants in street races has been growing exponentially. A survey by the São Paulo State Athletics Federation (FPA, in the Portuguese acronym) shows an increase of about 10% per year compared to the number of participants between the years 2010 and 2014 (http://www.atletismofpa.org.br/Corrida-de-Rua/Estat%C3%ADstica-2014). The growth of street races positively influences the regular practice of physical exercise by its competitors, but it is important to recognize that the risks also tend to grow. Therefore, it is critical that such events be practiced safely and with adequate contingency plans, especially with regard to responding to medical emergencies by trained professionals.

The objective of this article was to report a case of fulminant liver failure in a street runner who developed heat stroke.

Case report

Our patient is a 35 year-old male from London, England. He was married, worked in the marketing department of a tobacco company, and had been living in Rio de Janeiro for six months. He was participating in a relay marathon (10 km race for each participant) at Aterro do Flamengo, Rio de Janeiro, on a summer morning (local temperature of 35°C/95°F), when he lost consciousness and was taken by ambulance to a public municipal hospital. According to reports, the patient was hyperthermic (axillary temperature [TAx] = 40.2°C/104.3°F) and had tachycardia (regular rhythm, heart rate [HR] = 140 bpm), psychomotor agitation and disorientation. Other than that, the physical examination was normal. He was given venous esmolol hydrochloride (150 mg/5 minutes) and hydration with saline solution (1,000 mL). Five hours later, he was transferred to a private hospital. He was still disoriented and agitated, with TAx = 39°C/102.2°F, HR = 132 bpm, blood pressure (BP) = 160 x 80 mmHg; respiratory rate (RR) = 22 breaths per minute, peripheral O_2 saturation = 97%, capillary blood glucose = 104 mg/dL. Other than that, the physical examination was also normal. Thorough venous hydration was performed, yielding relative improvement of the patient's state of consciousness. We requested more clinical tests (D1) (Table 1). An electrocardiogram revealed sinus tachycardia, without other abnormalities, while an echocardiogram showed only hyperkinesia. Arterial blood gas (ABG): pH = 7.45; pO2 = 94.7 mmHg; pCO2 = 29.3 mmHg; base excess (BE) = -8.5; HCO3 = 15 mmol; O_2 saturation = 98%. Urine sediment examination revealed hemoglobinuria. Head computed tomography (no alterations) and face sinuses were performed, the latter revealing maxillary sinusitis. IV hydration was maintained and antibiotic therapy with amoxicillin/clavulanate was started for sinusitis treatment.

The following day, the opinion of a specialist in sports medicine was requested. The patient remained very sleepy

and so the story was taken from a coworker who had accompanied him in the race. The coworker informed that beginning in the fifth kilometer of the race, the patient started to breathe "in a strange way" and that in the ninth kilometer he did not respond to any request and used disconnected words, to the point where, in the tenth kilometer, the patient lost consciousness and fell to the ground. It was not possible to obtain details on the hydration measures adopted during the race. Despite having participated in races in England, this was his first race in Rio de Janeiro. He had not been training over the past few months. He made regular use of alcohol (not quantified) and had attended a company party the day before the race. In addition, there was a history of influenza-like illness in the previous week, treated with non-steroidal anti-inflammatory drugs. There were no other relevant data in the history and it was not possible to gather information about the patient's previous family or disease history.

Considering the diagnosis of heat stroke and the possibility of rhabdomyolysis, we implemented vigorous hydration (6 L/day of saline solution), maintenance of the patient in a refrigerated environment and alkalinization of urine with bicarbonate, leading to improvement of his general condition. In the following hours, the patient regained consciousness, with proper orientation and without psychomotor agitation. He was tachypneic (RR = 24 breaths per minute), with BP = 120 x 80 mmHg, Tax = 37°C/98.6°F. Serum lactate = 1.9 mmol/L. However, the next day, there was clinical worsening again, progressing to coma (Glasgow Coma Scale = 4). Orotracheal intubation was performed and the patient was transferred to the ICU (test results shown in Table 2, D2). Scores usually adopted in intensive care yielded SOFA = 8 and APACHE II = 10. As shown in Table 1, the patient progressed with rhabdomyolysis, thrombocytopenia, coagulopathy and hepatic failure. Thorough hydration and alkalinization of urine were maintained. Serologies and antibody testing were negative for HIV, and hepatitis B and C. Toxicological tests were also negative. In order to avoid potential bleeding, aprotinin and vitamin K were administered.

This was therefore a case of severe fulminant liver failure (Child-Turcotte-Pugh score: 12 points), resulting from heat stroke, an event with mortality estimated to be 65-90% at one year. The possibility of liver transplantation was considered. However, as shown in Table 1, after nine days, the patient progressed with important laboratory and clinical improvement (D9), being discharged in good general condition the following week.

TABLE 1 Blood test results, patient's evolution.

Test	D1	D2	D3	D9
Hemoglobin (g/dL)	11.9	13.2	12.8	11.8
WBC count (n/mm^3)	11,000	9,600	7,800	8.9
Platelet count (n/mm^3)	138,000	42,000	50,000	203,000
Potassium (mEq/L)	3.6	3.4	3.4	4.3
Sodium (mEq/L)	146	144	142	138
Calcium (g/dL)	9.0		8.5	8.7
Phosphorus (g/dL)			2.2	4.3
Urea (mg/dL)	39	42	21	26
Creatinine (mg/dL)	1.7	1.6	1.3	1.1
CPK (U/L)	278	6,496	10,220	350
Lactate (mmol/L)	5.9	1.9	2.4	1.0
Total bilirubin (mg/dL)		2.5	1.9	1.0
Gamma-glutamyl transferase (U/L)		139	135	113
Glutamic pyruvic transaminase (U/L)	35	2,329	4,985	100
Glutamic oxaloacetic transaminase (U/L)	51	1,596	3,836	120
Alkaline phosphatase (U/L)		82		60
Fibrinogen (U/L)	212			1
Activated partial thromboplastin time (%)	59	18	11	89
INR	1.39	3.67	5.69	1.5
D-dimer (ng/mL)		7,972	8,801	
pH urine	5.0	5.0		

WBC: white blood cells; CPK: creatine phosphokinase; INR: International Normalized Ratio; D: day of hospitalization.

TABLE 2 Stages of heat stroke.

Stage	Characteristics
Hyperthermic	Neurologic deficit and hyperthermia
Hematologic and enzymatic	Leukocytosis, coagulopathy, increased cellular enzymes
Renal and hepatic impairment	Acute kidney and liver failure

Discussion

Heat stroke is a potentially fatal condition characterized by central body temperature above 40°C/104°F and central nervous system disorders including delirium, seizures, and coma.[1] US data show that there were 7,000 heat deaths in that country between 1979 and 1997.[2] According to Casa et al.,[3,4] these deaths continue to occur due to lack of information regarding diagnosis and treatment of heat stroke. Although there is no Brazilian statistic, considering the weather, we can infer that heat stroke also causes victims in the country.

Heat stroke can be induced by exposure to high temperatures (unrelated to physical exercise) or secondary to strenuous physical exercise. Bouchama & Knochel[1] proposed a pathophysiological definition for heat stroke that applies perfectly to the case reported here: "A form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates." The main complications of heat stroke are related to multiorgan dysfunction. Three phases are proposed for heat stroke, as shown in Table 2.

Exposure to heat or strenuous exercise at high temperatures does not always progress to heat stroke. Genetic factors may determine the susceptibility of certain individuals to the development of heat stroke, such as changes in the production of cytokines, coagulation proteins and heat shock proteins involved in thermal adaptation.[5]

In the case reported here, it is possible to identify some factors that probably contributed to the development of heat-induced multiorgan organic failure. The patient had not become properly acclimatized. Although he had been in Rio de Janeiro for about six months, he had not been training since he moved from England. Armstrong et al.[6] demonstrated the importance of acclimatization, not only regarding environmental temperature, but also in relation to the performance of training in the competition clothing in order to avoid the occurrence of heat stroke.

The initial care provided to the patient should also be carefully evaluated. The low rate of suspicion of heat stroke by first responders clearly contributed to the catastrophic progression of the patient's condition. Early recognition of heat stroke and proper treatment at the competition site could have prevented multiorgan dysfunction. Measures to facilitate heat loss should have been promptly initiated.[4] It is known that rapid cooling and adequate management of circulatory shock can prevent tissue damage and death.[7] Although there is no preferred method for cooling, immersion in ice water proved to be effective in cases of exercise-induced heat stroke. Although no controlled studies comparing the effectiveness of immersion and evaporative cooling were conducted, a meta-analysis published in 2007 suggests that immersion in ice water is the most effective method.[7] However, this method is less practical, making it difficult to access submerged body parts and requiring continuous monitoring of patients due to the risk of drowning.

Some medications can facilitate the occurrence of heat stroke, namely alcohol, alpha-adrenergics, amphetamines, anticholinergics, antihistamines, benzodiazepines, beta-blockers, calcium channel blockers, diuretics, laxatives, neuroleptics and tricyclic antidepressants.[8,9] Alcohol use on the eve of competition and beta-blocker administration at first care may have contributed to the unfavorable outcome in this case.

Finally, we must comment on the occurrence of liver failure. Weigand et al.[10] reported two cases of liver failure associated with exertion-induced heat stroke, suggesting that heat stroke and exhaustion were underestimated causes of liver failure. Later, Garcin et al.[11] followed a cohort of 110 patients with heat stroke and concluded that 22.7% (25 subjects) of them progressed with liver failure.

Recently, the Acute Liver Failure Study Group[12] identified eight patients with heat stroke in a prospective American cohort of 2,675 patients with acute liver injury. One of these patients underwent liver transplantation. In fact, cases in which hepatic transplants were performed under these conditions are rare.[13]

Hepatocellular necrosis is consequent to thermal and circulatory shock, endotoxemia and high concentration of cytokines and acute-phase proteins.[11] However, the only predictor for the occurrence of liver failure was hypophosphatemia, also seen in our patient.[11,14] It is noteworthy that there is no evidence that hypophosphatemia is the cause of liver dysfunction.

A report from the Acute Liver Failure Study Group found 25% of deaths in patients with liver failure secondary to heat stroke diagnosed between January 1988 and April 2015 in the United States.[12] Varghese et al.[15] followed 28 victims of heat stroke and concluded that the high mortality of these cases is due to multiple organic dysfunction.

Predictive factors for the development of multiple organ dysfunction in these patients include: increased creatine phosphokinase (> 1,000 U/L), metabolic acidosis and increased liver enzymes.

Conclusion

Heat stroke is a potentially fatal entity whose complications can be avoided if simple therapeutic measures are promptly initiated. Awareness of health professionals working in sports and emergency settings is crucial to achieving the best prognosis for these patients.

Resumo

Insuficiência hepática fulminante em corredor de rua: efeitos do colapso por calor

Apresentamos um caso de insuficiência hepática decorrente de colapso por calor. Trata-se de entidade pouco conhecida e, provavelmente, subdiagnosticada em nosso país.

Palavras-chave: Insuficiência Hepática. Golpe de Calor. Febre.

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Both glucocentric and cardiocentric approaches are necessary for a resilient disease such as diabetes

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Summary

Diabetes mellitus (DM) is a complex disease that compromises almost all systems in the human organism. Independently of the intrinsic mechanisms, the source of all consequences of DM is hyperglycemia, a condition associated to intense metabolic changes that will lead to increased morbidity and mortality in the long term. Several different therapeutic hypoglycemic oral agents were developed and significantly facilitated the treatment of hyperglycemia acting at different sites, since patients could take more than one agent. This glucocentric approach was somehow criticized as those hypoglycemic drugs have shown weaker than expected benefits in terms of cardiovascular outcomes and there was a sub use of statins and antihypertensive agents in this population. On the other hand, the catastrophic cardiovascular consequences of hypoglycemia in older adults submitted to tight glycemic control and the results of recent clinical trials that showed impressive reduction in cardiovascular outcomes with less potent antidiabetic agents seem to pave the way to a cardiocentric approach including a lax treatment of DM. Interestingly, the results obtained in recent studies with SGLT2 inhibitors are being mostly attributed to mechanisms other than its hypoglycemic effect in spite of including patients at high cardiovascular risk already taking hypoglycemic agents. Considering the worldwide growing number of patients with diabetes, caregivers must follow a dialectical thinking and choose a synthesis approach where glycemic control is the first and foremost target to be achieved, followed by control of cardiovascular risk factors.

Keywords: Atherosclerosis. Diabetes Mellitus. Risk Factors. Coronary Artery Disease.

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Diabetes mellitus (DM) is a complex disease that compromises almost all systems in the organism. Regardless of the intrinsic mechanisms, the cornerstone of all consequences of DM is hyperglycemia, a condition associated to intense metabolic changes leading to increased long-term morbidity and mortality. The introduction of hypoglycemic treatment, mainly insulin and the first oral antidiabetic agents in the first part of the 20th century has changed this scenario, promoting an epidemiologic transition. Indeed, in the second half of the last century, the life expectancy of patients with diabetes increased and cardiovascular-renal diseases became the leading causes of death. As a natural consequence, cardiovascular endpoints became the holy grail in clinical trials with patients with diabetes. The UKPDS trial demonstrated that metformin significantly decreased myocardial infarction rate in patients with diabetes and body weight > 120% of their ideal mass.[1] It is important to notice, however, that, in the UKPDS trial, the average LDL-cholesterol level was 141 mg/dL at baseline and remained above the recommended target for this high-risk cardiovascular group after the long-term follow-up suggesting suboptimal cardiovascular risk factors control.[1,2]

Several different therapeutic hypoglycemic oral agents were developed for the treatment of hyperglycemia acting at different sites. In 2009, a pathophysiological approach was proposed as a new paradigm to achieve durable glycemic control in patients with DM. The new paradigm is based on a creative scheme called *the ominous octet* that has hyperglycemia in its core.[3] According to this algorithm, a triple combination of hypoglycemic drugs should be added to lifestyle intervention targeting HbA1c < 6.0%.

The ACCORD trial, however, put a damper on the glucocentric approach and was stopped earlier than anticipated due to higher mortality in patients enrolled in the intensive glycemic control group, without benefit in major cardiovascular events during 3.5 years of follow-up.[4] In addition, concerns rose for the consequences of severe hypoglycemia seen in the UKPDS trial that revealed a two-fold increase in the occurrence of major hypoglycemic events with the use of glibenclamide, a first generation sulphonylurea.[5] The development of second generation sulphonylureas has significantly decreased the occurrence of severe hypoglycemic events. The incidence of severe hypoglycemia in the intensive treatment arm in the ADVANCE trial that included the second generation modified release sulphonylurea gliclazide was 2.7%.[6] Interestingly, in the second 5-year-phase of this study (ADVANCE-ON), the use of oral antidiabetic drugs was at discretion of the attending physician, and the results showed that the mean between-group difference in glycated hemoglobin levels (lower in the intensive arm in the first phase) was no longer evident. Moreover, in spite of the increased glycated hemoglobin levels in both arms in the ADVANCE-ON, the occurrence of severe hypoglycemia was higher, 8.4% on average, suggesting that both safer drugs and closer follow-up care are necessary for DM patients.[7] Unfortunately, optimal glycemic control remains far below desirable rates in recent studies, indicating careless glycemic control, especially for the treatment of older DM patients.[8]

In conjunction with the concerns related to severe hypoglycemia and increased focus on cardiovascular prevention for DM patients, the results of recent clinical trials showing impressive reduction in cardiovascular outcomes with less potent antidiabetic agents seemed to pave the way to a cardiocentric approach.[9] Actually, the results obtained in recent studies with SGLT2 inhibitors are being mostly attributed to mechanisms beyond the hypoglycemic effect and directed only to patients with diabetes presenting high cardiovascular risk and that were already under an "essential" therapy that includes, most of the time, insulin and sulphonylureas.

In conclusion, we recognize that severe hypoglycemia is a condition to be absolutely avoided but not at the expense of a lax glycemic control.[10] Both the glucocentric and cardiocentric approaches are necessary for a disease as resilient as diabetes mellitus. In addition, the adequate care of patients with DM must involve early diagnosis of hypoglycemia, the control of cardiovascular risk factors (dyslipidemia and hypertension), as well as the identification of patients with established or high risk for heart failure, a major complication. Considering the worldwide growing number of patients with diabetes, caregivers must follow a dialectical thinking and choose a synthesis approach where glycemic control is as important as control of cardiovascular risk factors and should remain a target to be achieved.

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Esophageal lichen planus: An unusual cause of dysphagia in the elderly

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Summary

An 82-year-old man sought our service with dysphagia and was referred for upper endoscopy with biopsies, which evidenced multiple ulcers of the esophagus and oropharinx. Histopathology confirmed the unusual diagnosis of esophageal lichen planus. The correct clinical suspicion of this disease can facilitate the diagnosis and guide specific treatment, which can drastically change the natural course of the disease.

Keywords: Deglutition Disorders. Lichen Planus. Aged.

Case report

An 82-year-old man sought our service with oropharyngeal and esophageal dysphagia for solid foods for the preceding three months. He had a previous history of hypertension, diabetes and coronary angioplasty. Differential diagnoses were suspected, such as tumors, Zenker diverticulum, extrinsic structural lesions, cervical spondylosis, strictures, reflux and eosinophilic esophagitis. The patient was referred for upper endoscopy, which showed multiple ulcers and friable mucosa involving the upper esophagus and oropharynx, without changes in the distal esophagus, gastroesophageal junction, stomach and duodenum (Figure 1). Esophageal biopsies were obtained for histopathology, which revealed squamous epithelial hyperplasia with chronic T-cell lymphocytic infiltrate (CD4, CD8 positive) with interface aggression, apoptotic basal, covered by fibrinous exudate. There was no immunohistochemical evidence of viral or fungal infection. Due to this findings, the diagnosis of esophageal lichen planus (Figures 2 and 3) was confirmed. The patient was referred for specific treatment and remains asymptomatic at follow-up.

Discussion

Lichen planus (LP) is an idiopathic disorder, affecting 0.5% to 2% of the population, with clinical manifestation in the skin, nails, hair, genital and mucosal surface.[1] Esophageal lichen planus (ELP) is a rare and under-recognized disorder, with less than 100 cases described in the literature since its first report in 1982.[2] This disease affects more frequently middle-aged females and involves predominantly the proximal portions of the esophagus. It can present as dysphagia, odynophagia and food impaction, secondary to esophageal lesions and strictures.

Endoscopic findings include esophageal erosions, ulcers, friable mucosa, white papules, pseudomembranes and stenosis. Preservation of gastroesophageal junction in ELP is an important resource that helps in the differentiation of ELP and gastroesophageal reflux disease.[3] Malignant transformation of ELP to squamous cell carcinoma has been reported in the literature; due to this fact, endoscopic surveillance is recommended.[4,5]

Histological findings in the esophagus resemble those from oral mucosa and reflect chronic junctional inflammatory aggression mediated by mature T lymphocytes, which include a band-like lymphocytic infiltrate involving the superficial lamina propria and basal epithelium, besides basal layer degeneration with and apoptotic basal keratinocytes (Civatte bodies).[6]

ELP can be found in more than 50% of patients with proven mucocutaneous LP when clinical and pathologic

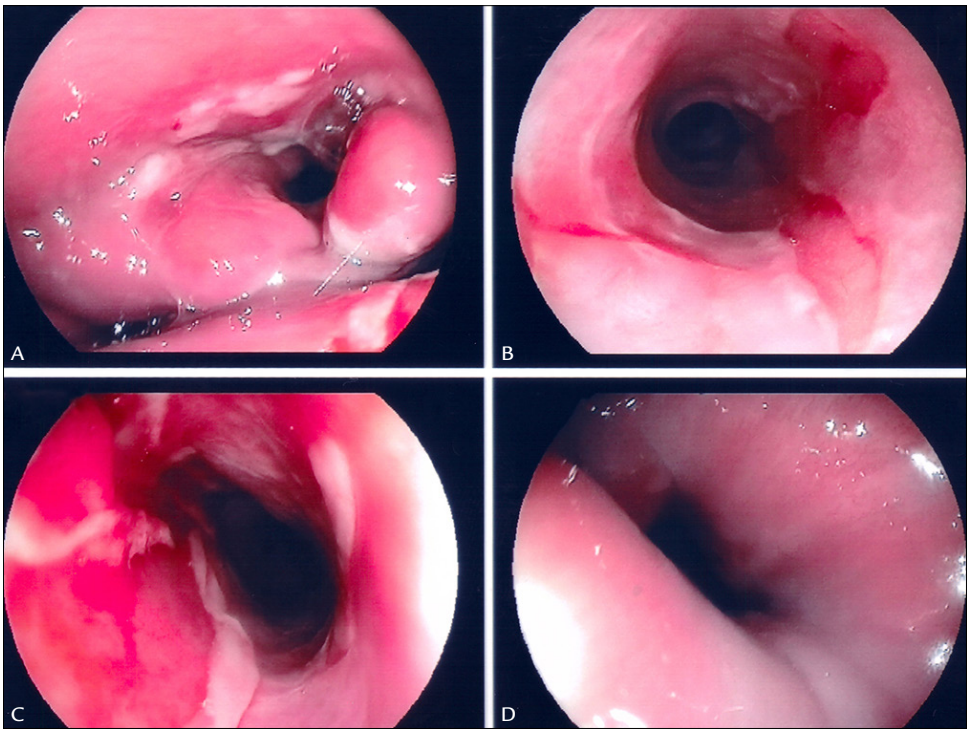

FIGURE 1 Endoscopic findings of esophageal lichen planus (multiple ulcers, friable mucosa), involving the oropharynx (A), the upper esophagus (B and C) and no changes in the distal esophagus and gastroesophageal junction (D).

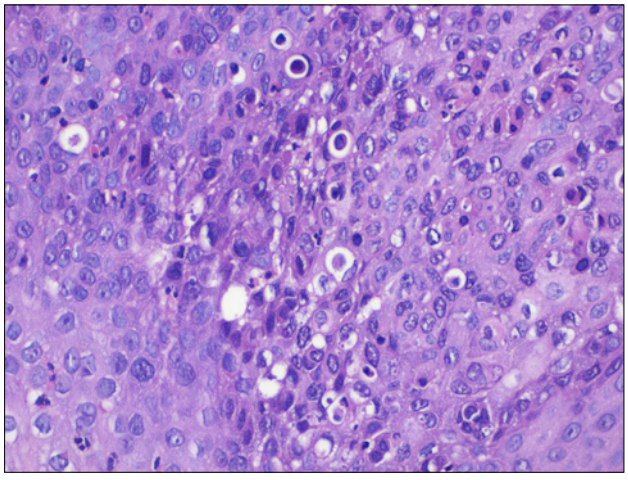

FIGURE 2 Pathology findings: esophageal basal layer with multiple Civatte bodies (apoptotic keratinocytes with anucleate remnants) (HE, x400).

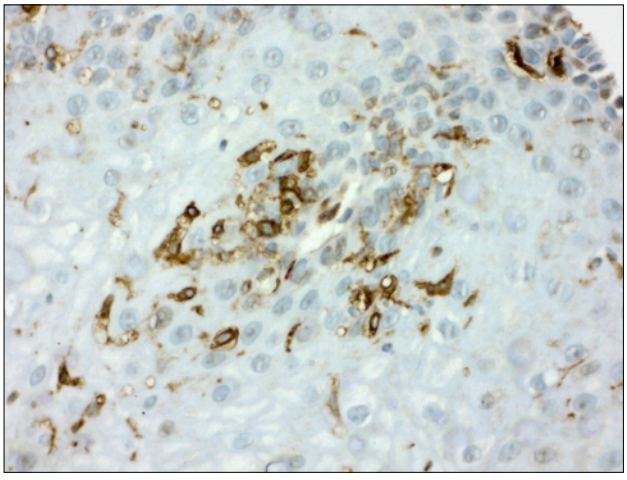

FIGURE 3 Pathology findings: CD4 lymphocytes evidenced by immunophenotype through immunohistochemistry (IHC, x400).

findings are correlated carefully.[7] Therapies for ELP include systemic and topical corticosteroids, cyclosporine, azathioprine and systemic retinoids. In cases of strictures, endoscopic treatment with dilation may be necessary.[8] The correct clinical suspicion of this disease can facilitate the diagnosis and guide specific treatment, which can drastically change the natural course of the disease.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Líquen plano esofágico: uma causa incomum de disfagia em idosos

Paciente do sexo masculino, de 82 anos, com disfagia, foi encaminhado para realização de endoscopia digestiva alta com biópsias, na qual foram evidenciadas múltiplas úlceras de esôfago e orofaringe. O estudo histopatológico confirmou o diagnóstico raro de líquen plano esofágico. A correta suspeita clínica dessa doença pode facilitar o diagnóstico e direcionar para um tratamento específico, o que pode drasticamente alterar o curso natural dessa comorbidade.

Palavras-chave: Transtornos de Deglutição. Líquen Plano. Idoso.

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Selenium supplementation in pediatric patients using parenteral nutrition: Is it time to do something?

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Summary

Objective: To analyze the nutritional status of selenium and verify the effect of its supplementation in pediatric patients during 14 days of parenteral nutrition (PN).

Method: This is a series of cases with patients followed for two weeks while using PN. Data collection was performed at the beginning (T0), in the 7th (T1) and 14th days of PN (T2). The supplemented group received 2 µg/kg/day of selenous acid. Weight and height were measured for nutritional status assessment. Tests requested: plasma selenium, albumin, pre-albumin, C-reactive protein (CRP), total cholesterol and HDL-cholesterol.

Results: Fourteen (14) patients with inflammatory process and with low or very low weight for their ages were evaluated. In both groups (with and without supplementation), all patients had low selenium levels. Median plasma selenium concentrations were 17.4 µg/L (T0), 23.0 µg/L (T1) and 20.7 µg/L (T2). Increase and reduction of selenium occurred both in patients with high CRP and in those presenting normalization of this parameter.

Conclusion: Lower plasma selenium levels have been detected since the start of the research and supplementation (2 µg/kg/day of selenous acid) was not to enough to approach the reference values.

Keywords: Selenium. C-reactive Protein. Supplementary Feeding. Parenteral Nutrition. Child.

Study conducted at Faculdade de Ciências Médicas da Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil

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Introduction

The essentiality of selenium to human health and the benefit this mineral adds to nutritional therapy from the first days following birth has been reported in recent decades.[1,2] In fact, selenium deficiency is associated with cardiomyopathy, prematurity, and clinical and nutritional changes.[1-4]

Considering that patients with inflammation have an exacerbated oxidative process and that selenium is an important component of glutathione peroxidase (GPx), an antioxidant enzyme, it has been assumed that these patients must present an increased need for selenium.[1,4]

Some studies have revealed selenium deficiency in patients using parenteral nutrition (PN), who had not been supplemented with selenium for an extended period of time.[3,4] As such, it has been stated that supplementation should be indicated when PN is used for a period lasting longer than four weeks[3] or after two weeks of PN when this is the main source of nutrition.[5] Since 2012, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends the addition of 2 µg/kg/day of selenium in all pediatric PN formulas from the start of PN.[6,7]

Selenium supplementation seems to contribute to a reduction in mechanical ventilation time, improved weight gain, decreased risk of sepsis and the prevention of cardiomyopathy.[1,2,4,8] However, this is not a commonly used practice, unlike other trace elements such as zinc, copper, chromium and manganese.

In several countries, including Brazil, PN formulas and trace element solutions do not contain selenium. The current alternative to supplementation is to add it separately. However, the beginning of supplementation, supplementation time, the selenium compound offered and the amount of selenium that should be offered are still under discussion in the literature.[1,4] Thus, the objective of our study was to analyze the nutritional status related to selenium and

to verify the effect of supplementation with this mineral in pediatric patients during 14 days of PN.

Method

Study characteristics

This is a prospective study of a case series of patients monitored during two weeks of use of PN. The inclusion criteria were: pediatric patients (aged 0 to 18 years); use of PN as the main source of nutrition (> 80% of nutritional needs); hospitalization at the Hospital de Clínicas da Unicamp; absence of kidney failure due to the risk of intoxication and signing of an Informed Consent Form by the person responsible for the patient.

Data collection was performed at the beginning (T0) and on the 7th (T1) and 14th day of PN (T2). This study was approved by the Ethics and Research Committee of the Unicamp Medical School (No. 538/2011).

Indication and prescription of PN

Parenteral nutrition was monitored by the Multiprofessional Nutritional Therapy Team (EMTN), composed by a nutritionist, nurse, pharmacist and two pediatric physicians that were specialists in PN and enteral nutrition (EN). The prescription of individualized PN was performed by the EMTN physician in accordance with the recommendations of ASPEN[9] and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).[10] When there were laboratory abnormalities, such as mineral disturbances, it was necessary to re-individualize them in accordance with the permitted pharmacotechnical limits. The pharmacochemical guidelines were followed and attested by the EMTN pharmacist, and the compounding company that makes the solutions, according to the MS/SUS Ordinance No. 272 of April 8, 1998.[11] After randomization, the supplemented group received 2 µg/kg/day of selenous acid via PN, according to the ASPEN recommendation.[6]

Nutritional status assessment

Anthropometry was performed based on weight and height measurements according to the World Health Organization (WHO)[12] and Lohman et al.[13] The equipment used in the measurement were a stadiometer (with 0.1 cm precision) and Filizola® electronic digital scales (capacity from 2.5 kg to 150 kg), as well as Toledo® electronic scales (capacity from 0.1 kg to 15 kg). With the data collected in the anthropometric assessment, the nutritional status was classified in accordance with that proposed by the WHO:[12,14]

- Weight/age: very low weight for age (z score < -3); low weight for age (z score between -3 and -2); suitable weight for age (z score ≥ -2 and ≤ +2); high weight for age (z score > +2).
- BMI/age (patients over 10 years of age): accentuated thinness (z score < -3); thinness (z score between -3 and -2); eutrophy (z score ≥ -2 and ≤ +1); overweight (z score between +1 and +2); obesity (z score between +2 and +3); severe obesity (z score > +3). BMI/age was not used in patients less than 10 years of age due to the difficulty in measuring height, especially in patients admitted to the intensive care unit (ICU).

Selenium status evaluation

For the determination of plasma selenium levels, 1 mL of blood was collected in dry tubes (free of trace elements) then centrifuged for plasma separation and stored at -20°C. The plasma samples were digested (via an acid) in Pyrex glass tubes containing 5 mL of nitric acid 68% P.A (Merk) and allowed to rest overnight. Subsequently, a digester block with an initial temperature of 50°C was used for the digestion, gradually increasing to 150°C (the maximum) for elimination of organic substances and reduction of selenium to IV selenium. Subsequently, 5 mL of 1.2 N HCL were added to the samples which were heated at 100°C for two hours. The solutions were then diluted to 25 mL with deionized water and submitted to selenium reading.[14-18] The method used in the reading was hydride generation atomic absorption spectrometry coupled to the quartz cell (HGQTAAS) (model Z5000, Hitachi, Tokyo, Japan) at the Laboratory of Nutrition – Minerals at the Pharmaceutical Sciences School of the University of São Paulo (USP). All materials used during the analysis and dosage of selenium were demineralized with a 30% nitric acid bath for at least 12 hours and rinsed 10 times consecutively with deionized water. As there are no reference values for the Brazilian pediatric population, we considered values ≥ 40 µg/L as normal. These values are within the normal range described in several studies with the same population.[4,7,19-21]

Laboratory assessment of the clinical picture

The other laboratory tests used in the research were those routinely used to accompany the patient in PN. Dosage and blood collection were performed by the Clinical Pathology Laboratory team of the Hospital de Clínicas. The exams computed, the method used and the values of normality are shown in Table 1.

Statistical analysis

The statistical treatment of the collected data was performed with the help of the Statistical Package for the Social Sci-

TABLE 1 Dosage method and values of normality used by the Laboratory of Clinical Pathology of the Hospital de Clínicas da Unicamp.

Laboratory tests	Investigation method	Reference values
Pre-albumin	Nephelometry	20-40 mg/dL
Albumin	Colorimetric (bromocresol green)	≤ 4 days: 2.8-4.4 g/dL
		≥ 5 days: 3.5-5.2 g/dL
C-reactive protein	Nephelometry	< 0.3 mg/dL
Total cholesterol	Enzymatic – colorimetric	2-19 years < 170 mg/dL
HDL-cholesterol	Enzymatic – direct colorimetric	< 10 years: desirable: ≥ 40 mg/dL
		10-19 years: desirable ≥ 35 mg/dL

ences® software version 17 (SPSS). An exploratory analysis was performed using summary measures (median, mean, standard deviation, minimum, maximum and frequency).

Results

The sample consisted of 14 pediatric patients undergoing PN that were hospitalized, mainly in the pediatric ICU, with an ongoing inflammatory process (evidenced by high C-reactive protein – CRP) and low or very low weight for age (Table 2).

Low plasma selenium concentrations were observed in all patients throughout the study, including patients who showed improvement in CRP and pre-albumin levels on day 14 (Table 3).

Table 4 shows that no patient had selenium levels within the reference range (n = 7/7) and CRP was high in only three cases after 14 days of evaluation.

Supplemented group

Among the four supplemented patients (numbers 11, 12, 13 and 14), all were male, two were hospitalized in the pediatric ICU and one died. Patient number 11, who died, started PN with selenium plasma levels below the reference range and which progressively decreased throughout the three assessment times. Albumin was low, and pre-albumin, which was initially normal, decreased. CRP fell in the third assessment but was still above the reference values. This patient was diagnosed with primary immunodeficiency and inflammatory disease.

Among the other three supplemented patients (numbers 12, 13 and 14), none reached normal levels. Patient number 14, who reached the closest levels (34.9 µg/L) of the reference, had normal albumin and pre-albumin, which started low and became normalized after the second dose. CRP concentrations started high but decreased and reached the reference range. Furthermore, the patient had an adequate weight.

Non-supplemented group

Among the ten non-supplemented patients, it was not possible to perform the second and third blood levels measurements in three cases (numbers 1, 3 and 6). Among these, all had low selenium concentrations and, above all, the values were lower for those who died (number 1 and 3). Meanwhile, patient number 6, who was discharged, had plasma selenium of 34.4 µg/L (close to normal) and CRP of 2.25 mg/dL.

Regarding the other seven non-supplemented patients, death occurred in three cases (numbers 5, 7 and 10). Among these, it was verified that patient number 10, with the most critical selenium levels (6.3 µg/L), had adequate CRP (0.18 mg/dL).

In general, after 14 days of assessment, selenium levels did not reach the reference values (patients 2, 4, 8, 9 and 10) and CRP was high in two cases (numbers 4 and 9).

Discussion

The sample consisted mainly of patients hospitalized in the pediatric ICU with an ongoing inflammatory process (evidenced by high CRP and low high density lipoprotein [HDL], pre-albumin and albumin values) and low or very low weight for age. All of the patients evaluated had plasma selenium levels below the reference values throughout the study. Among those patients receiving supplementation (2 µg/kg/day of selenium as selenous acid), it was found that this was insufficient for the normalization of plasma levels over 14 days.

In clinical practice, plasma selenium appears to be the best marker of the nutritional status of individuals in relation to selenium.[7] Unlike erythrocyte selenium, plasma selenium reflects the current nutritional status in relation to the mineral[22] and is the most commonly used marker in general.[7] However, for adequate interpretation of the plasma parameters related to selenium, the dosage of CRP and HDL-cholesterol is required. After all, elevation of CRP (acute phase protein) and reduction of HDL is what characterizes

TABLE 2 Description of patients according to age, place of hospitalization, outcome, nutritional status, main diagnosis and PN indication.

Patient	Age	Hospitalization setting	Outcome	Z score	Nutritional status classification	Days before PN[d]	Main diagnosis	PN indication
1	5 months	PICU	Death	-6.39[b]	Very low weight	112	CHF + kidney failure + sepsis	Subocclusion (clinical)
2	5 years	PICU	Non-death	-1.43[b]	Normal weight	65	Volvulus	SBS (surgical)
3	8 months	PICU	Death	-5.28[b]	Very low weight	99	Cerebral palsy	Refractory diarrhea + SBS (clinical)
4	13 years	WARD, PED	Non-death	–	–	7	Myelomeningocele	Fistula (surgical)
5	2 days	PICU	Death	-0.99[b]	Normal weight	0	Congenital heart disease	Ileum (surgical)
6	7 months	PICU	Non-death	-2.12[b]	Low weight	4	Bowel cancer	Ileum (surgical)
7	4 months	PICU	Death	-3.78[b]	Very low weight	7	Septic shock	Ileum (clinical)
8	15 years	WARD, PED	Non-death	-3.12[c]	Severe emaciation	1	Pancreatitis	Pancreatitis (clinical)
9	1 year	PICU	Non-death	-7.04[b]	Very low weight	78	Rubinstein-Taybi syndrome	Chylothorax (clinical)
10	5 years	WARD, PED	Death	-0.74[b]	Normal weight	28	CMPA + colectomy + SBS	SBS (surgical)
11[a]	3 years	PICU	Death	-1.41[b]	Normal weight	10	Primary immunosuppression + Crohn's disease	LGIB (clinical)
12[a]	11 years	PICU	Non-death	-3.13[c]	Severe emaciation	4	GI paresis + GI distension + meningitis	Ileum (clinical)
13[a]	1 year	WARD, PED	Non-death	-3.6[b]	Low weight	6	Gastroschisis + CMPA	Ileum (surgical)
14[a]	4 months	WARD, PED	Non-death	-1.43[b]	Normal weight	2	Congenital diaphragmatic hernia + Crohn's disease	Ileum (clinical)

PICU: pediatric intensive care unit; WARD, PED: pediatric ward; PN: parenteral nutrition; CHF: congestive heart failure; CMPA: cow's-milk protein allergy; SBS: short bowel syndrome; LGIB: lower gastrointestinal bleeding; GI: gastrointestinal.
[a]Supplemented with selenous acid (2 µg/kg/day); [b]weight/age; [c]BMI/age; [d]days of hospital stay before the beginning of PN.

TABLE 3 Evolution of the biochemical tests in the three points of evaluation.

Tests	N	Mean (SD)	Median	Range	Altered results
Selenium (µg/L)					
Time 0	14	20.83 (8.71)	20.67	6.50-34.46	14/14 (↓)
Time 1	10	17.39 (5.16)	17.43	6.50-24.46	10/10 (↓)
Time 2	9	20.6 (9.60)	23.05	6.22-34.93	9/9 (↓)
CRP (mg/dL)					
Time 0	11	9.84 (11.33)	4.78	0.04-33.10	10/11 (↑)
Time 1	7	4.70 (6.10)	3.24	0.02-17.00	5/7 (↑)
Time 2	6	2.07 (2.14)	1.83	0.02-4.42	3/6 (↑)
Pre-albumin (mg/dL)					
Time 0	14	14.16 (8.69)	11.40	5.46-38.50	11/14 (↓)
Time 1	10	22.09 (12.06)	20.70	9.47-41.60	5/10 (↓)
Time 2	7	25.91 (14.04)	20.70	11.40-45.60	3/7 (↓)
Total cholesterol (mg/dL)					
Time 0	12	1.08 (41.87)	96.00	50.00-193.00	2/12 (↑)
Time 1	10	1.27 (54.18)	1.195	48.00-201.00	2/10 (↑)
Time 2	6	1.60 (59.82)	1.40	101.00-261.00	2/6 (↑)
HDL-cholesterol (mg/dL)					
Time 0	12	23.42 (8.51)	23.00	10.00-42.00	11/12 (↓)
Time 1	10	22.30 (12.93)	22.50	7.00-44.00	8/10 (↓)
Time 2	7	35.86 (13.03)	36.00	16.00-58.00	4/7 (↓)
Albumin[a] (g/dL)					
Time 0	12	3.46 (0.82)	3.65	1.90-4.70	7/14 (↓)

SD: standard deviation; CRP: C-reative protein; (↑) above the reference value; (↓) below the reference value; [a]albumin was dosed only once because of long half-life (21 days).

TABLE 4 Evolution of plasma selenium and C-reactive protein concentration of each patient over the three evaluation points.

Patient	Selenium T0 (µg/L)	CRP T0 (mg/dL)	Selenium T1 (µg/L)	CRP T1 (mg/dL)	Selenium T2 (µg/L)	CRP T2 (mg/dL)	Behavior of selenium[c]
1[a]	17.7	1.54	–	–	–	–	–
2[a]	13.4		10.9	0.02	23.0	0.02	9.6 (↑)
3[a]	20.9	17.4	–	–	–	–	–
4[a]	14.6	–	–	–	18.8	4.12	4.2 (↑)
5[a]	6.5	4.78	22.7	–	–	–	16.2 (↑)
6[a]	34.4	2.25	–	–	–	–	–
7[a]	30.9	–	24.4	4.9	–	–	–6.5 (↓)
8[a]	30.8	0.04	14.2	0.02	23.5	–	–7.3 (↓)
9[a]	12.6	26.5	17.0	3.24	24.9	4.42	12.3 (↑)
10[a]	10.6	1.66	17.9	0.37	6.3	0.18	–4.3 (↓)
11[b]	27.8	7.09	19.2	7.39	6.2	3.45	–21.6 (↓)
12[b]	21.9	12.8	23.8	17	29.6	–	7.7 (↑)
13[b]	20.4	1.09	10.6	–	18.7	–	–1.7 (↓)
14[b]	29.0	33.1	13.1	–	34.9	0.22	5.6 (↑)

CRP: C–reactive protein; [a]patient without selenium supplementation; [b]patient supplemented with selenous acid (2 µg/kg/day); [c]evolution from the first to the last investigation; (↑) increase in the levels of selenium; (↓) decline in the levels of selenium.

the inflammatory process,[23-25] and this may contribute to the reduction of plasma selenium values.

In the present study, plasma selenium concentrations were low from the onset of PN and did not reach normal levels over the 14-day follow-up regardless of the CRP and/or supplementation values. This may have occurred due to the supplementation time and/or selenium dosage offered.

In the supplemented group, one patient attained selenium concentrations closer to normal levels after supplementation. In this patient, it is possible that the increase occurred due to the reduction of inflammation (evidenced by the fall in CRP). However, it is also plausible that selenium and CRP values also improved due to the effect of supplementation, since selenium has antioxidant and anti-inflammatory functions.[26]

In an investigation by Leite et al.[21] including infants and children with systemic inflammatory response syndrome, 90.9% of the patients were found to have selenium concentrations below the reference (the mean selenium plasma concentration was 23.4 µg/L). However, even during the acute phase of the inflammatory process, reduced ventilation and ICU length of stay were associated with increased selenium levels, indicating that supplementation may be beneficial in this population.

There is variation between the studies in relation to the supplementation time. In a study by Masumoto et al.,[4] the four surgical patients (use of nutritional support without selenium) who developed a deficiency showed clinical and laboratory improvement after supplementation for more than two months. In a study by Etani et al.[20] with 95 patients aged from 7 months to 20 years with intestinal dysfunction and/or neurological disorders (use of PN and/or EN with little or no selenium), it was found that 28/95 patients presented selenium concentrations below 40 µg/L and clinical manifestations associated with low selenium levels. Among the 28 patients, five presented concentrations below 20 µg/L of selenium, as in our study. After a year of supplementation, the five patients showed improvement in the clinical manifestations.

Regarding the amount of selenium that should be offered, studies suggest selenium supplementation of over 2 µg/kg/day.[4,7] According to the Australasian Society for Parenteral and Enteral Nutrition, selenium requirements in PN can increase, even in the short term (< 20 days) because the current illness or surgical procedure intensifies the metabolic and antioxidant needs.[27,28] For adult patients, the ASPEN[6] recommends 60-100 µg/day of selenium and mentions that, in cases of inflammatory process, the supply should be close to the upper or surplus limit without exceeding 400 µg/day. However, this observation regarding the inflammatory process was not made for the pediatric population.

In addition to the inflammatory process and metabolic stress, age can also be a risk factor for selenium deficiency. The most susceptible to deficiency are infants, as they store less selenium and therefore have a lower stock than children and adults.[29]

In relation to nutritional status, the assessment with laboratory tests was complex given that albumin and pre-albumin undergo changes due to the inflammatory process.[30] However, according to the anthropometric assessment, the majority of patients were evaluated as having severe malnutrition, another factor that can influence the body's demand and nutrient reserves, and harm a patient's prognosis.

In fact, the selenium values detected in our study were similar to or lower than those observed in other studies, which associated low levels of selenium with diseases and serious clinical complications.[4,18-21] Therefore, laboratory monitoring of plasma selenium may contribute to the prevention of a number of future complications with the use of supplementation from the start of PN in patients undergoing the inflammatory process.

Limitations of the study

The number of patients reported was lower than desired due to death or withdrawal from PN before the 14th day of monitoring. Furthermore, the diversity of diseases, clinical complications and age range of the patients characterized a heterogeneous and complex sample. However, heterogeneity is a feature commonly found in intensive care – which was the hospitalization setting of most of the patients studied. The indication of selenium supplementation for pediatric patients does not vary according to the underlying disease, age and intensity of inflammation.

Conclusion

Plasma selenium levels were very low and supplementation with 2 µg/kg/day of selenous acid was not sufficient for the normalization of these levels. We therefore emphasize the importance of monitoring selenium status and supplementation from the onset of PN in patients undergoing the inflammatory process. However, it should be noted that more studies are needed in order to establish the amount of selenium supplied and the appropriate time of intervention.

Resumo

Suplementação de selênio nos pacientes pediátricos em uso de nutrição parenteral: é hora de fazer algo?

Objetivo: Analisar o estado nutricional relativo ao selênio e verificar o efeito da suplementação desse mineral em pacientes pediátricos durante 14 dias de nutrição parenteral (NP).

Método: Trata-se de estudo prospectivo de uma série de casos de pacientes acompanhados durante duas semanas de uso de NP. A coleta de dados foi realizada no início (T0), no 7º (T1) e no 14º dia de NP (T2). Após randomização, o grupo suplementado recebeu 2 µg/kg/dia de ácido selenioso. Peso e altura foram aferidos para avaliação do estado nutricional. Exames coletados: selênio plasmático, albumina, pré-albumina, proteína C-reativa (PCR), colesterol total e HDL-colesterol.

Resultados: Foram avaliados 14 pacientes com processo inflamatório em curso e com baixo ou muito baixo peso para a idade. Os pacientes (grupo suplementado e não suplementado) tinham baixas concentrações de selênio. A mediana dos valores de selênio plasmático foi de 17,4 µg/L (T0), 23,0 µg/L (T1) e 20,7 µg/L (T2). Aumento e redução de selênio ocorreram tanto nos pacientes com PCR elevada quanto naqueles que apresentaram normalização desse parâmetro.

Conclusão: Os níveis de selênio detectados foram muito baixos e a suplementação (2 µg/kg/dia de ácido selenioso) não foi suficiente para normalização dos níveis plasmáticos.

Palavras-chave: Selênio. Proteína C-reativa. Suplementação Alimentar. Nutrição Parenteral. Criança.

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Is serum angiotensin converting enzyme level a useful non-invasive marker for liver fibrosis in patients with chronic hepatitis C?

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Summary

Objective: Chronic hepatitis C (CHC) continues to be a critical problem. The liver fibrosis score is the most valuable tool in determining treatment and prognosis. Liver biopsy is still considered a gold method but, due to unmet needs, new non-invasive markers are required. The aim of this study was to investigate any possible relationship between serum angiotensin-converting enzyme (ACE) levels and the stages of liver fibrosis in patients with CHC.

Method: A total 100 CHC and 100 healthy subjects were enrolled in this study. The relationship between serum ACE level and the stages liver fibrosis was investigated using three different formats, as follows: (group [G]-I, classic Ishak's Score from F1 to F6; G-II, mild [F1-2], moderate [F3-4] and severe [F5-6]; G-III, mild [≤ F2] and advanced [F > 2]). The clinical usability of serum ACE level for both groups was also investigated.

Results: Median serum ACE levels were higher in the healthy group than in CHC (42.5 [7-119] vs. 36 [7-91] U/I, p=0.002). There was no statistical difference among the three different fibrosis groups (G-I, G-II, G-III, p=0.797, p=0.986, and p=0.874) and no correlation between serum ACE level and the stages of liver fibrosis (r=0.026, p=0.923). The usability of serum ACE for evaluated patients with CHC and healthy subjects were calculated as 47% and 64%, respectively.

Conclusion: Our study indicated that there is no relationship or correlation between serum ACE levels and stages of liver fibrosis in patients with CHC. The assessment of serum ACE level using genetically corrected reference values may provide more accurate results.

Keywords: Hepatitis C, Chronic. Peptidyl-Dipeptidase A. Liver Cirrhosis.

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Introduction

Chronic hepatitis C (CHC) infection continues to be a serious problem worldwide despite the advent of new direct-acting antiviral therapy and increased public and individual awareness of the hepatitis C virus.[1,2] The burden of chronic hepatitis B virus infection that was the foremost cause and the most important agent in the past decade is decreasing as expected due to the use of efficient and well-organized national vaccination programs and treatment, while the burden of CHC is increasing even now due to expensive new generation treatments and lack of the preventive vaccination.[1-3] In the decision-making process of a patient newly diagnosed with CHC, ascertaining the stage of liver fibrosis is one of the most important actions in the selection of treatment options and predicting long-term outcomes.[3,4] Consequently, the stage of liver fibrosis is also accepted as the most valuable and well-considered marker in the context of important guidelines such as The European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD).[5,6]

For a better understanding of current liver condition regarding fibrosis stage and other related etiologies, liver biopsy is still considered the gold standard method. There is, however, a significant amount of needs unmet using this technique, such as the very reduced size of the biopsy sample, which is not representative of the entire liver, sampling or intraobserver errors, and invasive procedure complications including risk of minor or major bleeding, or death. In addition, liver biopsy may be con-

traindicated or unfeasible due to physical anomalies (namely, the ribs), thrombocytopenia, and prolonged prothrombin time.[7-9] Given these limitations, non-invasive methods or markers are needed as an alternative to liver biopsy and are currently under intense scrutiny.[10] A non-invasive method should be easy to perform, inexpensive and yield reliable, reproducible results that can characterize early and/or advanced fibrosis. Many markers, measurements and methods have been evaluated so far for this aim, but none was able to prevail over liver biopsy for liver fibrosis evaluation.[11] Moreover, the performance and usability of these methods are claimed to be good, but many do not produce a stricking effect due to poor study design and an insufficient number of patients and/or controls.[12]

The measurement of circulating angiotensin-converting enzyme (ACE) levels is one of the mentioned methods promising some good results in the early studies.[13] The idea of measuring serum ACE levels to point out the stage of liver fibrosis dates back to the studies concerning the role played by renin-angiotensin-aldosterone (RAS) axis and angiotensin in liver fibrosis.[14] In these studies, the RAS system and related factors such as angiotensin I, II and serum ACE were claimed to be the key elements affecting and regulating liver fibrosis. At the same time, the effect of some drugs that block the RAS system on liver fibrosis has been investigated.[15,16] However, a few studies have been conducted on the importance of serum ACE level during the stage of liver fibrosis before until now. Up to today, the measurement of serum ACE level for liver fibrosis has only been studied in the context of hepatitis B and autoimmune hepatitis, with promising results according to the authors.[17,18] However, in these studies, the value of serum ACE could not be assessed in deepth due to the insufficient number of patients and controls, as well as a lack of studies on usability. Many patients with chronic liver disease are usually detected and treated later in life and so plenty of comorbidities that often affect the serum ACE level can exist. Despite a lack of data regarding the issue, many patients initially presumed eligible for these studies are ultimately excluded on the account of diseases that affect their serum ACE levels. In this study, we investigated the importance and suitability of serum ACE level as a marker of liver fibrosis in a relatively large cohort group including CHC patients and a healthy control group.

Method

This study was designed at a reference and research center for liver diseases, and was approved by the local ethics committee on 6/29/2016 as clinical trial no. 2016-79-29/06. The patients' files were first reviewed retrospectively to determine suitability for this study between May 2010 and May 2016. In brief, a total of 213 hepatitis C patients were searched, but 79 and 34 of all patients were excluded from the study due to chronic diseases affecting serum ACE levels and the deficiency of diagnostic data, respectively. 156 dyspeptic but otherwise healthy subjects were evaluated in order to compose a control group. Of these, 56 were excluded for presenting conditions or minor illnesses that could affect their serum ACE levels. Thus, the study and control groups comprised 100 hepatitis C patients and 100 healthy subjects, respectively. To be part of the study group, patients were required to present positive anti-HCV antibodies and detectable levels of HCV RNA, as well as yield a proper liver biopsy sample for evaluation of liver fibrosis, and blood samples for measurement of serum ACE levels using a specific commercial kit. Plasma anti-HCV antibody was tested using Abbott AxSYM Anti-HCV 3.0 (Abbott Laboratories, Germany) and HCV RNA levels were measured by using COBAS TaqMan HCV RNA assay, version 2.0 (Roche Diagnostics Systems Inc, USA), with a lower limit of detection of 10 IU per milliliter. Serum ACE activity was measured by observing the alteration in absorbance at 340 nm of the hydrolysis of furylacrylolylphenylalanylglycylglycine (FAPGG) to FAP and GG (Sigma-Aldrich, Poole, UK) using an analyzer (Roche MIRA Analyser; Roche Diagnostic Systems, Welwyn Garden City, UK). Liver biopsy specimens were accepted eligible if they included 10 or more complete portal tracts, had more than 20-25 mm in length, were stained with Masson's trichrome and reticulin dyes, and were evaluated according to modified Ishak's scoring system (1995). The stage of fibrosis was stratified into tree groups as following: (group [G]-I, classic modified Ishak's Score from F1 to F6; group-II, mild [F1-2], moderate [F3-4] and severe [F5-6]; group-III, mild [≤ F2] and advanced [F>2]).

Some of the patients with conditions that might affect the serum ACE level were excluded from the study. These conditions were accepted as following; 1) hypertension; 2) receiving any antihypertensive or other drugs that might potentially interact with the RAS system such as ACE inhibitors; 3) diabetes mellitus; 4) any renal parenchymal diseases; 5) sarcoidosis; 6) acute or chronic inflammation with elevated C-reactive protein or sedimentation; 7) concomitant chronic liver disorders; 8) moderate or severe cardiopulmonary problems. All CHC patients were categorized as Child-Plug grade A and, as expected, those with Child-Plug grade B and C as well as esophageal varices or any signs of decompensated

cirrhosis were excluded. The healthy control group was equivalent to the patient group regarding age and gender and consisted of those who did not have chronic health problems other than dyspeptic complaints. Serum ACE levels were obtained from healthy controls using the same method as for the CHC patient group. The study was performed in agreement with the guidelines of the Helsinki declaration.

Statistical analysis

Statistical analyses were conducted using SPSS 19 (Chicago, Illinois, USA). Patient and control groups were investigated in terms of distribution, frequency and the difference between the two groups. A p-value lower than 0.05 was accepted as statistically significant. Gender, age and serum ACE levels were investigated using Chi-square tests, Student's t-test and Mann-Whitney U test, respectively. Spearman's correlation coefficient was used to evaluate the correlations between serum ACE levels and liver fibrosis stages. Normally distributed data are demonstrated as means and standard deviation (SD), while non-normally distributed data are represented by median and minimum-maximum.

Results

A total of 100 patients with hepatitis C and 100 dyspeptic healthy subjects were included in this study. Clinical suitability and usability of serum ACE level were calculated as 47% for CHC group and 64% for healthy subjects. The median age was 56.5 (36-73) years for the CHC group and 55 (35-79) years for the healthy subjects. There were 30 females and 70 males in the CHC group and 40 females and 60 males in the healthy group. There was no statistically substantial difference in both groups regarding age and sex. The important demographic data are illustrated in Table 1. The median serum ACE level was higher in the healthy group than in patients with CHC (42.5 [7-119] vs. 36 [7-91] U/I, p=0.002) (Figure 1). The proportion of patients in terms of different fibrosis stages was calculated as follows: group-I was F1=5 (5%), F2=17 (17%), F3=31 (31%), F4=18 (18%), F5=22 (22%) and F6=7 (7%). The group-II was mild (F1-2) = 22 (22%), moderate (F3-4) = 48 (48%), and severe (F5-6) = 29 (29%), and the group-III was mild (F ≤ 2) = 22 (22%) and advanced (F > 2) = 78 (78%). There was no statistically significant difference among the different fibrosis groups regarding serum ACE levels (Figure 2). There was no correlation between the serum ACE and HAI, MELD and the scores of fibrosis (r=-0.058, r=-0.121, r=-0.026 and p=0.567, p=0.231, p=0.923, respectively).

Discussion

CHC is still considered a major problem all over the world. When choosing the optimal and the best treatment modality for these patients, the stage of liver fibrosis is accepted to be the key element, according to EASL and AASLD guidelines.[5,19] For instance, some new and effective drugs are used in CHC patients with early fibrosis, but are contraindicated to CHC patients with advanced fibrosis.[20,21] As mentioned in the introduction, liver biopsies are still considered the best method for detecting liver fibrosis. However, due to unmet needs, a growing number of non-invasive markers has been suggested for prediction of the stage of liver fibrosis.[10] Also, there is an increasing number of ongoing studies for this purpose.[22] Measuring serum ACE levels is one of them, showing promising results in early studies, although some paradoxical outcomes have also been reported recently.[16-18,23] The issue of non-invasive methods has increasingly attracted many researchers, and frequently new studies on the topic are added to the literature.

In the present study, we investigated the relationship between serum ACE levels and the stage of liver fibrosis in a relatively large cohort including 100 CHC patients and 100 healthy control subjects. Interestingly, our results are different from previous studies due to the following points. To our knowledge, this is the first study to investigate the relationship between serum ACE level and the stages of liver fibrosis in patients with CHC, as well as the

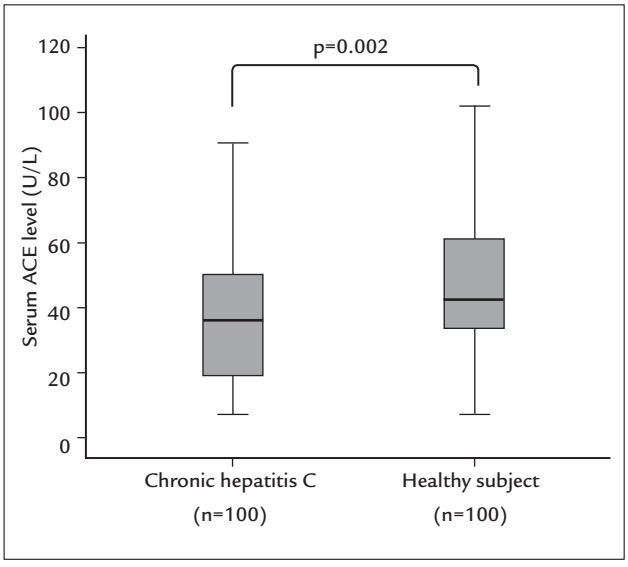

FIGURE 1 The median serum ACE level was higher in the healthy group than in patients with chronic hepatitis C (42.5 [7-119] vs. 36 [7-91] U/L, p=0.002) (95% confidence interval and median values are shown).

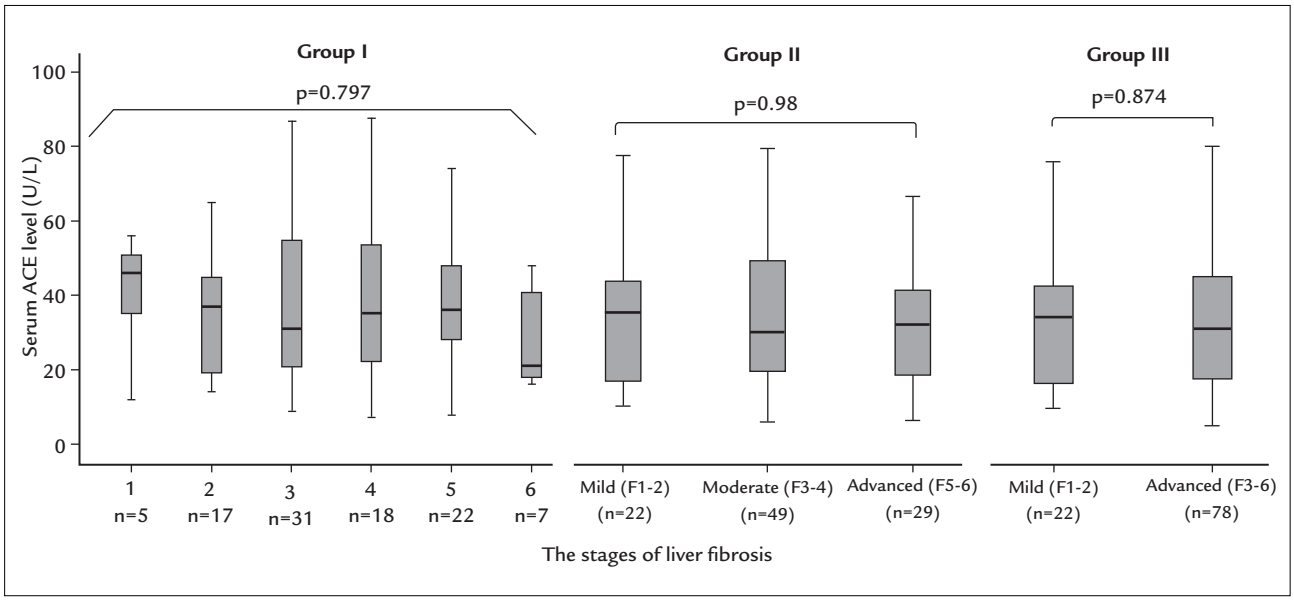

FIGURE 2 The median serum ACE level was not different statistically among groups I, II and III and there was also no relationship between serum ACE levels and the different liver fibrosis stages (95% confidence interval and median values are shown).

TABLE 1 Important characteristics of the study population.

	Chronic hepatitis C patients (n=100)	Healthy group (n=100)	p
Age (years [min-max])	56.5 (36-73)	55.0 (35-79)	0.082
Gender (n [%])			0.138
Male	30 (30%)	40 (40%)	
Female	70 (70%)	60 (60%)	
Blood pressure (mmHg)			NS
Systolic	112±18	121±22	
Diastolic	62±13	71±13	
Creatinin (mg/dL)	0.97±0.2	0.88±0.1	NS
Serum ACE (U/L) (median [min-max])	36 (7-91)	**42.5** (7-119)	0.002
HAI	10±3.2		
MELD	7±1.3		
AFP (ng/mL)	4.1±3.4	3.1±1.9	NS
T.Bil. (N<1.2 mg/dL)	0.97±0.17	0.85±0.1	NS
Child-Plug Score	A (100%)		

ACE: angiotensin-converting enzyme; HAI: histologic activity index; MELD: Model for End-Stage Liver Disease, T.Bil: total bilirubin; NS: non-significant; AFP: alpha-fetoprotein.

suitability and usability of serum ACE levels in patients with chronic liver disease. According to the literature, a non-invasive marker to be used for detecting of the stage of liver fibrosis should be easy to perform, inexpensive and yield reliable, reproducible results, as well as remain unaffected by other chronic diseases and medication. Unfortunately, the levels of serum ACE could be affected by many drugs and chronic diseases that are commonly present in most of the CHC patients. Consequently, we researched this issue and finally found that the usability of serum ACE in our patients with CHC was only 47%. This means that serum ACE may not be a suitable non-invasive marker for all CHC patients. In addition, studies on serum ACE levels and liver fibrosis usually include a relatively small number of the patients and healthy controls.[17,18]

Also, contrary to other studies, we found a higher level of serum ACE in the healthy controls (42.5 U/L) compared to the patients with CHC (36 U/L), and no correlation between serum ACE and the stages of liver fibrosis. In previous studies, the most striking results

regarding the relationship between serum ACE and the stage of liver fibrosis have been found first by Purnak et al.[17] and Efe et al.[18] in patients with chronic hepatitis B and autoimmune hepatitis, respectively. Interestingly, both authors found nearly the same results that serum ACE was higher in the patient groups compared to the healthy control groups (hepatitis B study results: chronic hepatitis B vs. healthy control, 48.4 [14-83] U/L vs. 26.2 [12-48] U/L, p<0.001, and autoimmune hepatitis study: autoimmune hepatitis vs. healthy control, 58 [38-142] vs. 34.5 [10-59] p<0.001).[17,18] Moreover, they both found a significant correlation between serum ACE and the stages of liver fibrosis, and identified an optimum serum ACE cutoff level for advanced fibrosis as 52.5 U/L and 65 U/L with high specificity and sensitivity.[17,18] Based on data, Efe et al.[18] claimed that serum ACE might also be an attractive inflammation marker due to the fact that serum ACE levels increase proportionally with the severity of the interface hepatitis. When these two studies are considered together, the most critical problem is that the number of researched patients and control group is very small (Purnak et al.[17] included 50 chronic hepatitis B patients vs. 20 healthy controls, and Efe et al.[18] had 73 patients with autoimmune hepatitis vs. 32 healthy controls); some patients in the study group had signs of cirrhosis. Also, these results are not confirmed in a relatively wide range of studies performed by Turhan et al.[23] as well as our study.

A similar discrepancy that has been noticed in some of the drug studies refers to blockage of RAS. In early studies on the latter, despite a reduction in liver fibrosis with the use of some ACE inhibitors, the results were not confirmed by any new studies performed with lisinopril, known as one of angiotensin-converting enzyme inhibitors.[14,24,25] Lisinopril has shown no major histomorphological alterations in regenerating fibrotic liver tissues and has a beneficial effect on the regression of liver fibrosis.[16] These conflicting results may also be explained by the lack of consideration of the polymorphism of ACE gene in the study population. Polymorphism of the ACE gene has the greatest impact on serum ACE levels with a strong genetic influence and large interindividual differences.[26] Studies investigating I/D polymorphism in the ACE gene have demonstrated that, while individuals with D allele have advanced ACE activity, individuals with I allele have lower ACE activity than those with D allele.[27] Moreover, the ACE gene polymorphism can cause a considerable amount of changes, up to 28% increase in serum ACE levels, depending on the ethnic background of the study population.[28] Consequently, the interpretation of serum ACE values without regard to ACE gene polymorphism may cause a masking effect regarding the exact values.[23] Based on these conflicting results, we suggest that serum ACE levels should be interpreted in view of the polymorphism of ACE gene and used with genotype-corrected reference values.

Conclusion

In conclusion, our results showed that the measurement of serum ACE for assessment of the stage of liver fibrosis is not usable and suitable in patients with CHC. Also, there is no correlation between serum ACE levels and the stages of liver fibrosis. Based on recent research, it is not possible to interpret the level of serum ACE correctly without considering the polymorphism of the ACE gene. This hinders the use of serum ACE as an easy, cost-effective and reliable marker of liver fibrosis.

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The clinical efficacy and safety of paclitaxel combined with avastin for NSCLC patients diagnosed with malignant pleural effusion

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Summary

Objective: The current study aimed to investigate the clinical efficacy of paclitaxel combined with avastin for non-small cell lung cancer (NSCLC) patients diagnosed with malignant pleural effusion (MPE).
Method: Total of 33 patients diagnosed with NSCLC as well as malignant pleural effusion were included. All of them received paclitaxel (175 mg/m2) and avastin (5 mg/kg). Clinical efficacy was evaluated using the total response rate, overall survival, progression-free survival and changes in MPE volume. Adverse events and rates of toxicities were examined as well.
Results: The total response rate reached 77% while the overall survival and the median progression-free survival were respectively 22.2 months and 8.4 months. Toxicities of grade 3-4 consisted of neutropenia in 57% of patients, anemia in 17% of them, febrile neutropenia in 11%, as well as anorexia in 7%. No treatment--correlated deaths were found.
Conclusion: Paclitaxel combined with avastin decreased MPE volume and increased survival rate of NSCLC patients via inhibiting vascular endothelial growth factor expression.

Keywords: Carcinoma, Non-Small-Cell Lung. Pleural Effusion, Malignant. Paclitaxel. Bevacizumab. Vascular Endothelial Growth Factor A.

Introduction

Lung cancer is found to be the major cause of cancer--correlated death in the most developed countries. Nearly 85% of lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC) histology.[1] Malignant pleural effusion (MPE) is one of the complications often found in patients with NSCLC.[2-4] MPE treatment approaches include an indwelling pleural catheter (IPC), therapeutic thoracentesis and chemical pleurodesis.[5] Avastin is a monoclonal antibody that can inhibit angiogenesis by inhibiting vascular endothelial growth factor (VEGF) expression,[6] which is a tumor angiogenesis factor and participates in the development of pleural effusion.[7] In the current study, we investigated the clinical efficacy of the traditional chemotherapy agent paclitaxel combined with avastin in the treatment of MPE. Our data suggested that paclitaxel combined with avastin was more effective to treat MPE.

Method

Patients and inclusion criteria

Total of 33 NSCLC patients diagnosed with MPE were recruited from January 2011 to December 2014. The inclusion criteria was (1) all patients were histopathologically diagnosed with adenocarcinoma at stages IV-M1a or IV-M1b in accordance with the International Association for the Study of Lung Cancer;[8] (2) Karnofsky Performance Status ≥ 60;[9] (3) MPE demonstrated by the identification of malignant cells in pleural fluid owing to metastases resulting from the tumors existing in the lung; (4) no abnormal findings on electrocardiography, bone marrow, liver and kidney function tests; (5) no allergic reaction to paclitaxel and avastin.

The study was approved by the Medical Ethics Committee of the West China Hospital (Chengdu, Sichuan, China). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was provided by all subjects.

Treatment

All patients were intra-pleurally injected with avastin (5 mg/kg, Roche Diagnostics GmbH., Mannheim, Germany) in 100 mL of a solution followed by the same dose of paclitaxel once every three weeks for 12 consecutive weeks. A pigtail catheter (Suzhou Jingxin Medical Supplies Co., Ltd., Suzhou, China) was applied to the patients with MPEs for chest drainage and infusion of drugs. All procedures were B-ultrasound-guided and done at the bedside.

Assessment of clinical efficacy and safety

After baseline assessment, tumor lesions were assessed every four weeks during induction therapy and subsequent maintenance using computer tomography was performed every eight weeks until there was evidence of disease progression. Tumor response was evaluated based on version 1.1 of the Response Evaluation Criteria in Solid Tumor (RECIST).[10] Toxicity was evaluated based on version 4.0 of the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Statistical analyses

IBM SPSS version 17.0 was applied to conduct statistical analysis. Student's t test was used to compare the continuous variables. Pearson Chi-square or Fisher exact test were used to categorical variables. A multiple logistic regression analysis was conducted to evaluate possible predictors of poor prognosis. The area under the receiver operating characteristic curve (AUC) was calculated to investigate the ability of serum Hcy level to predict patient prognosis.

Results

Patient characteristics

In all, 33 NSCLC patients diagnosed with MPE were recruited from January 2011 to December 2014. All patients were treated and evaluated for clinical efficacy and safety according to the study protocol. Baseline patient characteristics are summarized in Table 1, as follows.

TABLE 1 Patient characteristics.

Characteristics	n	%
Age		
Median range	65 (31-77)	
Sex		
Male	24	73
Female	9	27
ECOG PS		
0	19	58
1	14	42
Stage		
IIIB	4	12
IV	28	85
Relapse after surgery	1	3
Histology		
Adenocarcinoma	31	94
Other	2	6
EGFR gene mutation		
Wild-type	23	70
Mutated	7	21
Not evaluated	3	9

Clinical efficacy of paclitaxel combined with avastin in the treatment of MPE

Treatment response of 33 patients was evaluated. Partial response was eventually found in 25 patients, and the ORR was 77% (95CI 57-87%) as shown in Table 2. Median TTR was 1.7 months (range = 0.6-5.8 months), while the median progression-free survival (PFS) was 8.4 months (95CI 6.3-8.8 months), and the median OS was 22.2 months (95CI 13.8-28.1 months) (Figure 1).

Quality of life

EORTC QLQ-C30 includes five functional domains (physical, role, cognition, mood and social function), four

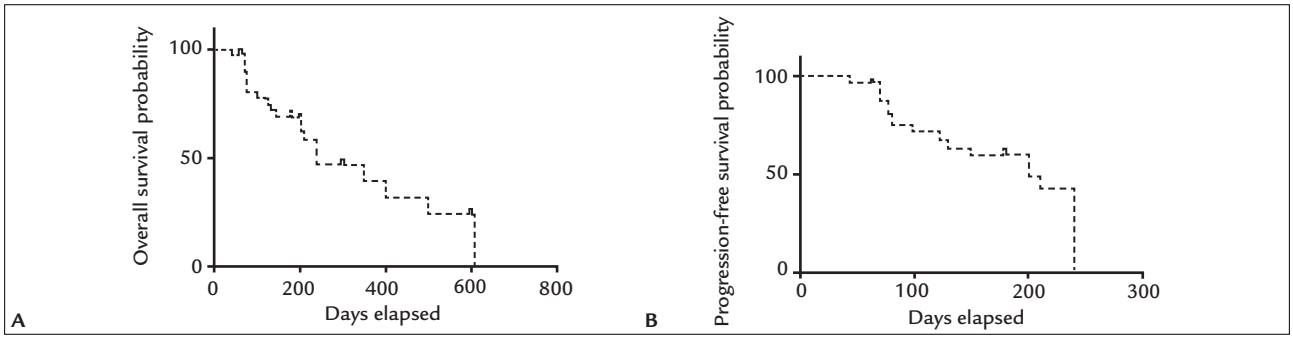

FIGURE 1 A. Overall survival (OS). B. Progression-free survival (PFS).

TABLE 2 Treatment response.

Treatment	n	%
CR	0	
PR	25	
SD	4	
PD	3	
NE	1	
Total	33	
CR+PR	25	58
Response rate		77
95CI		57-87

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

symptoms (fatigue, pain, nausea and vomiting), one general health item and five common single entry symptoms (dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Calculate standardized scores for each field (SS). Results showed that overall health improved after treatment, and dyspnea improved most during symptom assessment (Table 3).

Toxicity

The adverse events found in the total of 33 patients are listed below in Table 4. Hematological toxicities reaching grade 3/4 were neutropenia (18 patients, 55%), leukopenia (seven patients, 21%), anemia (six patients, 18%), thrombocytopenia (one patient, 3%) and febrile neutropenia (four patients, 12%). Non-hematological toxicities reaching grade 3/4 were anorexia (three patients, 9%), diarrhea (one patient, 3%) and aminotransferase elevation (one patient, 3%). The most common hemorrhage was nasal bleeding, which occurred in 14 patients (42%). Gingival bleeding appeared in two patients (6%), and hemorrhoid bleeding appeared in one (3%). All the cases of hemorrhage were grade 1. It is worth noting that only three patients (9%) had grade 2 neuropathy, and none of the patients had grade 3/4 neuropathy. One had grade 1 pneumothorax and two patients had hyperkalemia (grade 2 and grade 3). No treatment-related deaths were observed.

TABLE 3 Changes in mood, general health and dyspnea before and after treatment (x±s).

	Mood	General health	Dyspnea
Before treatment	48.3±6.5	37.6±5.2	80.1±3.9
After treatment	62.8±4.3	54.2±6.4	51.5±3.6

TABLE 4 Summary of adverse events.

	Grade (NCI-CTCAE)					Grade
	0	1	2	3	4	3/4 (%)
Hematological toxicity						
Leukopenia	5	6	15	7	0	21
Neutropenia	3	3	9	15	3	55
Anemia	0	14	13	6	0	18
Thrombocytopenia	9	19	4	1	0	3
Febrile neutropenia	29	0	0	4	0	12
Non-hematological toxicity						
Anorexia	13	15	2	3	0	9
Nausea	16	13	4	0	0	0
Vomiting	25	6	2	0	0	0
Diarrhea	26	4	2	1	0	3
Constipation	16	15	2	0	0	0
Fatigue	16	13	4	0	0	0
Infection	31	0	2	0	0	0
Alopecia	9	13	11	0	0	0
Neuropathy	11	19	3	0	0	0
Hypertension	30	2	1	0	0	0
Nasal bleeding	19	14	0	0	0	0
Other	30	3	0	0	0	0
Proteinuria	26	2	5	0	0	0
AST/ALT	16	14	2	1	0	3
Total bilirubin	24	7	2	0	0	0
Creatinine	28	4	1	0	0	0

NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events; AST/ALT: aspartate transaminase/alanine aminotransferase.

Discussion

The present study aimed to explore optimization therapy in treatment of MPE. The results have demonstrated that paclitaxel combined with avastin resulted in high ORR with good tolerance. These results suggested that use of avastin as a VEGF inhibitor resulted in an additive beneficial effects in treatment of MPE. In clinical practice, first-line treatment for MPE includes chemotherapy aimed at reducing pleural fluid volume. Nevertheless, it has been found that high levels of VEGF contribute to angiogenesis and serous cavity effusions in cancer patients,[9] and the occurrence of MPE is related to increased expression of VEGF receptor in lung cancer cells of human beings.[11] Avastin is a monoclonal antibody against VEGF and has been applied to treat NSCLC in clinical practice.[12,13] Therefore, it is reasonable to hypothesize that clinical efficacy of avastin in treatment of MPE was related to suppressing angiogenesis via inhibiting VEGF expression.[14-16]

In the present study, adverse events of the drugs were recorded according to the CTCAE v3.0.[17] The results have shown that most patients had side effects ranked from grade 1 to 2. Paclitaxel has an essential clinical activity in fighting against a wide range of tumor types such as lung cancer.[18]

The antineoplastic agent interferes with the growth of both cancer cells and normal body cells, which are eventually destroyed with occurrence of some unwanted effects.[19,20] Since these observed side effects were common and not serious for the patients taking paclitaxel, it is conceivable that intervention with avastin not only intensified the treatment effect of the anticancer drug in the patients but also shortened hospitalization time, reducing hospital costs.

Conclusion

We investigated the clinical efficacy of avastin along with paclitaxel in the treatment of MPE in patients diagnosed with NSCLC. The results demonstrated that avastin combined with paclitaxel was effective and safe in terms of improving treatment success and survival rates.

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Quality of life in a sample of Brazilian adults using the generic SF-12 questionnaire

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Summary

Objective: This study describes the summary scores of the Short Form-12 (SF-12) questionnaire, according to socio-demographic factors obtained in a probabilistic and representative sample of the Brazilian urban population.
Method: Five thousand (5,000) individuals, over the age of 15, were assessed in 16 capital cities, in the five regions of the country. The selection of households was random. Face-to-face approach was applied in the household interviews. The SF-12 questionnaire was used to assess quality of life. Demographic and socioeconomic characteristics were also evaluated: gender, age, marital status, skin color, region of the country and use of the public health service.
Results: The mean value (SD) of the SF-12 for the entire population was 49.3 (8.7) for the physical component (PCS-12) and 52.7 (9.7) for the mental component (MCS-12). Statistical differences were found for gender (PCS-12 and MCS-12), age (PCS-12) and working status (PCS-12 and MCS-12). Women, elderly, widowed and unemployed individuals, those with lower income and with complaints in the last seven days showed lower mean values (PCS-12 and MCS-12).
Conclusion: From this point forward, we can provide the basis for comparisons with future research that use the SF-12 for quality of life assessment in Brazil. The Brazilian population has a lower degree of quality of life related do the physical component, and the SF-12 is a useful and discriminative instrument for assessing quality of life in different socio-demographic groups.

Keywords: Quality of Life. Surveys and Questionnaires. Brazil. Health Surveys. Socioeconomic Factors.

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Introduction

Over the past years, there has been an increased recognition of the patient's point of view as an important component in the assessment of health care outcomes. There is now a general consensus that the health of a population cannot be well characterized based on the analysis of mortality and morbidity statistics alone and that there is also a need to view health in terms of people's assessment of their sense of well-being.[1]

Such acknowledgment has led to the concept of Health-Related Quality of Life (HRQoL), defined as an individual's perception of their life position in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[2] Therefore, an array of scores representing individual dimensions or domains of HRQoL can be provided by health profiles (or health status questionnaires). The rationale is that since such questionnaires focus on those aspects of existence that are affected by ill health, they may give some indication of the impact of illness on quality of life.[2-4]

One of the most widely used and psychometrically sound instruments is the Medical Outcomes Study 36-item Short Form (SF-36). This relatively brief and simple questionnaire contains 36 items covering eight health concepts chosen on the basis of reliability, validity and frequency of measurement in health surveys.[5] Two summary scores have also been developed for the SF-36. The reliability and validity of the SF-36 have been well documented by the developers of the instrument.[4-7] As a generic instrument, the SF-36 can be applied to a wide range

of types and severities of health conditions and can be used to compare patients who have different conditions or to compare patients with the general population.[5,6]

In order to provide a shorter more user-friendly alternative to the SF-36, the Short-Form 12 health survey (SF-12) was purposely designed for large-scale measurements for which the SF-36 was too lengthy.[7] The SF-12 measures physical and mental health by means of two summary scores; a physical component summary (PCS-12) and mental component summary (MCS-12). The SF-12 can be employed in multiple ways, i.e., SF-12 is often used to compare health status between two groups of patients, to identify predictors of health status, and to determine health status in a specific population.[7]

In Brazil, although some studies have already provided the assessment scores of the SF-12 in regional populations or certain diseases,[8-14] a comprehensive and representative assessment of the Brazilian population is still lacking. Therefore, the objective of this article was to present the descriptive measures of the summary measures composing the SF-12, according to socio-demographic factors obtained in a probabilistic and representative sample of Brazilian urban population.

Method

This study was part of the Brazilian Copcord Study (BRAZCO), a cross-sectional population-based study conducted between April and May 2013.[15-17] We surveyed 5,000 participants over the age of 15 from 16 capitals in the five regions of Brazil: North (Belém, Manaus), Northeast (Fortaleza, João Pessoa, Maceió, Natal, Recife and Salvador), Southeast (Belo Horizonte, Rio de Janeiro and São Paulo), South (Curitiba, Florianópolis and Porto Alegre) and Midwest (Brasília and Goiânia).

The sample was comprised of representative quotas of the Brazilian population, proportional to the population densities of the capitals in each region of the country, based on the Census conducted in 2010 by the Brazilian Institute of Geography and Statistics (IBGE – Instituto Brasileiro de Geografia e Estatística). The quotas of gender and age in each capital were based on the Census, and participants of all socioeconomic statuses, educational levels and occupations were included.

The households were randomly selected, with a systematic selection of streets and subjects by randomly choosing the census tract with a quota control for the seasonality factor. Regarding the list of households, one household was evaluated per street, with a total of up to ten households in the sector. If an entire sector was covered but not enough households were found to complete the required number, the process was carried out again in the sector, beginning in the first street, five houses after the house where the first interview took place. In each household, up to three visits were made on different days and at different times. In cases where the interview was not carried out after these three attempts, the household was replaced by another in the same Census sector. If the resident of the selected household could not be interviewed, that household was replaced by another in the same Census sector, seeking to ensure a respondent within the same gender and age group.

A success rate of 70% was established, so 42.9% more households than planned were randomly selected to ensure substitution. Ineligible households, such as collective households (vacant households, hotels, lodges, nursing homes etc.), agricultural, educational and healthcare establishments, and buildings under construction, were replaced by another household in the same Census sector. The maximum sampling error was ±1.39% for the country as a whole, with a 95% confidence level.

Residents who did not speak Portuguese and people with a cognitive disability, thus incapable of reliably and consistently answering the questionnaire, were excluded. Because of the small proportion of people living in rural areas (15.6%) and the difficulty in accessing this scattered population, only households in urban areas were considered.

The survey instrument was a household questionnaire conducted face-to-face by a specialized team, consisting of open and closed-ended questions about socioeconomic and demographic aspects. Ethnic group was declared by the respondents themselves (white, black, yellow, brown, or indigenous). Family income was expressed as multiples of minimum wages, where the values of the Brazilian minimum wage, originally in *reais* (Brazilian currency), were converted to United States dollar (US$) according to the exchange rate in 2013 using data from the Institute of Applied Economic Research (Ipea – Instituto de Pesquisa Econômica Aplicada).

For the proposed analysis, a translated and validated version for the Portuguese language of SF-12 questionnaire was used.[18] The SF-12 is a self-reported generic HRQoL measure consisting of 12 questions that can be scored to provide a physical component summary (PCS-12) score and a mental component summary (MCS-12) score.[7,19] The SF-12 PCS and MCS scores have been developed to produce a mean of 50 and a standard deviation of 10 in the adult US population.[7,19]

The questionnaires were reviewed by an independent supervisor and submitted to a process to evaluate consistency, where 50% of the questionnaires were double-checked through phone calls.

SPSS for Windows version 20.0 (IBM-SPSS, Chicago, IL) was used for statistical analysis. The variables were descriptively analyzed and data were presented as mean, standard deviation, percentage and confidence intervals for means. Student's t-test and ANOVA were used to evaluate scale scores composing the SF-12, according to sociodemographic factors of the Brazilian urban population. The probability level was set at a $p<0.05$.

All subjects were informed about the study and agreed to participate by signing a written free and informed consent form. The research protocol was examined and approved by the Ethics and Research Committee of Unifesp/EPM (Nº 2013/473524).

Results

Table 1 presents the main demographics and socioeconomic characteristics of the surveyed population. A total of 5,000 participants from 16 capitals in five Brazilian geographic regions were surveyed. Most of them from the southeast region (42.1%), 51.3% were women, 32% were married, 48.6% were between 15 and 34 years old, and 52.3% had a family income of up to two minimum wages (US$627.78) (Table 1).

Figure 1 shows the distribution of the SF-12 responses for each of the 12 questions. It was observed that all possible answers were potentially used. Almost half of the respondents considered their health as good (49.52%).

In regard to physical component, most respondents declared that they had no difficulties in performing moderate activities or climbing stairs and no difficulties in performing daily activities or labor tasks because of physical health.

In regard to mental component, most respondents did not accomplish less work because of emotional problems, had no pain that interfered with their normal work, felt calm and peaceful all the time or most of the time and had a lot of energy all the time or most of the time. In addition, most respondents said they did not feel downhearted or blue at all, or felt this way in a few occasions (42.90%) in recent weeks and that emotional problems do not interfere with their social activities (65.28%).

The mean (SD), minimum and maximum values of the SF-12 scores are shown in Table 2. The mean SF-12 scores (SD) for the entire population was 49.3 (8.7) for PCS-12 and 52.7 (9.7) for MCS-12. According to sociodemographic factors, there were statistical differences for all research variables (PCS-12 and MCS-12), except for skin color (MCS-12). Furthermore, women, elderly and widowed individuals, those unemployed and people with lower income and with complaints in the last seven days showed lower mean values to PCS-12 and MCS-12.

TABLE 1 Demographic and socioeconomic characteristics of a Brazilian urban population sample.

	Participants	
Characteristics	**n**	**%**
Sample total	5,000	100
Gender		
Male	2,433	48.7
Female	2,567	51.3
Age (years)		
15 to 24	1,270	25.4
25 to 34	1,160	23.2
35 to 44	915	18.3
45 to 54	692	13.8
55 to 64	490	9.8
65 or more	473	9.5
Marital status		
Single	2,053	41.1
Married/common law partner	2,442	48.8
Widowed	240	4.8
Divorced/separated	233	4.7
Not reported	32	0.6
Skin Color		
White	2,009	40.2
Black	753	15.1
Yellow	98	2.0
Brown	2,113	42.3
Indigenous	27	0.5
Region of the country (residence)		
North	415	8.3
Northeast	1,390	27.8
Midwest	370	7.4
Southeast	2,105	42.1
South	720	14.4
Family income (minimum wages)		
Less than 1 (US$313.89)	880	17.6
From 1-2	1,735	34.7
From 2-5	1,649	33.0
From 5-10	430	8.6
From 10-15	139	2.8
From 15-20	56	1.1
More than 20 (US$ 6,277.78)	23	0.5
Did not answer	88	1.8
Public health system user		
Yes	556	11.1
No	357	7.1

TABLE 2 Scores assessed by the SF-12 in the Brazilian population according to gender, age, marital status, regions, skin color, working status, family income and incidence of complaints.

		PCS-12*						MCS-12**					
Characteristics	**N**	**Mean**	**SD**	**Minimum**	**Maximum**	**CI**	**p-value**	**Mean**	**SD**	**Minimum**	**Maximum**	**CI**	**p-value**
Sample total	4,990	49.3	8.7	13.7	65.4	49.1-49.6		52.7	9.7	14.7	68.3	52.4-52.9	
Gender													
Male	2,429	50.7	7.8	18.3	63.6	50.4-51.1	<0.01	54.7	8.2	18.1	67.7	54.4-55.0	<0.01
Female	2,561	48.0	9.4	13.7	65.4	47.6-48.4		50.7	10.5	14.7	68.3	50.3-51.1	
Age (years)													
15 to 24	1,269	52.7	5.5	22.9	65.4	52.4-53.1	<0.01	54.4	8.1	18.9	67.7	54.0- 54.9	<0.01
25 to 34	1,158	51.0	7.0	20.8	62.2	50.6-51.4		53.0	9.2	18.1	67.4	52.4-53.5	
35 to 44	913	49.5	8.4	19.2	62.4	49.0-50.1		52.6	9.9	17.8	68.3	51.9-53.2	
45 to 54	690	47.0	10.0	13.7	62.8	46.2-47.7		51.2	10.4	16.3	64.6	50.4-52.0	
55 to 64	489	44.5	10.5	17.4	61.2	43.6-45.5		50.6	11.0	14.7	65.3	49.7-51.6	
65 or more	471	44.0	10.7	14.2	60.2	43.1-45.0		51.5	10.5	18.9	67.4	50.6-52.5	
Marital status													
Single	2,049	51.4	7.3	13.7	65.4	51.1-51.7	<0.01	53.6	9.1	14.7	67.7	53.2-54.0	<0.01
Married	1,629	48.1	9.0	18.8	62.5	47.6-48.5		52.6	9.5	20.7	67.4	52.1-53.0	
Common law partner	809	49.1	8.7	18.3	63.7	48.5-49.7		52.2	10.0	16.3	68.3	51.5-52.9	
Widowed	239	43.4	11.4	14.2	61.9	42.0-44.9		49.5	11.4	18.9	67.2	48.0-50.9	
Divorced / separated	232	46.8	10.1	19.5	62.8	45.5-48.1		50.2	11.1	17.8	64.6	48.8-51.7	
Not reported	32	49.8	8.2	24.3	57.9	46.8-52.7		54.5	9.4	24.1	63.1	51.1-57.9	
Region of the country (residence)													
North	414	49.0	7.8	18.3	60.4	48.2-49.7	<0.01	53.6	8.8	20.0	68.3	52.8-54.5	<0.01
Northeast	1,389	48.8	9.2	17.4	63.6	48.3-49.3		52.5	9.7	17.8	67.4	52.0-53.0	
Midwest	368	49.5	8.7	19.1	62.1	48.6-50.4		50.4	9.7	21.3	64.1	49.4-51.4	
Southeast	2,100	49.5	8.7	13.7	65.4	49.1-49.8		52.4	9.9	14.7	67.4	52.0-52.8	
South	719	50.2	8.3	14.2	62.8	49.6-50.8		54.3	8.9	18.1	64.6	53.7-55.0	

(*Continues*)

TABLE 2 (Cont.) Scores assessed by the SF-12 in the Brazilian population according to gender, age, marital status, regions, skin color, working status, family income and incidence of complaints.

		PCS-12*						MCS-12**					
Characteristics	**N**	**Mean**	**SD**	**Minimum**	**Maximum**	**CI**	**p-value**	**Mean**	**SD**	**Minimum**	**Maximum**	**CI**	**p-value**
Skin color													
White	2,007	49.7	8.5	14.2	65.4	49.4-50.1	0.01	52.7	9.6	16.3	67.4	52.3-53.1	0.69
Black	749	49.6	8.6	13.7	61.1	48.9-50.2		53.0	9.4	19.4	65.8	52.3-53.7	
Yellow	98	50.2	8.0	23.8	59.7	48.6-51.8		51.9	10.5	21.0	64.1	49.8-54.0	
Brown	2,109	48.9	9.0	17.5	63.7	48.5-49.3		52.6	9.7	14.7	68.3	52.2-53.0	
Indigenous	27	47.9	10.3	22.8	57.8	43.8-51.9		49.5	12.7	20.8	60.8	44.5-54.5	
Working status													
Working	2,389	50.4	7.7	19.1	62.8	50.1-50.7	<0.01	53.9	8.6	16.3	67.2	53.6-54.3	<0.01
Not working	2,601	48.4	9.5	13.7	65.4	48.0-48.8		51.5	10.4	14.7	68.3	51.1-51.9	
Family income (minimum wages)													
Less than 1***	879	48.0	9.6	13.7	65.4	47.4-48.7	<0.01	51.3	10.8	19.4	68.3	50.6-52.1	0.02
From 1-2	1,729	48.6	9.1	14.2	62.8	48.2-49.1		52.5	9.7	14.7	67.4	52.0-52.9	
From 2-5	1,647	49.8	8.3	18.3	62.5	49.4-50.2		52.8	9.4	18.1	67.2	52.3-53.3	
From 5-10	429	51.1	7.1	22.6	63.6	50.5-51.8		53.8	8.9	18.9	64.1	53.0-54.7	
From 10-15	139	51.1	6.9	29.0	61.2	49.9-52.3		54.1	8.2	22.9	64.3	52.7-55.5	
From 15-20	56	51.5	8.2	24.9	60.0	49.3-53.7		54.9	7.5	29.2	65.5	52.9-56.9	
More than 20****	23	52.1	6.3	36.5	56.6	49.4-54.8		53.9	7.4	38.7	60.8	50.7-57.1	
Not reported	88	53.7	5.9	24.9	61.1	52.4-54.9		57.9	6.1	24.2	67.7	56.6-59.2	
Incidence of complaints													
In the last 7 days	761	44.4	9.4	18.8	61.6	43.8-45.1	<0.01	48.3	10.6	18.6	65.8	47.5-49.0	<0.01
In the past	871	50.6	6.9	20.7	63.7	50.2-51.1		53.7	8.5	19.6	67.2	53.1-54.3	
In the last 7 days and in the past	855	40.5	10.4	13.7	62.5	39.8-41.2		47.0	11.6	14.7	67.2	46.2-47.8	
No complaints	2,503	53.4	4.6	20.8	65.4	53.2-53.6		55.6	7.4	17.8	68.3	55.3-55.9	

*Physical component summary of the SF-12.
**Mental component summary of the SF-12.
***Less than 1 = US$313.89.
****More than 20 = US$6,277.78.
PCS-12: physical component summary; MCS-12: mental component summary.

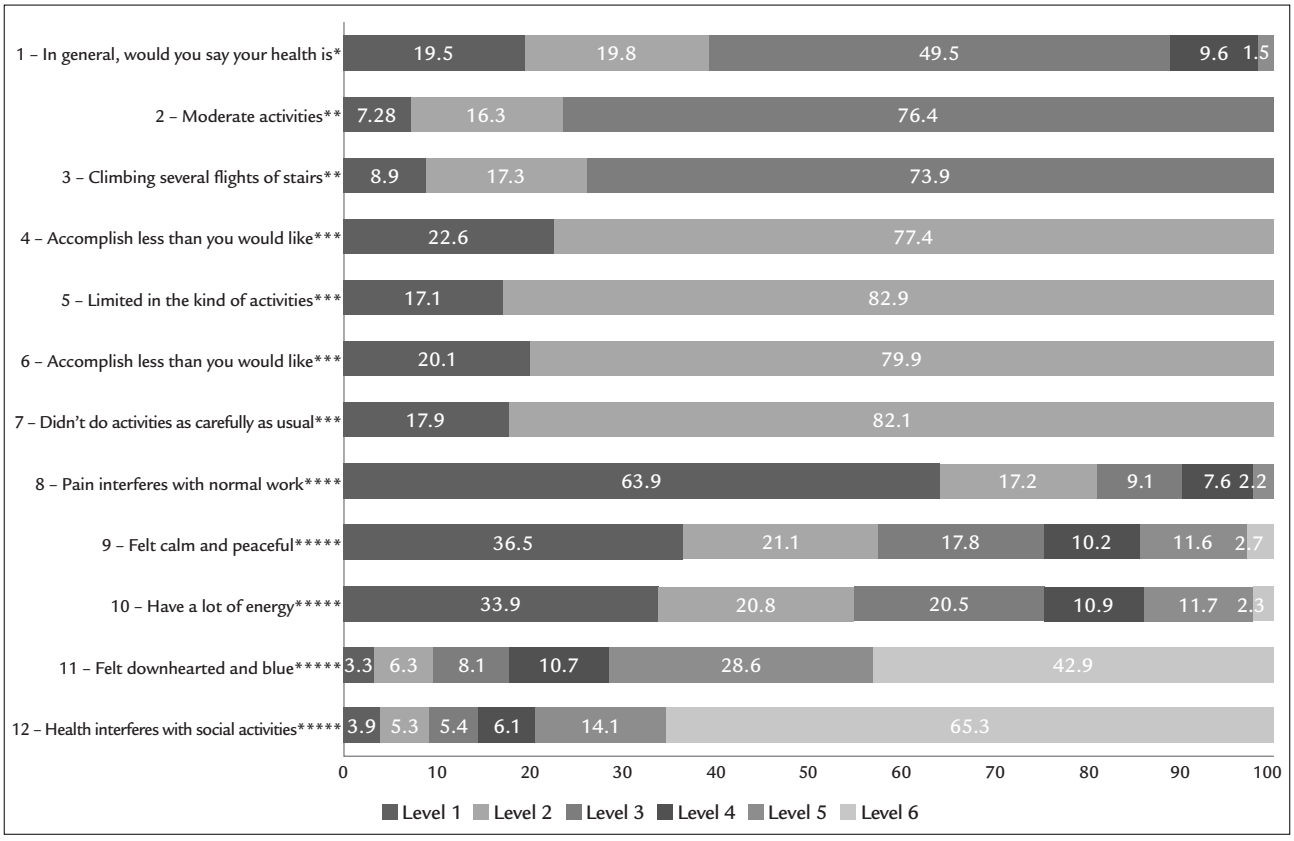

FIGURE 1 Frequency distribution of responses in the 12 items of the SF-12 (%).
*1) Excellent; 2) Very good; 3) Good; 4) Fair; 5) Poor.
**1) Yes, limited a lot; 2) Yes, limited a little; 3) No, not limited at all.
***1) Yes; 2) No.
****1) Not at all; 2) A little bit; 3) Moderately; 4) Quite a bit; 5) Extremely.
*****1) All of the time; 2) Most of the time; 3) Good bit of the time; 4) Some of the time; 5) A little of the time; 6) None of the time.

Discussion

Our study provides the mean values for the two summary scores of the SF-12, according to different sociodemographic factors, in the Brazilian population. Brazil is a country of continental dimensions with socioeconomic differences in their various regions and therefore the importance of an assessment that is representative of the different regions of the country.

The use of a quality-of-life measure to describe the health of a population makes it possible to identify the most compromised dimensions of well-being and to establish health policies.[5,20] Measures that offer normalized scores, such as the SF-12, also enable a direct comparison of the results to a reference population, allowing losses in quality of life to be interpreted in terms of deviations from normality.[21-23] Scores can be understood as separation from expected or typical scores. So, norm-based interpretation answers the questions of whether or not an observed score is typical: Is the score expected for this individual or group of individuals? In the present study, the assessment of the quality of life in a sample of the Brazilian population can be directly compared to that of the population of the United States, where the SF-12 was validated.[19]

The SF-12 values observed in our study are relatively low for the physical component and high for the mental component, namely 49.3 (8.7) for PCS-12 and 52.7 (9.7) for MCS-12 in the general Brazilian population. Similar to our results, the SF-36 version 2 normative data for Brazil, the study by Laguardia et al.[24] found the value of 49.3 (95CI 49.1-49.5) for physical scores (PCS) and 51.1 (95CI 50.9-51.3) for mental scores (MCS), but in another study evaluating specifically the SF-12 scores in 2,459 people of working age in the state of Minas Gerais, city of Montes Claros, the scores found were 49.6 (9.0) and 51.9 (8.6), respectively.[9] In another study, in the city of Belo Horizonte, the final score for the physical component of the SF-12 varied from 20.5 to 64.9, with a median of 50.56. The final score for the mental component varied from 11.0 to 65.5, with a median of 48.43.[11]

The distribution of the SF-12 responses as presented in Figure 1 shows that there was little impairment of the items evaluated, and for the questions about moderate activities, climb flights, accomplished less (physical), limited in kind of work and accomplished less (emotional), the frequency of individuals without impairment was greater than 70%. In other Brazilian studies, similar results were observed.[9-12,14]

The summary measures reveal a lower quality of life related to physical component among Brazilians. Some studies have shown that low socioeconomic development can lead to lower expectations in relation to health, causing individuals to assess their quality of life with values higher than expected. This effect has been noted mainly in males, so that different values assigned to the body, the pressing need of work, can be observed.[25,26] Thus, the observed values may be overestimated in relation to the US population, where the best socioeconomic status cannot exert the same influence as in Brazil.

We note that there is proportionality between the genders, with a slightly higher number of females, and, consistent with other studies, the female gender had worse quality of life scores than males.[27-29] The SF-12 scores were similar to another Brazilian study: self-perception of physical and mental health among women studied showed a mean score of 47.6 (SD = 8.9) and 43.6 (SD = 11.8), respectively.[14] The scientific literature has demonstrated that, although women have a longer life expectancy, they have shorter periods than males in which they are free of disabilities, which suggests a gender difference in terms of compromised quality of life. The factors commonly addressed to explain the poorer quality of life among women are related to gender differences in social opportunities and higher mortality rates among men at younger ages.[29,30]

A different distribution of chronic diseases and functional capacity by gender may also influence these differences between men and women. In a population-based study conducted in Brazil to evaluate the quality of life of seniors based on the SF-36, women were in a worse situation than men in all SF-36 scales. According to the authors, the fact that women exhibit a worse self-assessed level of health may be attributed to the greater perception and knowledge that they have regarding diseases and symptoms, considering their role as family health caregivers, which makes women dedicate more attention to the signs of diseases.[26]

The summary scores systematically fall according to age, which also occurs in the population of other countries.[21-23,31,32] PCS-12 was more influenced by advances in age. This suggests that losses related to normal ageing may be more related to the physical component, which undergoes inexorable transformations over time.[28] In Brazil, the assessment of primary health care received by the elderly and health-related quality of life, based on SF-12 scores, showed a PCS 38.1 ± 11.6 and a MCS 48.7 ± 10.4.[8] Compromised mental health, on the other hand, is more related to health complications, which become more prevalent in old age, compared with age per se, as demonstrated in previous studies carried out in Brazil.[13,29,33]

Another important factor is the employment status, because, according to the results found, being employed gives a better perception of quality of life compared to the group of inactive individuals. This was also observed in Portugal.[34] Although being employed is a positive impact factor on assessment, if a person has health problems that prevent him/her from performing their jobs, there is strong impairment of the perceived quality of life. This was observed in a study of health-related quality of life and working conditions on public transport workers in the Metropolitan Region of Belo Horizonte, Brazil. Using the SF-12, the mean values and 95% confidence intervals for the physical scores (PCS) and mental scores (MCS) for the whole sample were 39.90 (95CI 34.27-45.53) and 34.70 (95CI 23.41-45.99), respectively.[10]

Family income had an influence over the physical component. The economic factor has been addressed in a number of studies that compare the expectation of a healthy life in populations from regions with different socioeconomic levels.[35-37] The influence of income on health and well-being is well-known and our data underscore the importance of this aspect in a large country with striking social disparity, such as Brazil. In this sense, studies conducted in Brazil showed that the higher the presence of low income and lower educational levels, the worse the quality of life.[25-27]

Our study has limitations that should be addressed. The sample is not representative of rural areas and no individuals younger than 15 years were included. Although the epidemiological distribution was also respected in relation to educational level, it was not possible to analyze the data collected according to the length of formal education, as this information was not described in the study sample. Some studies also relate quality of life scores with associated diseases, which were not evaluated in this study either. It is important to notice that a univariate analysis cannot infer from some observed results; for example, was the low QoL score observed in widowers due to marital status or aging? Did inactive individuals also present low QoL score compared to active ones due to their employment status or because of their age? Since a multivariate analysis of the socio-demographic factors that affect quality of life in the Brazilian population was not performed, the results must

be interpreted with caution, concerning the influence of socio-demographic factors on quality of life.

Although the SF-12 method was developed in another culture, the use of this tool in our environment facilitates the comparison of quality of life of the Brazilian population with other international studies using the same measures. In addition, the norm-based score allows for an interpretation of population data as deviations of normality and they have the advantage of a direct interpretation in this regard, which facilitates decision-making.

The major contribution of this study is that, up to now, this is the first study assessing a large and representative sample of the Brazilian population in the various regions and subpopulations, and from this point forward, we can provide the basis for comparisons with future research that use this measure for quality of life assessment in Brazil.

Conclusion

The Brazilian population has a lower degree of quality of life related do the physical component, and the SF-12 is a useful and discriminative instrument for assessing health-related quality of life in different socio-demographic groups.

Resumo

Qualidade de vida em uma amostra de adultos brasileiros utilizando o questionário genérico SF-12

Objetivo: Este estudo descreve os escores sumários do questionário Short Form-12 (SF-12), de acordo com os fatores sociodemográficos obtidos em uma amostra probabilística e representativa da população urbana brasileira. **Método:** Cinco mil (5.000) indivíduos, com idade superior a 15 anos, foram avaliados nas cinco regiões do país, em 16 capitais. A seleção dos domicílios foi aleatória. A coleta de dados foi realizada através de entrevistas domiciliares. O questionário SF-12 foi utilizado para a avaliação de qualidade de vida. Características demográficas e socioeconômicas também foram avaliadas: sexo, idade, estado civil, cor da pele, região do país e uso do serviço público de saúde. **Resultados:** O valor médio (DP) do SF-12 para a população total foi de 49,3 (8,7) para o componente físico (PCS-12) e 52,7 (9,7) para o componente mental (MCS-12). Foram encontradas diferenças estatísticas para sexo (PCS-12 e MCS-12), idade (PCS-12) e estado laboral (PCS-12 e MCS-12). Mulheres, idosos, viúvos, indivíduos que não estavam trabalhando, pessoas com menor renda e queixas nos últimos sete dias apresentaram valores médios mais baixos (PCS-12 e MCS-12).

Conclusão: Os resultados apresentados fornecem bases populacionais para comparações com pesquisas futuras que utilizem o SF-12 para a avaliação da qualidade de vida no Brasil. A população brasileira tem um menor grau de qualidade de vida relacionada ao componente físico, e o SF-12 é um instrumento útil e discriminativo para a avaliação de qualidade de vida em diferentes grupos sociodemográficos.

Palavras-chave: Qualidade de Vida. Inquéritos e Questionários. Brasil. Inquéritos Epidemiológicos. Fatores Socioeconômicos.

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A review on the relationship between marital adjustment and maternal attachment

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Summary

Objective: To determine the relationship between marital adjustment of mothers who have babies between 1-4 months old and their maternal attachment; as well as the relationship of maternal attachment and marital adjustment with sociodemographic characteristics.
Method: The research is descriptive and correlational. Its sample consists of 113 mothers. Maternal Attachment Index (MAI) and Marital Adjustment Scale (MAS) are used as data collection tools.
Results: We found that, for mothers who participated in this research, the average level of maternal attachment is 92.17 ± 8.49, and the average level of marital adjustment is 43.06 ± 7.90. We discovered that the maternal attachment level is higher for mothers who have completed high school and university, those who breastfeed their babies exclusively and whose spouses help care for the baby. We also discovered that the Marital Adjustment Score is higher among mothers who are employed, get married by companionship (not arranged), continue attending pregnancy classes and whose duration of marriage is between 1-5 years and 10-15 years. There is weak positive relationship (r=0.38; p=0.00) between marital adjustment and maternal attachment; and the regression analysis that is run to explain this relationship is statistically significant (F=26.131; p<0.05).
Conclusion: In our study, the level of maternal attachment was high, while the level of marital adjustment was liminal. There are many factors affecting sociodemographic characteristics, pregnancy and baby care. The level of marital adjustment for mothers increases the maternal attachment.

Keywords: Mothers. Mother-child Relations. Family Relations. Marriage.

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Introduction

Family is the smallest building block of the society and good family relations is the guarantee of the future of the society.[1] The foundation of the family is laid through the marriage of couples who pledges many promises to each other, such as commitment, faithfulness and fulfilling responsibilities.[2,3] After marriage, individuals start to live together and raise their children that will be born in their family environment.[4,5] The quality of the marriage is determined with concepts of adjustment, satisfaction and happiness, as well as evaluations of married couples.[1] Marital adjustment is the satisfaction and happiness couples have in their marriage.[6] There are many factors affecting the marital adjustment of couples, such as ages of couples, duration of marriage, communication between them, fulfilling their desires and expectations, making common decisions, relations with the family and relatives, agreeing on leisure time activities and family budget.[1] The interaction of children who are raised in a family environment with marital adjustment, consistency and stability is more qualified and they have healthier adolescence.[7] According to the social learning theory of Bandura, a child learns negative behavior examples through observation.[8] Problems brought by marital maladjustment may cause couples to demonstrate negative behaviors which lead to the formation of problematic behaviors in

children and make them take negative behaviors as their role model.[7,9]

The word "attachment" is used for both "the attachment of the baby to mother" and "the emotional bonding between mother and children."[10] Maternal attachment is a unique relationship that develops between the mother and the baby, is persistent,[11,12] carries on its impact for lifetime by affecting the development, relationship and adjustment of the child.[10] Existence of a warm, persistent and close relationship between the mother and the baby,[13] and formation of satisfactory interaction and attachment[14] positively affect the development of maternal attachment. This is the basis of the attachment experiences that the child will have later. If there is no reliable attachment established in the first year of the life, the baby might have emotional, social, physical, mental and lingual development problems.[12] Midwives/nurses have critical roles in stimulating positive mother-infant relationship after delivery, supporting and evaluating the normal attachment process between mother and infant.

The purpose of this research was to determine the relationship between marital adjustment of mothers who have babies between 1-4 months old and their maternal attachment; as well as the relationship of maternal attachment and marital adjustment with sociodemographic characteristics. The research attempts to provide answers for questions of "Is there a relationship between marital adjustment and maternal attachment?" and "Is there a relationship between marital adjustment, maternal attachment and sociodemographic characteristics of parents?"

Method

This is a descriptive and correlational study, conducted in the Bağcılar Training and Research Hospital Pediatrics Clinic between December 2014 and April 2015, with the participation of mothers that had babies between 1-4 months old. Before starting the research, the approval of the institution and the Bağcılar Training and Research Hospital Ethics Committee approval (decision no:2015-353) was obtained.

It was calculated that at least 109 people were needed for the research in order to have 90% significance with α=0.05 level, when the correlation between Marital Adjustment Score and Maternal Attachment Score was projected to have mid-level (r:0.300) influence. The sample consisted of 113 mothers who had 1-4 months old babies receiving treatment in pediatric clinics during the period of the research.

Data collection tools

Information form, Maternal Attachment Index and Marital Adjustment Scale (MAS) were used as data collection tools.

Information form

It involved 19 questions that were prepared by researchers pondering information about sociodemographic characteristics, marriage, pregnancy, maternity and baby.

Maternal Attachment Index

Maternal Attachment Index (MAI) was developed by Mary E. Muller in 1994 to measure attachment with maternal love. Muller has formed the questions of the index through the literature examining maternal adaptation and maternal attachment. MAI, which measures maternal emotions and behaviors demonstrating love, is an index that illiterate women can apply by themselves.[11] Studies on validity and reliability tests for the Turkish version of the MAI were completed by Kavlak and Şirin in 2004 with the participation of 165 mothers who have healthy babies.[12] This index includes 26 articles with 4-point Likert scale varying between "always" and "never." Each article has direct statements and is calculated as "Always (a) = 4 points, Often (b) = 3 points, Sometimes (c) = 2 points and Never (d) = 1 point." The lowest score to be obtained from the index is 26 and the highest score is 104. The increase in the overall score obtained from the scale shows that mother's maternal attachment increases.[12]

Marital Adjustment Scale (MAS)

The scale has 15 articles in total and was developed by Locke and Wallace.[15] The validity and reliability tests for the Turkish version of the scale were completed by Kışlak-Tutarel.[16] In MAS, one question measures general adjustment, eight questions measure possible agreement spaces, and six questions measure the adjustment regarding conflict resolution, loyalty and communication. Scores to be obtained from the scale range between 1 and 60 and higher scores show marital adjustment, whereas lower scores show marital maladjustment. The breakpoint to differentiate individuals with adjusted and maladjusted marriages is determined to be 43.5.[16]

For mothers who agreed to participate in the research after being informed, a consent form was signed. The mothers were then informed about how to fill in the MAI and MAS. They were asked to fill them completely.

Evaluation of the data

Frequencies, percentages, means and standard deviations were used to analyze the data. Mann-Whitney U test and Kruskall Wallis test were used to compare the data. The correlation between variables was identified with Spearman Correlation and Regression Analysis. The statistical significance was defined to be $p<0.05$. In addition to the researchers, a statistics expert was also involved in the data analysis process.

Results

According to characteristics of the research group, we found that most of them were part of a nuclear family (80.5%), had one or two children (34.5%), were aged between 26-30 years (34.5%), had primary or secondary school degrees (34.5%) and were not working (85.8%). The age of getting married for 47.8% of mothers was 21-25 years old, the duration of marriage for 55.8% of them was 1-5 years and 56.6% of them got married by companionship (not arranged). 96.5% of them became pregnant in a natural way, and it was intentional in 81.4% of the cases; 57.5% of the babies were boys and 51.3% of them were breastfed exclusively (Table 1).

The average of the level of maternal attachment for mothers who participated in the research was 92.17 ± 8.49. Considering that the lowest score that can be obtained from the MAI is 26 and the highest score is 104, the maternal attachment level for mothers was high. The average of the level of marital adjustment for the research group ranges between 43.06±7.90. Considering that the breakpoint is 43.5 to differentiate between well-adjusted and maladjusted in the MAS, the marital adjustment for the research group was considered marginal (Table 2).

Table 3 presents comparison of maternal attachment and marital adjustment scores for mothers with descriptive characteristics of the group. We found a statistically significant ($p<0.05$) difference between average maternal attachment scores of mothers that participated in the research and their level of education; and maternal attachment scores of mothers who were high school or university graduates is higher than those who are only literate ($p=0.03$). A statistically significant difference was observed between the two types of marriage in terms of the participants' maternal attachment scores. The mean maternal attachment score was higher for those who got married by companionship in comparison to those participants who entered arranged marriages ($p=0.00$). We found a statistically significant relationship between maternal attachment and type of feeding for the baby; and the average of maternal attachment scores was higher for mothers who breastfeed exclusively compared to those breastfeeding as well as offering baby formula ($p=0.00$) (Figure 1). It was established that the average of maternal attachment scores for mothers whose spouses help caring for the baby care was statistically significant higher ($p=0.02$) (Figure 2). There was no statistically significant difference between maternal attachment and age of mother, employment status for mother, family type, number of children in the family, age at the time of marriage, duration of marriage and gender of the baby ($p>0.05$).

When descriptive characteristics of the group and average of their marital adjustment scores were compared, it was found that the marital adjustment scores were higher for working mothers compared to those who were not working ($p=0.04$), for those who got married by companionship compared to those with arranged marriages ($p=0.01$), for those whose duration of marriage was 1-5 years and 10-15 years compared to those whose duration of marriage was 6-10 years. There was a statistically significant difference between average of marital adjustment scores of mothers and their level of education; marital adjustment scores of mothers who were graduates of high school and university were higher than for those who were only literates and illiterates ($p=0.00$); additionally, marital adjustment scores for mothers who were university graduates were higher compared to those who were graduates of primary and secondary schools ($p=0.00$). In case of having spouses providing support for baby care, the average of marital adjustment scores was statistically significantly higher ($p=0.001$) (Figure 2). There was no statistically significant difference between marital adjustment and age of mother, family type, number of children in family, age of getting married, gender of baby and type of feeding for the baby ($p>0.05$).

Table 4 presents the comparison of maternal attachment and marital adjustment scores for mothers according to their pregnancy, natal and postnatal characteristics. The average of maternal attachment scores was statistically significantly higher for mothers who went to regular checks during their pregnancy compared to those who did not ($p=0.00$). There was no statistically significant difference between the average of maternal attachment scores and type of conception, actualization of pregnancy, experiencing problems during pregnancy, attending pregnancy classes, delivery method, experiencing problems during delivery and baby staying in the hospital after birth ($p>0.05$).

When the average of marital adjustment scores for mothers that participated in the research was examined, the average of marital adjustment scores was statistically significantly higher for those who became pregnant in a

natural way, got regular checks during pregnancy and attended pregnancy classes ($p<0.05$). There was no statistically significant difference between the average of marital adjustment scores and type of conception, experiencing problems during pregnancy, type of delivery, experiencing problems during delivery and baby staying at the hospital after birth ($p>0.05$).

Table 5 presents the correlation between level of maternal attachment and marital adjustment levels for mothers. There was a weak and positive correlation between marital adjustment and maternal attachment ($r=0.38$; $p=0.00$).

The regression analysis, which was run to identify the correlation between marital adjustment and maternal attachment, was statistically significant ($F=26,131$; $p<0.05$). The correlation between the variables maternal attachment and marital adjustment, which was a determinant of maternal attachment level (explanatory power), was weak ($R^2=0.183$). The level of marital adjustment for mothers increased their level of maternal attachment (ß=0.469) (Table 6) (Figure 3). According to these results, marital adjustment was a determinant of maternal adjustment. Its weight on maternal attachment was 18.3%.

Discussion

In this study, which was conducted to determine the relationship between marital adjustment of mothers who had babies between 1-4 months old and their maternal attachment, the level of maternal attachment for mothers was high (92.17 ± 8.49); and their level of marital adjustment was liminal (43.06 ± 7.90) (Table 2). In a study conducted by Alan and Ege[17] with 135 mothers that had 4-6 months old babies, the average MAI was 96.53 ± 9.25. In the research conducted by Kavlak and Şirin[12] on the adaptation of MAI for Turkish society, the average score of maternal attachment for mothers with 1-month old babies was found to be 94.87 ± 6.04, and for mothers with 4-months old babies, 95.85 ± 6.29. In a study conducted by Öztürk and Saruhan[18] on the relationship between depression and maternal attachment for mothers who had 1-4 month old premature babies treated in hospital, the average of maternal attachment scores was 87.18 ± 5.46. Shin and Kim[19] found, in a study with 196 Korean mothers, an average score of maternal attachment of 94.26 ± 9.74. While the average score of maternal attachment in the present study shows parallelism with findings of other studies about babies with similar age groups, it was relatively higher than scores of studies on mothers whose premature babies are treated in the hospital.[18] The findings of these studies demonstrate that the maternal attachment scores increase as babies grow up. Moreover, mothers are able to stay with their babies during their treatment period in hospital and the attachment process is not affected. It is thought that this information supports the high levels of maternal attachment.

We observed a statistically significant difference ($p<0.05$) between maternal attachment scores and their level of education; the maternal attachment scores for mothers who were graduates of high school or university was higher than those who were only literates (Table 3). In the research conducted by Alan and Ege,[17] there was no statistically significant relationship between the average MAI scores for mothers and their level of education. Also, in another research, it was demonstrated that there was no relationship between the level of education of the mother and attachment.[20]

Breastfeeding increases safe attachment by enabling mother to develop deep and lasting bond with her child and meet the child's needs with care and kindliness.[10] When the maternal attachment scores and type of feeding for the baby were compared, there was a statistically significant difference ($p<0.05$); the scores of mothers who breastfeed exclusively were higher than those who combined breastfeeding and baby formula (Table 3). In the study conducted by Himani and Kumar[21] examining the attachment between mothers and babies, breastfeeding within the first hour of birth increased the mother-baby attachment. In another research, the authors found that attachment problems increased with mothers who were not able to provide breast milk or provided additional baby formula for any reason.[22]

In order for parents to have marital adjustment, factors such as family type, type of marriage and duration of their marriage are influential.[7] In the research conducted by Ende İnce and Güdücü Tüfekçi[23] to evaluate marital adjustment and life satisfaction of parents with disabled children and to identify influential factors, marital adjustment was higher for parents who got married by companionship. We observed that the marital adjustment scores for those with compassionate marriage were higher than those with arranged marriages ($p<0.05$) (Table 3). In light of these findings, it can be commented that companionship of couples when getting married and taking responsibilities in it increases marital adjustment.

We found that there was a statistically significant difference ($p<0.05$) between duration of marriage and marital adjustment scores; the marital adjustment scores for those whose duration of marriage was 1-5 years and 10-15 years were higher than those whose duration of

TABLE 1 Distribution of mothers according to their descriptive characteristics (N=113).

Characteristics		N	%
Family type	Nuclear family	91	80.5
	Extended family	22	19.5
No. of children in the family	1	44	38.9
	2	39	34.5
	3	17	15
	4 and more	13	11.5
Age of mother	16-20	11	9.7
	21-25	34	30.1
	26-30	39	34.5
	31-35	15	13.3
	Above 35	14	12.4
Level of education for mother	Illiterate	20	17.7
	Literate	22	19.5
	Primary and elementary school	39	34.5
	High school	22	19.5
	University	10	8.8
Employment status for mother	Working	16	14.2
	Not working	97	85.8
Age at the time of marriage	15-20	48	42.5
	21-25	54	47.8
	Above 25	11	9.7
Duration of marriage	1-5 years	63	55.8
	6-10 years	31	27.4
	11-15 years	13	11.5
	More than 15 years	6	5.3
Type of marriage	Companionate marriage (not arranged)	64	56.6
	Arranged marriage (traditional marriage)	49	43.4
Type of conception	Normal	109	96.5
	Assisted reproductive techniques	4	3.5
Planning of pregnancy	Planned	92	81.4
	Unplanned	21	18.6
Delivery method	Normal	59	52.2
	C-section	54	47.8
Gender of the baby	Girl	48	42.5
	Boy	65	57.5
Type of feeding for the baby	Breastfeeding exclusively	58	51.3
	Breastfeeding and baby formula	44	38.9
	Breast milk by breast milking and baby formula	11	9.7

TABLE 2 Level of maternal attachment and marital adjustment for mothers.

	Mean±SD	Min.	Max.	Scale Min-Max.
Maternal attachment score	92.17±8.49	63.00	104.00	26-104
Marital adjustment score	43.06±7.90	21.00	58.00	0-60

TABLE 3 Comparison of maternal attachment and marital adjustment scores for mothers with descriptive characteristics of the group.

Descriptive characteristics		**Maternal Attachment Score**			**Marital Adjustment Score**		
	N=113	**Mean±SD**	**Test value**	**p-value**	**Mean±SD**	**Test value**	**p-value**
Age of mother							
16-20	11	91.18±11.67	3.21*	0.52	41.90±8.96	7.31*	0.12
21-25	34	92.94±7.95			45.23±7.69		
26-30	39	91.56±7.53			41.48±7.35		
31-35	15	94.80±8.21			45.13±7.08		
> 35	14	90±10			40.85±9.15		
Employment status for mother							
Working	16	93.93±7.99	655**	0.31	46.31±8.22	532**	0.04
Not working	94	91.88±8.57			42.52±7.76		
Level of education for mother							
Illiterate[1]	20	89.90±9.35	10.18*	0.03	38.50±9.6	13.48*	0.00
Literate[2]	22	89.13±7.89		Diff.	40.27±7.2		5>1,2,3
Primary and elementary school graduate[3]	39	92.79±8.24		4>2	44.00±5.96		4>1,2
High school graduate[4]	22	94.40±8.83		5>2	45.54±7.15		
University graduate[5]	10	96.10±5.80			49.20±8.20		
Family type							
Nuclear family	91	92.16±8.56	994.5**	0.96	43.70±7.90	744**	0.06
Extended family	22	92.22±8.38			40.40±7.51		
No. of children in the family							
1	44	92.61±7.78	1.58*	0.66	44.36±7.90	4.67*	0.19
2	39	92.87±8.68			43.41±7.89		
3	17	91.47±8.32			42.23±6.29		
4 and more	13	89.53±10.67			38.69±9.05		
Age of getting married							
15-20	48	93.50±8.09	2.98*	0.22	43.41±7.66	0.46*	0.79
21-25	54	91.81±8.12			42.66±7.72		
> 25	11	88.18±11.09			43.45±10.32		
Duration of marriage							
1-5 years[a]	63	91.95±8.66	3.07*	0.38	44.52±7.5	10.48*	0.01
6-10 years[b]	31	90.77±9.02			39.67±8.08		Diff.
11-15 years[c]	13	95.46±7.42			45.23±8.17		a>b
> 15 years[d]	6	94.667±3.93			40.50±5.01		c>b
Type of marriage (not arranged)							
Companionate marriage (not arranged)	64	94.31±7.59	1,013.0**	0.00	44.81±7.28	1,135.0**	0.01
Arranged marriage (traditional marriage)	49	89.38±8.85			40.77±8.17		

(*continues*)

TABLE 3 (Cont.) Comparison of maternal attachment and marital adjustment scores for mothers with descriptive characteristics of the group.

Descriptive characteristics		Maternal Attachment Score			Marital Adjustment Score		
	N=113	Mean±SD	Test value	p-value	Mean±SD	Test value	p-value
Gender of the baby							
Girl	48	92.18±7.54	1,485.5**	0.66	43.58±7.04	1,514.0**	0.78
Boy	65	92.16±9.18			42.67±8.52		
Type of feeding for the baby							
Breastfeeding exclusively	58	94.86±6.36	10.33*	0.00	43.53±8.42	0.82*	0.66
Breastfeeding + baby formula	44	89.20±9.37		Diff.	42.54±7.60		
Breast milk by breast milking and baby formula	11	89.90±10.61		1>2	42.63±6.69		
Having a spouse who helps caring for the baby care							
Yes	80	93.16±8.42	962.5**	0.02	44.87±6.46	811.5**	0.001
No	33	89.78±8.30			38.66±9.35		

p<0.05 indicates statistical significance.
*KW: Kruskall Wallis.
**MV: Mann-Whitney U test.

TABLE 4 Comparison of maternal attachment and marital adjustment scores for mothers according to their pregnancy, natal and postnatal characteristics.

		Maternal Attachment Score			Marriage Adjustment Score		
	N=113	Mean±SD	MWU value	p-value	Mean±SD	MWU value	p-value
Type of conception							
Normal	109	91.95±8.55	121.50	0.133	42.74±7.86	57.50	0.01
Assisted reproductive techniques	4	98.250±2.63			51.75±2.50		
Planning of pregnancy							
Planned	92	92.88±7.57	808.50	0.24	43.51±7.72	847.00	0.37
Unplanned	21	89.09±11.41			41.09±8.59		
Experiencing problems during pregnancy							
Yes	21	93.42±7.38	884.50	0.54	42.23±7.54	836.50	0.33
No	92	91.89±8.73			43.25±8.01		
Getting regular checks during pregnancy							
Yes	87	93.35±7.80	750.00	0.00	44.24±7.22	804.50	0.02
No	26	88.23±9.62			39.11±8.91		
Attending pregnancy classes							
Yes	10	95.50±4.03	409.50	0.28	49.20±5.71	240.00	0.00
No	103	91.85±8.75			42.46±7.85		
Type of delivery							
Normal	59	90.94±8.86	1,330.50	0.13	42.83±7.37	1,549.50	0.80
C-section	54	93.51±7.93			43.31±8.51		
Experiencing problems during delivery							
Yes	13	94.46±7.17	537.50	0.31	42.07±9.6	571.50	0.47
No	100	91.88±8.63			43.19±7.70		
Baby staying in hospital after birth							
Yes	39	91.308±8.38	1,279.00	0.32	41.61±8.65	1,190.00	0.12
No	74	92.63±8.57			43.82±7.43		

TABLE 5 Correlation between level of maternal attachment and marital adjustment levels for mothers.

		Maternal attachment
Marital adjustment	r	0.38
	p	0.00

TABLE 6 The impact of marital adjustment on maternal attachment.

Dependent variable	Independent variable	ß	t	p	F	Model (p)	R^2
Maternal attachment	Constant	71.995	17.938	0.000	26.131	0.000	0.183
	Marital adjustment	0.469	5.112	0.000			

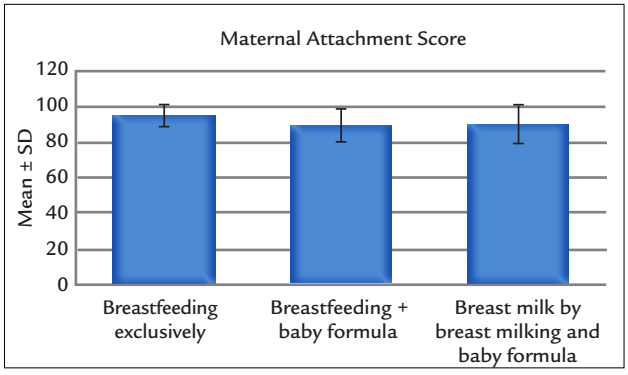

FIGURE 1 The relationship between type of feeding for the baby and maternal attachment.

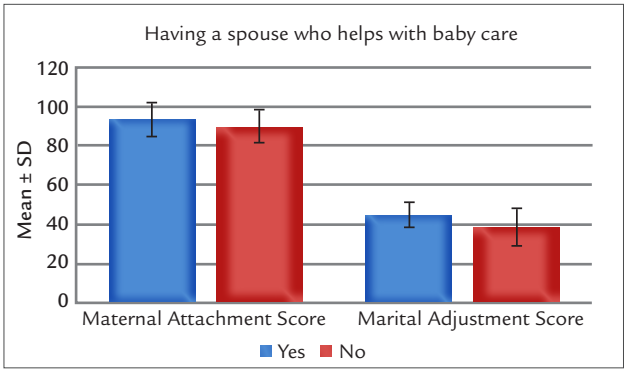

FIGURE 2 The relationship between having spouse who helps caring for the baby and maternal attachment and marital adjustment.

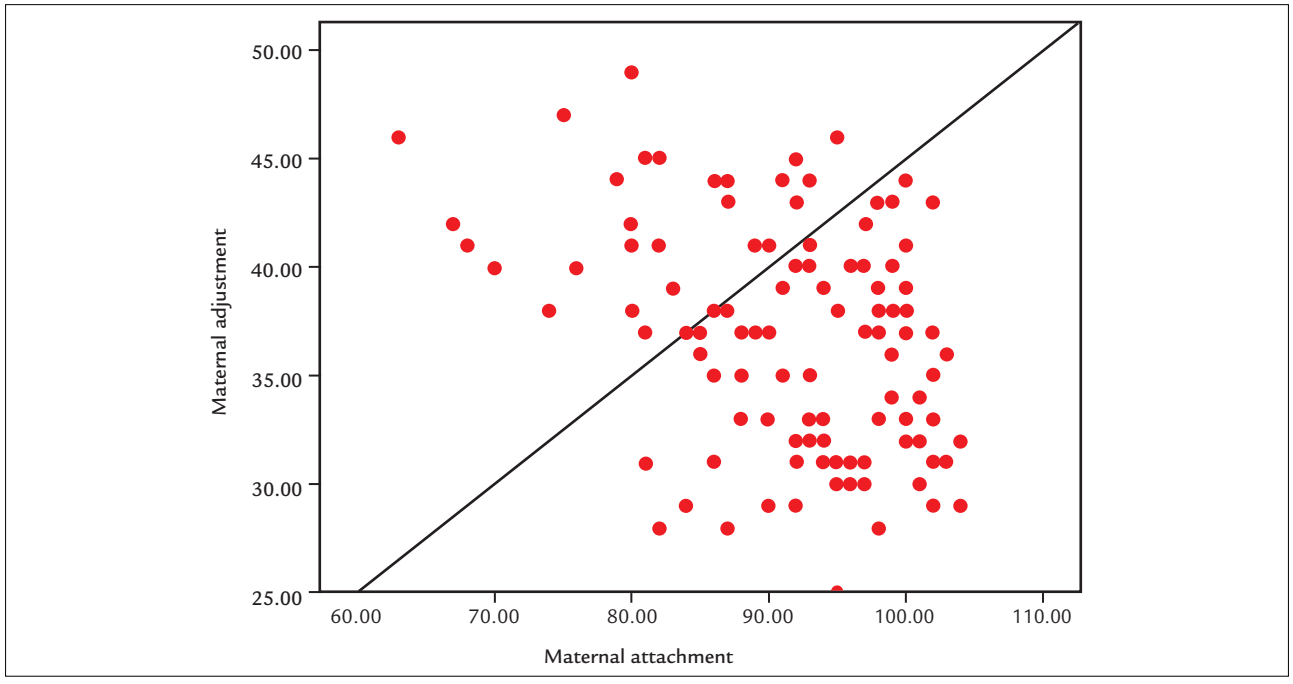

FIGURE 3 The relationship between maternal attachment and marital adjustment.

marriage was 6-10 years (Table 3). Duration of marriage influences marital adjustment. The literature shows that the marital adjustment is lower during the first years of marriage; however, as the duration of marriage increases and children leave home, it increases.[24] One study found that the marital adjustment is higher for those who are married for 6-10 years.[23] According to a study by Yalçın examining the relationship between sociodemographic characteristics of women and their marital adjustment, as duration of marriage increased, women's tendency to evaluate their marriage as "good" decreased. Additionally, conflicts decreased as they were discussed, violence and fights increased, and the tendency of 50% of the women was to remain silent.[24] In a research examining the marital adjustment status of graduate students, there was no statistically significant relationship between duration of marriage and their marital adjustment.[25]

We also observed that the marital adjustment scores for mothers who were working were higher compared to those who were not working; and the highest marital adjustment scores belonged to mothers who were university graduates (Table 3). As level of education increases, the rate of working for individuals also increases. For marriage and family life, working status of spouses positively contributes to the marriage and the family.[3] A study also found that the level of marital adjustment was higher for those having undergraduate and above degrees, civil servants and having more income than expenses.[23] These findings suggest that high level of education and income increases economical, social and cultural prosperity of individuals; and the adjustment in marriages increases in such conditions. Education is a variable related to marital adjustment. As level of education increases, couples may express their emotions and ideas to each other more comfortably and accurately and understand their spouses by experiencing empathy. Moreover, as level of education increases, both spouses may try to resolve conflicts and disagreements by respecting opinions and ideas of each other.[24]

The level of maternal attachment and marital adjustment for mothers is affected by numerous factors related to pregnancy, natal and postnatal period. In our study, there was no statistically significant difference ($p>0.05$) between maternal attachment and type of conception, planning of pregnancy, experiencing problems during pregnancy, attending pregnancy classes, delivery method and experiencing problems during giving birth. We observed that the maternal attachment scores for mothers who undergone regular checks were statistically significantly higher compared to those who did not ($p<0.05$) (Table 4). Similarly, in the study conducted by Öztürk and Saruhan, it was determined that maternal attachment scores were higher in the mothers who received prenatal care.[18] Based on these findings, we can say that having regular checks before giving birth reduces problems that may be experienced in the pre and postnatal periods, in addition to the fact that mother-baby attachment is positively effected in this health period. Also, mothers who received information about birth and postpartum care during pregnancy demonstrate better attachment to their babies after birth.[26] This positively affects mother-baby attachment after giving birth.

There was a statistically significant relationship between the perception of spouses towards their marriage or their level of satisfaction with their relationship and being sensitive parents. The consistency in the relationship between spouses is also important for the baby to understand relationship connections. Tension between parents causes negative affectivity in mother-father-baby relationships.[27] Moreover, lack of adjustment between spouses may negatively affect the parents' roles as mother and father.[7] Parents demonstrate more positive attitudes towards their children in a coherent and happy marriage life with well-developed communication.[17] In our study, we found a statistically significant, weak and positive relationship between marital adjustment and maternal affection ($p<0.05$). The regression analysis performed to identify the relationship between marital adjustment and maternal attachment proved to be statistically significant ($F=26.131$; $p<0.05$). We observed that the correlation between the maternal attachment and marital adjustment variables, which is a determinant of maternal attachment level (explanatory power), is weak ($R^2=0.183$). The level of marital adjustment for mothers increases their level of maternal attachment (ß=0.469) (Table 6) and its weight on maternal attachment is 18.3% (Table 5). In their research, Alan and Ege[17] found a statistically significant correlation between average of MAI scores for mothers and their overall communication with their spouses. In other words, the MAI scores for mothers who stated that they had good communication with their spouses were higher. A study by Akkoca[22] investigating the mother-baby attachment after birth revealed that marital maladjustment negatively affects mother-baby attachment. These results support the findings of our research. In light of the research findings and information in the literature, we can say that the expected adjustment between spouses occurs in a happy marriage, this adjustment makes parents develop appropriate and desired relations with their children and strengthens the attachment between mother and baby.

Conclusion

We found that the maternal attachment level for mothers of babies aged 1-4 months who were treated in hospital was high. Their level of marital adjustment was liminal, and there was a weak and positive correlation between marital adjustment and maternal attachment. As the level of marital adjustment increased, the level of maternal attachment increased as well. According to our findings, there are many factors affecting levels of maternal attachment and marital adjustment for mothers. We found that the level of maternal attachment was higher for mothers who had a high school or university degree, got married by companionship, breastfed exclusively, got regular checks during pregnancy, and whose spouses helped care for the baby. In terms of marital adjustment, the marital adjustment scores were higher for mothers who were working, had a university degree, were married for 1-5 years and 10-15 years, got married by companionship, became pregnant with the aid of reproductive techniques, got regular checks during pregnancy and attended pregnancy classes, and whose spouses helped care for the baby. Still in accordance with our findings, in order to support mother-baby attachment and marital adjustment, the importance of improving the level of education, getting married by companionship, benefits of getting regular checks and pregnancy classes during pregnancy, breastfeeding exclusively during the first 6 months after birth, and having a spouse that helps care for the baby should be explained. In this context, nurses and other healthcare employees should support mothers since before giving birth by providing counseling to spouses and training. Spouses should be included in the process of mother-baby attachment, and the importance of marital adjustment for both mother and baby should be emphasized for couples during pregnancy observations and classes. It should be explained that there is a relationship between marital adjustment and maternal attachment; and marital adjustment increases maternal attachment.

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Efficacy and safety of ceftazidime-avibactam in the treatment of complicated intra-abdominal infections (CIAIs) and complicated urinary tract infections (CUTIs): A meta-analysis of randomized controlled trials

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Summary

Objective: The aim of this study was to assess the efficacy and safety of ceftazidime-avibactam in the treatment of complicated intra-abdominal infections (CIAIs) and complicated urinary tract infections (CUTIs) with meta-analysis method.
Method: We included six randomized clinical trials identified from Medline, Embase, Cochrane Library, "ISRCTN Register" and "ClinicalTrials.gov" which compared ceftazidime-avibactam with comparison group. The meta-analysis was performed using Review Manager software version 5.3.
Results: Ceftazidime-avibactam versus active comparisons demonstrated a statistically significant higher rate of microbiological response success on microbiological evaluable populations at the test-of-cure visit (95CI 1.10-2.38, p=0.02) and late-follow-up visit (95CI 1.09-2.23, p=0.02) for the treatment of CUTIs. Ceftazidime-avibactam versus active comparisons demonstrated a statistically significant higher rate of microbiological response success on EME populations at the test-of-cure visit (95CI 1.08-4.27, p=0.03) and late-follow-up visit (OR=1.75, 95CI 1.33-2.29, p<0.0001) for the treatment of CUTIs. Similar results were obtained at the late-follow-up visit (OR = 1.58, 95CI 1.26-1.97, p<0.0001) on microbiologically modified intent-to-treat (mMITT) populations for the treatment of CUTIs. We can find better eradication rates for *E. coli* and *Klebsiella pneumoniae* based on mMITT populations. In terms of AEs, SAEs and mortality, ceftazidime-avibactam had a safety and tolerability profile broadly similar to the comparison group.
Conclusion: This meta-analysis provides evidence of the efficacy of ceftazidime-avibactam as a potential alternative for the treatment of patients with CUTIs, and CIAIs.

Keywords: Meta-analysis. Ceftazidime. Azabicyclo Compounds. Urinary Tract Infections. Intra-abdominal Infections. Efficacy. Safety.

Yue Zhang and Li-na Tao are both first coauthors, having contributed equally to the study

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Introduction

The incidence of infection with antibiotic-resistant bacteria is steadily increasing in the world, and the treatment of drug-resistant bacterial infection has become a challenge.[1] Complicated urinary tract infections (CUTIs) and complicated intra-abdominal infections (CIAIs) are problematic conditions frequently encountered by physicians. CIAIs generally result from perforation or necrosis of the gastrointestinal tract and release of bacteria into the peritoneal and retroperitoneal space[2] as well as postoperatively due to leaks or deep surgical wound infections. Among the Gram-negative pathogens associated with CIAIs, the most common are the Enterobacteriaceae, especially *Escherichia coli* (*E.coli*) and *Klebsiella*

spp.[3] CUTIs include emphysematous pyelonephritis, emphysematous pyelitis/cystitis, xanthogranulomatous pyelonephritis, renal/perirenal abscess and renal papillary necrosis.[4] The bacterial epidemiology of CUTIs in this study is similar to that generally reported elsewhere in North America, Latin America and Europe. *E. coli* remains the most frequently isolated uropathogen, followed by *Pseudomonas aeruginosa (P. aeruginosa)* and *Proteus spp.*[5,6] *E. coli* is the predominant Gram-negative uropathogen.[7] In the past three decades, β-lactam antibiotics including second- and third-generation cephalosporins, β-lactam/β-lactamase inhibitor combinations and carbapenems have been widely used in clinical practice for the treatment of CIAIs and CUTIs because of their broad coverage of clinically important Gram-negative bacteria.[8] Pathogens in these infections are often highly-resistant to standard antibiotics[9,10] in some regions and countries. Thus, there is an urgent requirement for CIAI and CUTI therapies.[11,12] Ceftazidime-avibactam has been shown to be effective in phase II clinical trials conducted in patients with CIAIs or CUTIs and has also been shown to be generally well tolerated, with a safety profile so far seen to be broadly similar to the established safety profile of ceftazidime.[13-15] Ceftazidime-avibactam is an important new option for such cases in CIAIs (in combination with metronidazole) and CUTIs patients. Ceftazidime is a widely used expanded-spectrum anti-pseudomonal cephalosporin and avibactam with a novel non-β-lactam β-lactamase inhibitor.[13,14] Ceftazidime-avibactam was recently granted accelerated approval by the FDA for the treatment of CUTIs and CIAIs combined with metronidazole in adult patients when treatment options are limited.[16] Ceftazidime-avibactam is an antibacterial agent that consists of an existing third-generation cephalosporin combined with a novel β-lactamase inhibitor. An important advantage of ceftazidime-avibactam is that avibactam can expand the antibacterial activity of ceftazidime against Enterobacteriaceae and *P. aeruginosa* by inhibiting AmpC, extended-spectrum β-lactamase, and carbapenemase producing strains.[17] We conducted a meta-analysis of RCTs to clarify whether the use of ceftazidime-avibactam could be associated with improved outcomes in comparison with those achieved with other antibiotics for the treatment of infections, including CIAIs and CUTIs.

Method

Search strategy and selection criteria

To identify relevant randomized trials, we searched the literature through PubMed, Embase and Cochrane Library up to 30 June 2016 with the search strategies "ceftazidime-avibactam" or "ceftazidime/NXL104" and "randomized controlled trials" or "randomized" or "randomized." To identify relevant unpublished studies, we searched "ISRCTN Register" and "ClinicalTrials.gov" with the same search strategies up to 30 June 2016. In addition, we searched all references in the relevant articles and reviews for additional eligible studies.

Two reviewers (Zhang and Tao) searched and examined relevant studies independently. Individual RCTs on the efficacy and safety of ceftazidime-avibactam in comparison with other antibiotics for the treatment of patients with CIAIs and CUTIs were included for analysis. We excluded the following articles: experimental trials researched in animals, articles focusing on pharmacokinetic or pharmacodynamic variables and trials focusing on the in-vitro activity of ceftazidime-avibactam.

Data extraction

The following data were extracted from each study: year of publication, type of trial design, number of patients, antimicrobial agents and dosage used, treatment duration, time from treatment to test of cure, clinical and microbiological outcomes and adverse effects. Two reviewers (Zhang and Tao) independently extracted the relevant data. Disagreements were resolved by discussion with a third author (Qu).

Analyzed outcomes

The efficacy outcomes of this meta-analysis were clinical treatment success (defined as "clinical cure"), clinical response and microbiological response, respectively assessed at the test-of-cure (TOC) visit, late-follow-up (LFU) visit and end-of-treatment (EOT) visit based on modified intent-to-treat (MITT) population, microbiologically modified intent-to-treat (mMITT) population, clinically evaluable (CE) population, microbiological evaluable (ME) population or extended microbiologically valuable (EME) population in each individual study and incidence of adverse events (AEs).

The MITT population consisted of patients who received at least one dose of the study drug and followed intention-to-treat principles. The mMITT population consisted of patients who met the clinical disease criteria and had ≥ 1 pathogen identified at baseline. The CE population consisted of patients who met the disease definition and had received the scheduled study drug, with sufficient information to determine clinical outcome. The ME population was a subset of the CE population who also had microbiologically documented infections.

The EME population was a subset of ME population. The safety population included all patients who received any IV study therapy.

Clinical cure was the disappearance of acute signs and symptoms related to infection with no requirement for further antibiotic therapy. Clinical response was defined as resolution of all or most pre-therapy signs or symptoms with no further requirement for antibiotics or surgery. Microbiological response was defined as eradication of baseline pathogen.

Quality assessment

The two reviewers (Zhang and Tao) independently extracted the relevant data. The methodological quality of the RCTs was evaluated using the Jadad scoring system[18] on the basis of details of randomization, generation of random numbers, details of the double-blinding procedure, information on withdrawals and allocation concealment. One point was awarded for the specification of each criterion, with a maximum of 5. High-quality RCTs scored 3 or more points. The study quality assessment for unpublished trials could not be done because information on study design was not available from clinical trial registries.

Statistical analysis

The meta-analysis was done using Review Manager, version 5.3. We assessed heterogeneity with Q statistics generated from the χ^2 test and inconsistency with I^2 measure.[19] Significant heterogeneity was judged with p-values less than 0.10 or I^2 more than 50%. The publication bias was assessed by using the funnel plot. We chose to use a Mantel-Haenszel fixed-effect model (FEM) for pooling odds ratio (OR) and 95% confidence interval (CI) for all outcomes (including the MITT, mMITT, ME, EME and CE population) when heterogeneity was not significant. We chose to use a DerSimonian and Laird random-effects model (REM) when heterogeneity was obvious.

Results

Study selection outcomes

A total of 56 articles related to this study were retrieved from the literature and subjected to the selection process. Among the 56 potentially relevant articles, 35 were excluded because the studies described in these articles were non-RCTs or had no results available. Another 15 articles were excluded, as they described part of RCTs that had been already included in the meta-analysis. Finally, six randomized studies were included in the meta-analysis: five published trials and one unpublished trial (NCT01726023 as study 1).

Study characteristics

Table 1 shows the following characteristics of the included RCTs: study design, type of infection, number of patients (MITT, mMITT, CE, ME, EME), mean age, drug information and Jadad score. The meta-analysis was composed of six RCTs for CIAIs and CUTIs. All included studies were RCTs conducted between 2012 and 2016. All included trials were multinational studies. The total sample of the included trials was 3,259 subjects and all trials were conducted exclusively in populations aged 18-90 years. Most subjects in ceftazidime-avibactam groups (for CIAIs in combination with metronidazole) received ceftazidime-avibactam 2,000 mg of ceftazidime and 500 mg of avibactam as intravenous infusion every 8 hours, followed by metronidazole (500 mg as intravenous infusion every 8 hours) for CIAIs.[13,20-22] That, except for one study, in which patients received different doses of ceftazidime-avibactam (500 mg of ceftazidime and 125 mg of avibactam as intravenous infusion every 8 hours).[14] The mean Jadad score of the five publication RCTs was 4.6 (rang 3-5) and four trials had a high score of 5.

Clinical cure success for the treatment of CIAIs

Clinical cure success rate for the treatment of CIAIs in the mMITT sample was provided in three trials totaling 1,139 subjects. The ceftazidime-avibactam group was associated with lower rate of clinical cure success, but the difference was not significant at TOC visit (p=0.11, Table 2), EOT visit (p=0.44, Table 2) and LFU visit (p=0.23, Table 2). Data on MITT patients for the treatment of CIAIs was provided only in one trial, and the clinical cure success rate of ceftazidime-avibactam group was also lower than that of the comparison group at TOC visit (1,043 patients, OR = 0.84, 95CI 0.60-1.17, p=0.30, Table 2), EOT visit (1,043 patients, OR = 0.64, 95CI 0.42-0.97, p=0.04, Table 2) and LFU visit (1,043 patients, OR = 0.94, 95CI 0.68-1.30, p=0.71, Table 2), but again the difference was not significant at TOC visit and LFU visit. The comparison therapy group was associated with significantly more patients achieving clinical cure treatment success at EOT visit in MITT patients. Clinical cure success rate for the treatment of CIAIs in the CE sample was provided in two trials. The ceftazidime-avibactam group was associated with lower rate of clinical cure success, but the difference was not significant at TOC visit (p=0.66, Table 2), EOT visit (p=0.33, Table 2) and LFU visit (p=0.81, Table 2). Data on ME patients for the treatment of CIAIs were provided only in one trial. In both comparisons, ceftazidime-avibactam shows lower success rate than comparison group at TOC visit (212 patients, OR = 0.74,

TABLE 1 The main characteristics of the trials included.

Authors (reference)	RCT study design	Type of infection	Drug regimen		Treatment duration (days)	Time to test of cure visit (days)	Time to end of treatment visit (hours)	Time to late follow-up visit (days)	No. of patients enrolled	Study quality score
			Ceftazidime-avibactam	Comparison						
Mazuski et al.[21]	Multicentre, double-blind, phase III	CIAIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. over 2 h, plus metronidazole at 500 mg i.v. over 60 min q8h	Meropenem at 1,000 mg i.v. over 30 min q8h	8 vs. 8.3	28-35	24	42-49	1,066	5
Lucasti et al.[13]	Multicentre, double-blind, phase II	CIAIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. over 30 min, plus metronidazole at 500 mg i.v. over 1 h q8h	Meropenem at 1,000 mg i.v. q8h	5-14	14	—	28-42	204	5
Vazquez et al.[14]	Multicentre, single-blind*, phase II	CUTIs	Ceftazidime-avibactam at 500 mg/125 mg i.v. over 30 min q8h	Imipenem-cilastatin 500 mg i.v. over 30 min q6h	5 vs. 6	5-9	—	28-42	137	5
Wagenlehner et al.[22]	Multicentre, double-blind, phase III	CUTIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. over 1 h q8h	Doripenem 500 mg i.v. over 1 h q8h	7 vs. 8	21-25	—	45-52	1,033	5
Carmeli et al.[20]	Multicentre, open-label, phase III	CIAIs, CUTIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. for CUTI, plus metronidazole at 500 mg i.v. for CIAI q8h	Best available therapy	5-21	7-10	28	FU1:21-25 FU2:28-32	333	3
NCT01726023	Multicentre, double-blind, phase III	CIAIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v., plus metronidazole at 500 mg i.v. q8h	Meropenem at 1,000 mg i.v. q8h	14	28-35	24	42-49	486	—

*This study was investigator and patient-blind.

CIAIs: complicated intra-abdominal infections; CUTIs: complicated urinary tract infections.

95CI 0.24-2.27, p=0.60, Table 2) and LFU visit (202 patients, OR = 0.76, 95CI 0.25-2.35, p=0.64, Table 2), but at EOT visit shows higher success rate than comparison group (224 patients, OR = 1.52, 95CI 0.35-6.52, p=0.57, Table 2) and the difference was not significant. Data on EME patients was provided in one trial, and the clinical cure success rate of the ceftazidime-avibactam group was also lower than that of the comparison group at TOC visit (219 patients, OR = 0.71, 95CI 0.23-2.17, p=0.54, Table 2), EOT visit (232 patients, OR = 1.44, 95CI 0.34-6.19, p=0.62, Table 2) and LFU visit (209 patients, OR = 0.73, 95CI 0.24-2.24, p=0.58, Table 2), but again the difference was not significant at TOC visit, EOT visit and LFU visit.

Clinical cure success for the treatment of CUTIs

Clinical cure success rate for the treatment of CUTIs on the mMITT sample was provided only in one trial. The ceftazidime-avibactam group was associated with lower rate of clinical cure success, but the difference was not significant at TOC visit, EOT visit or LFU visit (for TOC visit, p=0.42; for EOT visit, p=0.60; for LFU visit, p=0.88, Table 2). In our meta-analysis, the study of Carmeli et al.[20] was split because in this study the LFU visit was divided into FU1 visit (21-25 days post-therapy) and FU2 visit (28-32 days post-therapy).

Microbiological response success for the treatment of CIAIs

Data on the microbiological response success for the treatment of CIAIs were provided in two of the included RCTs with mMITT and EME patients. For mMITT patients, in total, 127 (83.0%) of the 153 patients in the ceftazidime-avibactam therapy group and 141 (86.5%) of the 163 patients in the comparison therapy group achieved microbiological response success. The ceftazidime-avibactam therapy group failed to produce a significant difference in

TABLE 2 Effect of study/patient characteristics for the treatment of CIAIs of clinical cure success and microbiological response success and for the treatment of CUTIs of clinical cure success.

	Type of infection	Treatment success by population	Patients	Analysis model	Odds ratio (95CI)	Heterogeneity (I^2, p-value)
Clinical cure success	CIAIs	mMITT-TOC	1,139	FEM	0.77 (0.56-1.06)	21%, 0.11
		mMITT-EOT	1,139	REM	0.74 (0.35-1.58)	54%, 0.44
		mMITT-LFU	1,139	FEM	0.82 (0.60-1.13)	21%, 0.23
		MITT-TOC	1,043	—	0.84 (0.60-1.17)	—, 0.30
		MITT-EOT	1,043	—	0.64 (0.42-0.97)	—, 0.04
		MITT-LFU	1,043	—	0.94 (0.68-1.30)	—, 0.71
		CE-TOC	1,187	FEM	0.91 (0.59-1.41)	0%, 0.66
		CE-EOT	1,212	FEM	0.78 (0.47-1.29)	13%, 0.33
		CE-LFU	1,173	FEM	0.95 (0.64-1.43)	0%, 0.81
		ME-TOC	212	—	0.74 (0.24-2.27)	—, 0.60
		ME-EOT	224	—	1.52 (0.35-6.52)	—, 0.57
		ME-LFU	202	—	0.76 (0.25-2.35)	—, 0.64
		EME-TOC	219	—	0.71 (0.23-2.17)	—, 0.54
		EME-EOT	232	—	1.44 (0.34-6.19)	—, 0.62
		EME-LFU	209	—	0.73 (0.24-2.24)	—, 0.58
Microbiological response success	CIAIs	mMITT-TOC	316	REM	1.11 (0.23-5.29)	61%, 0.89
		mMITT-EOT	316	REM	1.68 (0.16-18.03)	73%, 0.67
		mMITT-LFU	316	REM	1.12 (0.25-5.08)	59%, 0.88
		ME-TOC	212	—	0.74 (0.24-2.27)	—, 0.60
		ME-EOT	224	—	1.52 (0.35-6.52)	—, 0.57
		ME-LFU	202	—	0.76 (0.25-2.35)	—, 0.64
		EME-TOC	232	—	0.71 (0.23-2.17)	—, 0.54
		EME-EOT	246	—	1.44 (0.34-6.19)	—, 0.62
		EME-LFU	221	—	0.73 (0.24-2.24)	—, 0.58
Clinical cure success	CUTIs	mMITT-TOC	281	—	0.68 (0.27-1.72)	—, 0.42
		mMITT-EOT	281	—	0.52 (0.05-5.82)	—, 0.60
		mMITT-LFU	562	REM	0.96 (0.59-1.58)	0%, 0.88

"—" shows that data in this study was provided only in one trial.

CIAIs: complicated intra-abdominal infections; CUTIs: complicated urinary tract infections; MITT: modified intent-to-treat; mMITT: microbiologically modified intent-to-treat; TOC: test-of-cure; LFU: late-follow-up; EOT: end-of-treatment; ME: microbiological evaluable; CE: clinically evaluable; EME: extended microbiologically valuable; FEM: fixed-effect model; REM: random-effects model.

the number of patients achieving microbiological response sucess at TOC visit (OR = 1.11, 95CI 0.23-5.29, Table 2), EOT visit (OR = 1.68, 95CI 0.16-18.03, Table 2) and LFU visit (OR = 1.12, 95CI 0.25-5.08, Table 2). Similar results were confirmed in the EME analysis with patients with lower rate of microbiological response success in the ceftazidime-avibactam therapy group (at TOC visit, 232 patients, OR = 0.71, 95CI 0.23-2.17; at EOT visit, 246 patients, OR = 1.44, 95CI 0.34-6.19; at LFU visit, 221 patients, OR = 0.73, 95CI 0.24-2.24, Table 2). Data on the microbiological response success for the treatment of CIAIs were provided in one of the included RCTs on ME patients. In both comparisons, ceftazidime-avibactam shows lower success rate than comparison group at TOC visit (p=0.60, Table 2) and LFU visit (p=0.64, Table 2), but at EOT visit shows higher success rate than comparison group (p=0.57, Table 2) and the difference was not significant.

Microbiological response success for the treatment of CUTIs

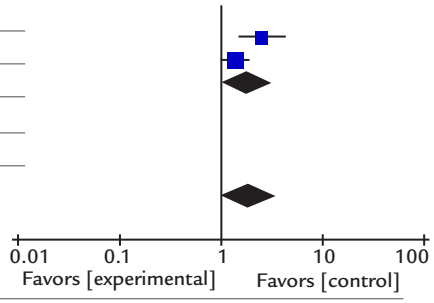
Data on the microbiological response success for the treatment of CUTIs were provided in two of the included RCTs with mMITT patients. The ceftazidime-avibactam group was associated with higher rate of microbiological response success, but the difference was not significant at TOC visit and EOT visit (for TOC visit, p=0.05, Figure 1A; for EOT visit, p=0.87, Figure 1B). In total, 470 (69.0%) of the 681 patients in the ceftazidime-avibactam therapy group and 405 (58.6%) of the 691 patients in the comparison therapy group achieved microbiological response success at LFU visit. The ceftazidime-avibactam therapy group was associated with significantly more patients achieving microbiological response success at LFU visit (OR = 1.58, 95CI 1.26-1.97, p<0.0001, Figure 1C). Data on the microbiological response success for the treatment of CUTIs were provided in one of the included RCTs on MITT patients. In both comparisons, ceftazidime-avibactam shows higher success rate than comparison group at TOC visit (95 patients, OR = 1.20, 95CI 0.51-2.80, p=0.67, data not shown in the figure) and LFU visit (95 patients, OR = 1.13, 95CI 0.51-2.53, p=0.77, data not shown in the figure), but at EOT visit shows lower success rate than comparison group (95 patients, OR = 0.59, 95CI 0.16-2.25, p=0.44, data not shown in the figure) and the difference was not significant. Data on the microbiological response success for the treatment of CUTIs were provided in two of the included RCTs on ME patients. In all, 260 (83.1%) of the 313 patients in the ceftazidime-avibactam therapy group and 250 (75.1%) of the 333 patients in the comparison therapy group achieved microbiological response success at TOC visit. The ceftazidime-avibactam therapy group was associated with significantly more patients achieving microbiological response success at TOC visit (OR = 1.61, 95CI 1.10-2.38, p=0.02, Figure 1D). In all, 197 (72.7%) of the 271 patients in the ceftazidime-avibactam therapy group and 184 (63.0%) of the 292 patients in the comparison therapy group achieved microbiological response success at LFU visit. The ceftazidime-avibactam therapy group was associated with significantly more patients achieving microbiological response success at LFU visit (OR = 1.56, 95CI 1.09-2.23, p=0.02, Figure 1F). The ceftazidime-avibactam group was associated with a lower rate of microbiological response success and the difference was no significant at EOT visit (p=0.85, Figure 1E). The treatment success of two RCTs was based on EME populations. There was no significant difference in treatment success at EOT visit between patients treated with ceftazidime-avibactam and those treated with comparisons (p=0.97, Figure 1H). However, in EME populations, the success of ceftazidime-avibactam treatment in the CUTIs subgroup was significantly higher than that in the comparison groups at the TOC visit and LFU visit (for TOC visit, 858 patients, OR = 2.15, 95CI 1.08-4.27, p=0.03, Figure 1G; for the LFU visit, 1,001 patients, OR = 1.75, 95CI 1.33-2.29, p<0.0001, Figure 1I). In our meta-analysis, this part of the study of Carmeli et al.[20] was split because in this study the LFU visit was divided into FU1 visit (21-25 days post-therapy) and FU2 visit (28-32 days post-therapy) for mMITT patients and EME patients.

Microbiological response success in the treatment of mMITT populations infected with *E. coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*

Four RCTs included in the meta-analysis reported data on mMITT patients. In our meta-analysis, the study of Carmeli et al.[20] was split according to the treatment of CUTIs and CIAIs. The total microbiological treatment success for the ceftazidime-avibactam group was numerically higher than that for the comparison group in the mMITT population at the TOC visit with significant difference (FEM, OR = 1.36, 95CI 1.01-1.82, p=0.04, data not shown in the figure). More specifically, treatment with ceftazidime-avibactam was associated with numerically higher eradication rates for *E. coli* and *Klebsiella pneumoniae* (for *E. coli*, REM, OR = 1.11, 95CI 0.51-2.43, p=0.79; for *Klebsiella pneumoniae*, FEM, OR = 1.56, 95CI 0.97-2.49, p=0.06, data not shown in the figure). Treatment with ceftazidime-avibactam was associated with numerically lower eradication rates for *P. aeruginosa* (FEM, OR = 0.71, 95CI 0.31-1.64, p=0.43, data not shown in the figure). However, there were no significant differences in eradication for all these species.

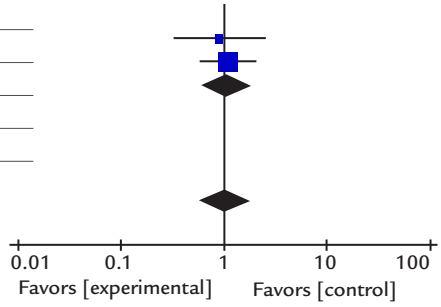
Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, random, 95CI	M-H, random, 95CI
A mMITT-TOC							
Carmeli et al.[20]	118	144	88	137	42.8%	2.53 [1.46, 4.38]	
Wagenlehner et al.[22]	299	393	291	417	57.2%	1.38 [1.01, 1.88]	
Subtotal (95CI)		537		554	100.0%	1.79 [0.99, 3.22]	
Total events	417		379				

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 3.54$, df = 1 (p=0.06); $I^2 = 72\%$
Test for overall effect: Z = 1.93 (p=0.05)



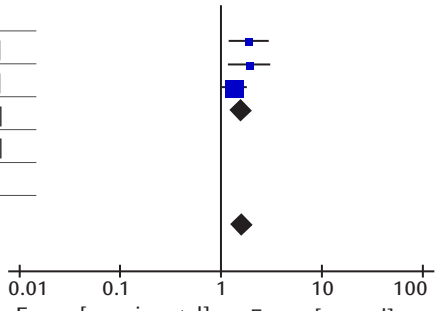
Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
B mMITT-EOT							
Carmeli et al.[20]	136	144	130	137	28.5%	0.92 [0.32, 2.60]	
Wagenlehner et al.[22]	374	393	395	417	71.5%	1.10 [0.58, 2.06]	
Subtotal (95CI)		537		554	100.0%	1.04 [0.61, 1.79]	
Total events	510		525				

Heterogeneity: $Chi^2 = 0.08$, df = 1 (p=0.77); $I^2 = 0\%$
Test for overall effect: Z = 0.16 (p=0.87)



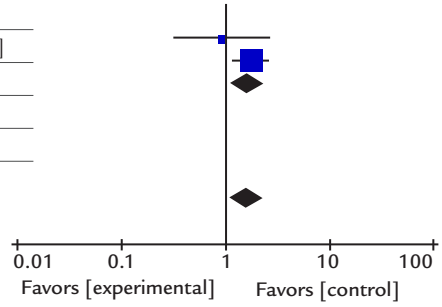
Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
C mMITT-LFU							
Carmeli et al.[20]	99	144	73	137	18.8%	1.93 [1.19, 3.14]	
Carmeli et al.[20]	103	144	78	137	18.3%	1.90 [1.16, 3.12]	
Wagenlehner et al.[22]	268	393	254	417	62.9%	1.38 [1.03, 1.84]	
Subtotal (95CI)		681		691	100.0%	1.58 [1.26, 1.97]	
Total events	470		405				

Heterogeneity: $Chi^2 = 2.06$, df = 2 (p=0.36); $I^2 = 3\%$
Test for overall effect: Z = 4.01 (p<0.0001)

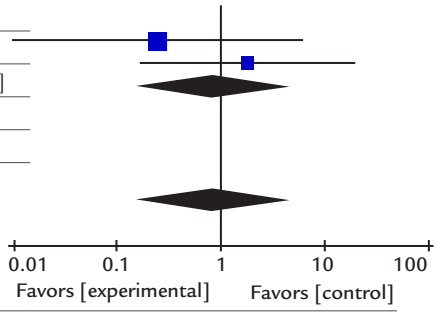


Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
D ME-TOC							
Vazquez et al.[14]	19	27	25	35	15.7%	0.95 [0.31, 2.87]	
Wagenlehner et al.[22]	241	286	225	298	84.3%	1.74 [1.15, 2.63]	
Subtotal (95CI)		313		333	100.0%	1.61 [1.10, 2.38]	
Total events	260		250				

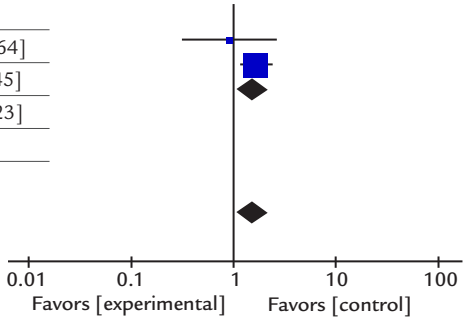
Heterogeneity: $Chi^2 = 1.01$, df = 1 (p=0.32); $I^2 = 1\%$
Test for overall effect: Z = 2.43 (p=0.02)



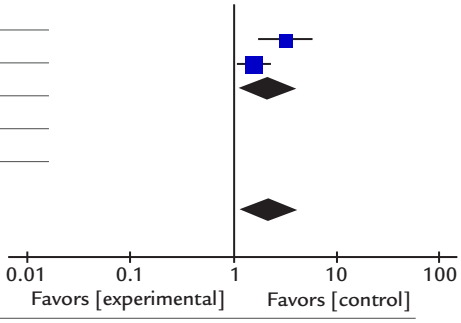
Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
E ME-EOT							
Vazquez et al.[14]	25	26	34	34	61.5%	0.25 [0.01, 6.30]	
Wagenlehner et al.[22]	324	325	359	361	38.5%	1.81 [0.16, 20.00]	
Subtotal (95CI)		351		395	100.0%	0.85 [0.15, 4.87]	
Total events	349		393				
Heterogeneity: $Chi^2 = 0.94$, df = 1 (p=0.33); $I^2 = 0\%$							
Test for overall effect: Z = 0.19 (p=0.85)							



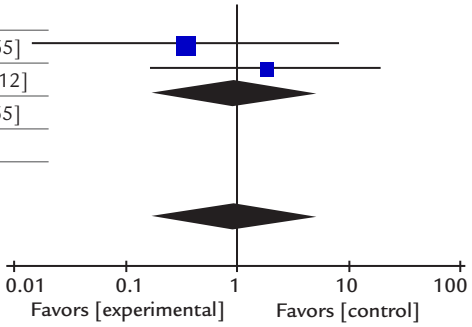
Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
F ME-LFU							
Vazquez et al.[14]	15	26	18	30	14.6%	0.91 [0.31, 2.64]	
Wagenlehner et al.[22]	182	245	166	262	85.4%	1.67 [1.14, 2.45]	
Subtotal (95CI)		271		292	100.0%	1.56 [1.09, 2.23]	
Total events	197		184				
Heterogeneity: $Chi^2 = 1.11$, df = 1 (p=0.29); $I^2 = 10\%$							
Test for overall effect: Z = 2.43 (p=0.02)							



Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, random, 95CI	M-H, random, 95CI
G EME-TOC							
Carmeli et al.[20]	114	131	84	124	43.7%	3.19 [1.69, 6.02]	
Wagenlehner et al.[22]	243	292	236	311	56.3%	1.58 [1.05, 2.36]	
Subtotal (95CI)		423		435	100.0%	2.15 [1.08, 4.27]	
Total events	357		320				
Heterogeneity: $Tau^2 = 0.18$, $Chi^2 = 3.40$, df = 1 (p=0.07); $I^2 = 71\%$							
Test for overall effect: Z = 2.18 (p=0.03)							



Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
H EME-EOT							
Carmeli et al.[20]	133	134	127	127	58.2%	0.35 [0.01, 8.65]	
Wagenlehner et al.[22]	335	336	369	371	41.8%	1.82 [0.16, 20.12]	
Subtotal (95CI)		470		498	100.0%	0.96 [0.16, 5.65]	
Total events	468		496				
Heterogeneity: $Chi^2 = 0.65$, df = 1 (p=0.42); $I^2 = 0\%$							
Test for overall effect: Z = 0.04 (p=0.97)							



Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
I EME-LFU							
Carmeli et al.[20]	85	117	68	115	23.4%	1.84 [1.06, 3.18]	
Carmeli et al.[20]	98	126	75	120	21.3%	2.10 [1.20, 3.67]	
Wagenlehner et al.[22]	184	251	173	272	55.3%	1.57 [1.08, 2.28]	
Subtotal (95CI)		494		507	100.0%	1.75 [1.33, 2.29]	
Total events	367		316				
Heterogeneity: $Chi^2 = 0.76$, df = 2 (p=0.69); $I^2 = 0\%$							
Test for overall effect: Z = 4.04 (p<0.0001)							

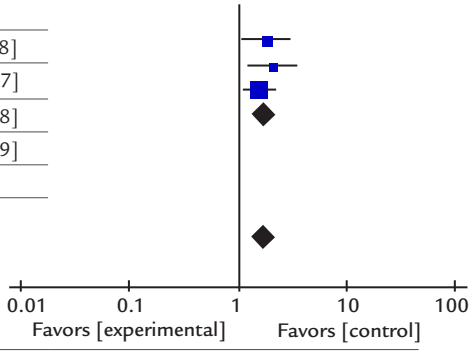


FIGURE 1 Meta-analysis of microbiological response success for the treatment of CUTIs based on mMITT populations, ME populations and EME populations: (A) microbiological response success at test-of-cure visit on mMITT populations; (B) microbiological response success at end-of-treatment visit on mMITT populations; (C) microbiological response success at late-follow-up visit on mMITT populations; (D) microbiological response success at test-of-cure visit on ME populations; (E) microbiological response success at end-of-treatment visit on ME populations; (F) microbiological response success at late-follow-up visit on ME populations; (G) microbiological response success at test-of-cure visit on EME populations; (H) microbiological response success at end-of-treatment visit on EME populations; (I) microbiological response success at late-follow-up visit on EME populations. Vertical line indicates no difference between linezolid and vancomycin. The size of each square denotes the proportion of information given by each trial. CI: confidence interval.

Microbiological response success in the treatment of ME populations infected with *E. coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*

Three RCTs included in the meta-analysis reported data on ME patients. The total microbiological treatment success for the ceftazidime-avibactam group was numerically lower than that for the comparison group in the ME population at the TOC visit, but there was no significant difference (144 patients, OR = 0.73, 95CI 0.21-2.50, p=0.61, data not shown in the figure). More specifically, treatment with ceftazidime-avibactam was associated with numerically lower eradication rates for *E. coli, Klebsiella pneumoniae*, and *P. aeruginosa* (for *E. coli*, 309 strains, OR = 0.88, 95CI 0.42-1.87, p=0.74; for *Klebsiella pneumoniae*, 68 strains, OR = 0.75, 95CI 0.04-12.70, p=0.84; for *P. aeruginosa*, 42 strains, OR = 1.86, 95CI 0.15-23.00, p=0.63, data not shown in the figure). However, there were no significant differences in eradication for all these species.

Adverse effects

Data on AEs possibly or probably related to the study medications were reported in all of the included trials. According to the data in the meta-analysis, ceftazidime-avibactam was numerically higher than comparisons on incidence of AEs, but the difference was not significant (3,180 subjects, OR = 1.09, 95CI 0.94-1.25, p=0.26, data not shown in the figure). There was no significant difference in the proportions of patients who developed serious adverse events (SAEs) in the ceftazidime-avibactam groups and comparison groups (six RCTs, 3,180 subjects, OR = 1.14, 95CI 0.84-1.54, p=0.40, data not shown in the figure). In our meta-analysis, the study of Carmeli et al.[20] was split because the treatment of CIAIs and CUTIs were both used in this study.

Mortality

All-cause mortality and mortality possibly related to the study drug during the study period were available in four of the six included trials. Although numerically higher mortality was found in the ceftazidime-avibactam groups, there was no significant difference in mortality between the ceftazidime-avibactam and comparison groups (2,029 patients, FEM, OR = 1.36, 95CI 0.70-2.65, p=0.37, data not shown in the figure). In our meta-analysis, the study of Carmeli et al.[20] was split because the treatment of CIAIs and CUTIs were both used in this study.

Discussion

Our study is the first systematic review with meta-analysis comparing the efficacy and safety of ceftazidime-avibactam with comparison for CIAIs and CUTIs. Therefore, it provides valuable information for clinicians and represents an important addition to the ceftazidime-avibactam trial program, providing supporting data for the treatment of CIAIs and CUTIs.

The results of our meta-analysis suggest that ceftazidime-avibactam is as effective as comparison antibiotics for

the treatment of patients with CUTIs and CIAIs. Six RCTs, five published and one unpublished (four double blinded, one open labeled), met the inclusion criteria of our meta-analysis. Our findings suggest that ceftazidime-avibactam shows comparable efficacy in clinical cure and microbiological response compared with meropenem and best available therapy for CIAIs on mMITT, ME and EME populations at the TOC visit, EOT visit and LFU visit. Similarly, there was no significant difference in the numbers of clinical cure success between patients treated with ceftazidime-avibactam and the imipenem-cilastatin, doripenem or best available therapy for CUTIs based on mMITT populations at the TOC visit, EOT visit and LFU visit in these RCTs. Ceftazidime-avibactam versus active comparison drugs demonstrated a statistically significant higher rate of microbiological response success in ME and EME populations at the TOC visit and LFU visit for the treatment of CUTIs. Similar results are presented at the LFU visit on mMITT populations for the treatment of CUTIs. *E. coli* remains the most frequently isolated uropathogen, followed by *P. aeruginosa* and *Proteus spp*. Although ceftazidime-avibactam therapy showed no significant difference in eradiation rate from that of the comparison groups for almost all types of pathogens, we can find better eradication rates for *E. coli* and *Klebsiella pneumoniae* based on mMITT populations. Based on statistics of these three pathogens, we found no significant difference in eradication rate. One possible reason for that is the relatively small number of patients included. If more RCTs were included in the meta-analysis, the bacterial eradication rate would be more convincing.

Our meta-analysis revealed that there was no significant difference in the numbers of AEs, SAEs and mortality between patients treated with ceftazidime-avibactam and the comparison drugs. AEs occur predominantly in the gastrointestinal tract (including diarrhea, nausea, vomiting), nervous system (including headache, dizziness) and liver (including alanine aminotransferase increased, aspartate aminotransferase increased), and were also confirmed to be the adverse drug reactions most often reported in both comparison groups and clinically infected patients in many other studies of ceftazidime-avibactam treatment. Considering the known safety profile for metronidazole (for the treatment of CIAIs), no new safety signals for ceftazidime-avibactam were identified, and the overall safety profile was similar to that reported for ceftazidime alone and the cephalosporin class. Most AEs were mild or moderate in both groups, with low incidences of discontinuations or death due to AEs and few SAEs.

We attempted to apply best practices in this systematic review. Its strengths are: (1) as far as we know, this is the first systematic review with meta-analysis comparing the efficacy and safety of ceftazidime-avibactam with comparison for CIAIs and CUTIs; (2) in the present meta-analysis, we considered each infection separately (CUTIs and CIAIs) thereby reducing clinical heterogeneity at the design level; (3) in the present meta-analysis, we considered each populations separately (mMITT populations, MITT populations, CE populations, ME populations and EME populations) thereby reducing clinical heterogeneity at the design level; (4) in the present meta-analysis, we considered clinical cure success and microbiological response success thereby reducing clinical heterogeneity at the design level.

The findings of the present study must be viewed in the context of potential limitations. First, in most of the included trials, the comparison antibiotic was not the first-line recommended antibiotic for the assessed indication. Second, all RCTs included in our review were industry sponsored, involving authors related to the drug company. Such trials are more likely to report positive outcomes than trials funded by other sources.[23] Third, the meta-analysis is based on a relatively small number of RCTs and we acknowledge that using a limited number of studies raises the possibility of a second-order sampling error.[24] Fourth, there is heterogeneity in some of the relevant aspects (for example: comparative drugs included and different kinds of pathogens). Given this uncertainty resulting from clinical heterogeneity, subgroup analysis should be performed on different patients and comparative drugs about treatment success.

Conclusion

In conclusion, ceftazidime-avibactam as a potential alternative to carbapenems for treating CUTIs and CIAIs was effective and comparable to those of ceftazidime, metronidazole, meropenem and best available therapy and so on. It can play an important role in patients with Gram-negative pathogens resistant to ceftazidime and similar to its own efficacy against ceftazidime-susceptible infections. However, to obtain more definite conclusions, further investigation on ceftazidime-avibactam treatment is warranted.

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Ethical approval

Not required.

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Dyslipidemia and maternal obesity: Prematurity and neonatal prognosis

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Summary

Objective: To identify the changes caused by dyslipidemia and obesity in pregnancy suggesting causes for premature birth, and the prognosis for the newborn.
Method: Systematic review based on the Medline, Lilacs, Embase and Cochrane library databases between 1996 and 2016. The search for studies included the following keywords: "dyslipidemia, pregnancy, obesity, preterm birth." A protocol was programmed and a protocol for inclusion/exclusion of studies was implemented.
Results: Of the 5,789 articles initially selected between March 1996 and July 2016, only 32 were in accordance with the established criteria. Of these, 28.12% discussed risk factors of prematurity; 37.50%, metabolic alterations and gestational dyslipidemia; 21.87%, dyslipidemic complications in preterm birth; and 12,50%, lipid metabolism, glycemic and placental transfer.
Conclusion: There is a reduced adaptation of obese pregnant women to the metabolic changes of gestation. This favors dyslipidemic intercurrences in the mother, which, directly or indirectly, suggests the occurrence of premature births and high lipid transfer to the fetus. Therefore, preterm newborns, whose mothers were dyslipidemic during pregnancy, have greater risk of epicardial fat, both in early (first year of life) and in later (adult) phases of life.

Keywords: Dyslipidemias. Pregnancy. Obesity. Premature Birth.

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Introduction

Prematurity results from multifactorial and unpredictable circumstances in all social classes and locations, and implies better understanding of perinatal causes and outcomes. Among other comorbidities, the relationships between a preterm birth and the newborn's low weight and a prognosis of growth deficit are evident.[1] A study carried out in the last decade emphasizes that prematurity increases the likelihood of developing cardiovascular diseases and other chronic diseases.[2] Still, despite a rather recent interest in it, a reduced number of papers on the subject and its specific etiological factors, a higher survival rate of premature infants favored by the advancement in health technologies is suggested.[3]

Dyslipidemia is characterized by abnormal levels of cholesterol and triglycerides, which generally increases the overweight rates and, when associated with pregnancy, is a worrisome change that can increase adverse pregnancy outcomes.[3] Among the various gestational outcomes, a study revealed that, in the year 2000, premature births accounted for 28% of neonatal deaths in 193 countries.[4] Risk factors for prematurity are relevant elements pending further research.[5,6]

Accordingly, it is of the utmost importance that we understand the relationships between dyslipidemia and obesity with prematurity and the specificities and peculiarities regarding changes during the gestational period, such as the isolated increase in serum cholesterol and

triglycerides, and mixed hyperlipidemic changes.[6,7] However, during pregnancy, physical, psychological and social behavior are altered due to the special conditions of the pregnant state, which is neither physiologically normal neither clinically abnormal.[8,9] Hence, based on scientific publications from 1996 to 2016, our study was aimed at identifying the changes brought about by dyslipidemia and obesity that may suggest the causes of premature birth and the prognosis for the newborn.

Method

Identification of studies

We undertook a selective review of the literature between March 1996 and July 2016 on which are the changes caused by dyslipidemia and obesity that suggest causes of premature birth and their coadjuvancy regarding the prognosis for the newborn. At first, we developed a protocol establishing the sources to be searched, languages, keywords and dates of publication over the past 20 years. Among methodological criteria, we prioritized sample size and the most recent years of publication. Papers published between 1996 and 2016 were extracted from the Medline, Lilacs, Embase and Cochrane databases. We selected the keywords "dyslipidemias," "pregnancy," "obesity" and "premature birth," which we checked against the DeCS – Descritores em Ciências da Saúde (Descriptors in Health Sciences), associated with the Boolean operators "AND" and "OR," published in Portuguese, English or Spanish.

Inclusion criteria

The papers to be evaluated and/or selected for our study should present research results on obesity and dyslipidemia in pregnancy and the predisposing factors therefore suggestive of the causes of prematurity and its relationship with the prognosis for the newborn (NB). Our selection included clinical trials; cross-sectional studies; cohort studies; case-control studies; epidemiological studies; and bibliographic reviews. In clinical trials, cohort studies; and case-control studies, in addition to the abovementioned criteria, we prioritized studies having a longer follow-up period. Literature reviews and epidemiological studies needed to be related to the subject and goal of our research. All members of our group participated in selecting the articles. Whenever there were any divergences regarding two or more articles, the scholars then analyzed the study in its entirety, discussing and debating it at previously scheduled meetings.

Population

Overweight pregnant women with a dyslipidemic profile, aged 18 years or older, and preterm NBs.

Exclusion criteria

Non-relevant scientific articles dealing with dyslipidemias in non-gestational conditions or articles published in languages other than Portuguese, English or Spanish.

Selection process of theoretical references for systematic reviews

From the initial selection of publications, together with the chosen databases and the proposed criteria, we obtained a total of 5,789 articles compatible with the proposed subject. Subsequently, we proceeded to select the references for systematic reviews (Figure 1) by following the exclusion steps: identification of repeated studies; reading of titles; reading of abstracts and methodological analysis; and identification of studies having no correlation with our study's goal. After double-checking the criteria and acquiring the articles to be used, we reorganized the number of selected studies into four topics: prematurity outcomes; metabolic changes and gestational dyslipidemia; dyslipidemic complications during preterm birth; lipid and glycemic metabolism and placental transfer.

Results and Discussion

In the systematic review, after applying the selection criteria mentioned above, we obtained 32 scientific studies, of which 28.12% (n=9) were on prematurity outcomes; 37.50% (n=12) on metabolic changes and gestational dyslipidemia; 21.87% (n=7) on dyslipidemic complications during preterm birth; and 12.50% (n=4) on lipid and glycemic metabolism and placental transfers. The scientific studies that met the selection criteria and were used in our study are shown in Table 1. Consecutively, we developed a schematic model for lipid alteration from tumor necrosis factor alpha (TNF-α), according to Figure 2. Figure 3 depicts the representation of an artery with dyslipidemia.

Prematurity outcomes

As from the last decades, prematurity has been considered the main cause of infant mortality and some important pulmonary, neurocognitive and ophthalmologic morbidities. Due to these factors, it was recognized as a serious public health problem.[10,11] Studies on prematurity indicated high neonatal morbidity and mortality rates and the occurrence of sequelae of varied natures.[4,10]

Some authors showed the associations between prematurity and the development of some complications related to glucose intolerance and dyslipidemias, both in children and in preterm-born adults who presented with increased blood pressure and insulin resistance at 30 years of age.[11]

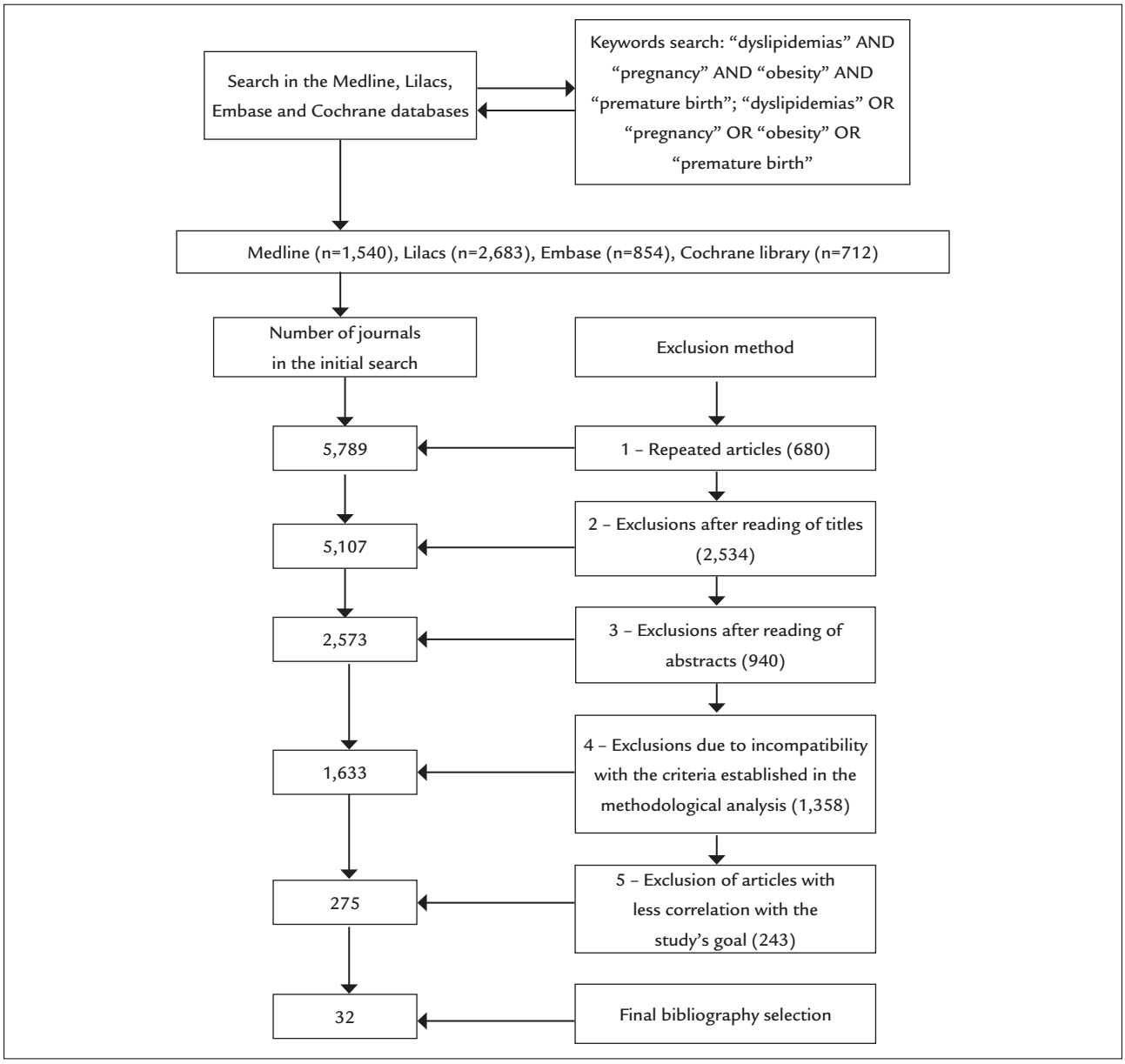

FIGURE 1 Flowchart of the activities of the selection process in the years 1996-2016.

TABLE 1 Studies that met the selection criteria (1996–2016).

Authors	Type of study	Year of publication	Population
Pessoa et al.[1]	Retrospective cohort	2015	Newborns
Bassareo et al.[2]	Prospective cohort	2016	Newborns
Castaño et al.[3]	Retrospective cohort	2013	Pregnant women
Lawn et al.[4]	Review study	2010	Newborns
Herrera et al.[5]	Review study	2006	Pregnant women
Nucci et al.[6]	Retrospective cohort	2001	Pregnant women
Stulbach et al.[7]	Retrospective cohort	2007	Pregnant women
Oliveira et al.[8]	Cross-sectional study	2012	Pregnant women
Cheung et al.[9]	Prospective cohort	2004	Newborns

(*Continues*)

TABLE 1 (Cont.) Studies that met the selection criteria (1996–2016).

Authors	Type of study	Year of publication	Population
Lorena et al.[10]	Cross-sectional study	2009	Newborns
Dalziel et al.[11]	Prospective cohort	2007	Newborns
Tomashek et al.[12]	Retrospective cohort	2006	Newborns
Shapiro-Mendoza et al.[13]	Retrospective cohort	2008	Newborns
Machado et al.[14]	Retrospective cohort	2016	Pregnant women
Hentges et al.[15]	Prospective cohort	2010	Newborns
Luz et al.[16]	Cross-sectional study	2008	Pregnant women
Oliveiros Donohue et al.[17]	Retrospective cohort	2003	Newborns
Ywaskewycz Benitez et al.[18]	Case-control	2010	Pregnant women
Ghio et al.[19]	Review study	2011	Pregnant women
Mangucci et al.[20]	Prospective cohort	2014	Pregnant women
Oliveira et al.[21]	Case-control	2016	Pregnant women
Mudd et al.[22]	Prospective cohort	2012	Pregnant women
Adamo et al.[23]	Clinical trial	2013	Pregnant women
Jelliffe-Pawlowski el al.[24]	Retrospective cohort	2014	Pregnant women
Joy et al.[25]	Case-control	2009	Pregnant women
Berkowitz et al.[26]	Retrospective cohort	1998	Newborns
Merzouk et al.[27]	Prospective cohort	2000	Newborns
Sebire et al.[28]	Cross-sectional study	2001	Pregnant women
Higa et al.[29]	Review study	2013	Pregnant women
Crume et al.[30]	Prospective cohort	2015	Pregnant women
Watkins et al.[31]	Case-control	2003	Pregnant women
Hull et al.[32]	Review study	2008	Pregnant women

Tomashek et al.[12] highlighted the group of borderline preterm newborns, i.e. the group of late preterm newborns (L-PTNB) defined as premature with a gestational age (GA) between 34 complete weeks and 36 weeks and 6 days. The researchers identified a percentage of deaths among preterm infants born at 36 weeks twice as high as compared to that among infants born at 34 weeks. Another study revealed a seven-fold higher risk of morbidity among L-PTNB when compared to term newborns (TNB).[13]

Nevertheless, it is noteworthy that the L-PTNB group has begun to be studied more systematically as from the 2000s, with a significant increase in morbidity and mortality and associated risks related to respiratory pathologies, thermal instability, a greater number of neurological alterations and lower Apgar scores.[13,14] Even though there are studies identifying a diversity of risks related to neonatal morbidity and mortality and high-incidence rates of prematurity-related sequelae of varied natures, both L-PTNB and their diversity of high risk when compared to TNB deserved our special consideration in this systematic review.[11,13,15] It is a well-known fact that the main cause of maternal death is complications caused by high blood pressure during pregnancy or at the time of delivery, as well as hemorrhages and other morbidities.[16,17]

However, studies on birth weight and changes in arterial blood pressure throughout the child's life were more unanimous in investigating possible risks, especially when compared with studies on GA and current infant weight.

Metabolic changes and gestational dyslipidemia

Despite the fact that most studies focused on gestational concerns, which correspond to several factors arising from dietary imbalance and caloric expenditure, the relationship between physiological changes and lipid and glycemic metabolism during pregnancy deserved special attention in the studies.[3,6,7] It was thus found that, over the course of gestation, adipose tissue and its lipolytic activity cause an increase in serum levels of glycerol being converted into glucose in the liver, which in turn is gradually made available to the fetus.[6]

During pregnancy, investigators found an increase in the levels of high-density lipoprotein cholesterol (HDL-c) and very-low-density lipoprotein cholesterol (VLDL), as well as in the concentrations obtained from lipid and lipoprotein

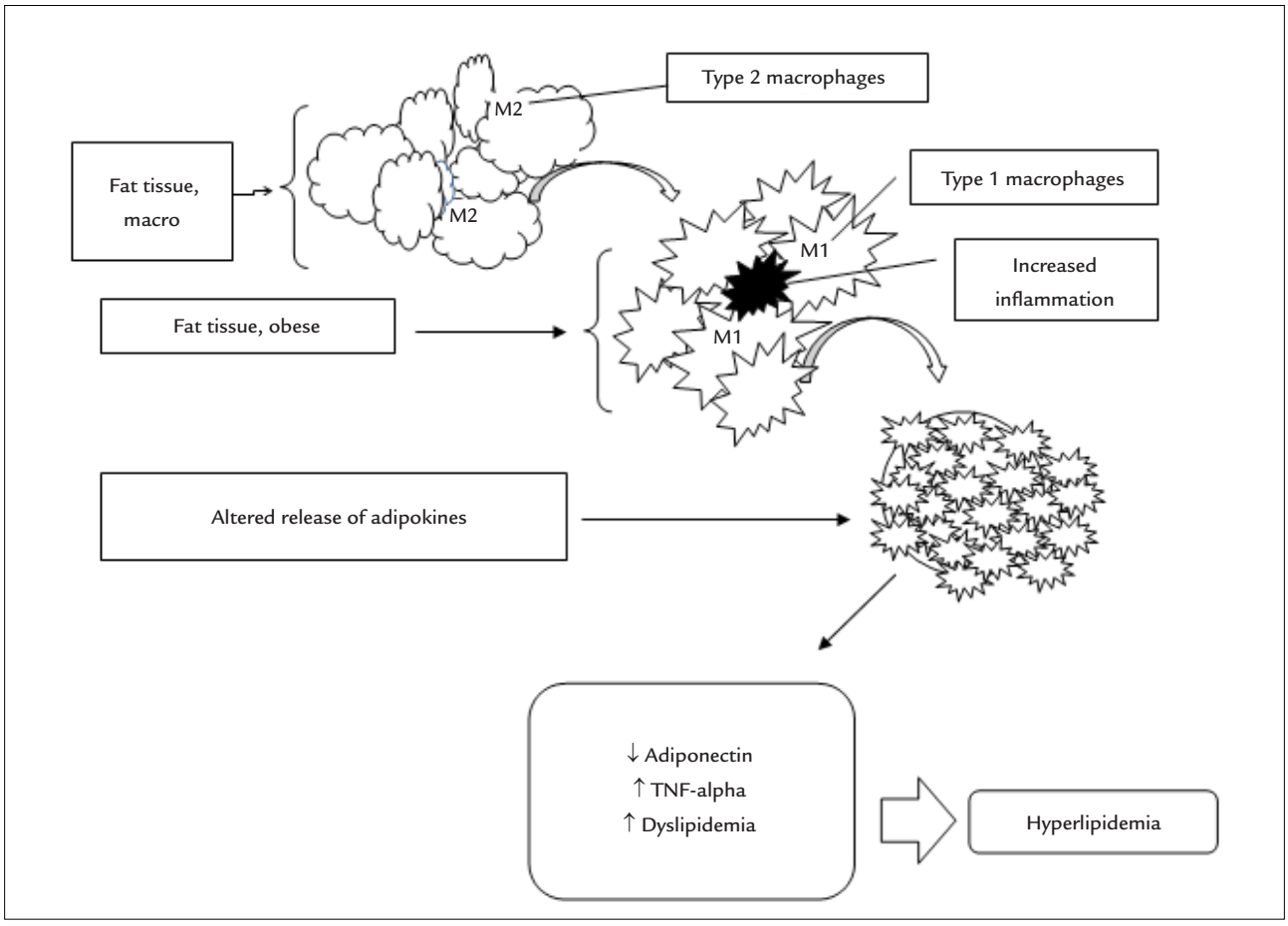

FIGURE 2 Schematic model of tumor necrosis factor alpha (TNF-α) altering the lipid profile.

measurements by a comparative study with non-pregnant women. That study provided guidelines as to when a physiological indicator may be associated with pregnancy diseases and/or disorders.[18] Ghio et al.[19] observed a gradual increase in the triglycerides, total cholesterol (TC), VLDL and HDL-c lipid patterns from the 12th week of pregnancy, especially in the second and third trimesters in response to estrogen stimulation and insulin resistance, as well as an increase in the risk of pre-eclampsia and premature birth.

In previous scientific studies including overweight and obese women, the hypotheses and suggestions pertaining to a consecutive increase in dyslipidemic changes and gestational complications are notorious. The studies conducted by Callegari et al.[20] in an attempt to identify cardiometabolic risks comparing normal-weight pregnant women with overweight pregnant women found an increase in the levels of triglycerides, TC, VLDL and low-density lipoprotein cholesterol (LDL-c) in both groups. Yet, the HDL-c levels remained unchanged in normal-weight pregnant women, in contrast with the significantly low levels found in overweight pregnant women.

In carrying out this study, we conclude that, among pregnant women with an adequate weight, ancestry or descent on HDL-c parameters showed diversities in some scientific studies. The alternating patterns allow for suggestions for pathological indicators, including prematurity and future cardiac events for the newborn.[21]

Hence, with respect to each variable analyzed, these correlations make it possible for the reader to identify the events caused by maternal overweight and to deem dyslipidemic alternations as indicators of complications, such as predisposition to high systemic arterial blood pressure, cardiometabolic events and the outcomes of a premature delivery.[18,22,23]

Dyslipidemic complications in preterm birth

Even though changes in pregnancy are evident, the likelihood of a clinical and physiological imbalance during the gestational period is indisputable. It is therefore essential that pregnant women be followed up and have their weight controlled to ensure both maternal and fetal health.[1,3] Mudd et al.[22] demonstrated an existing relationship between

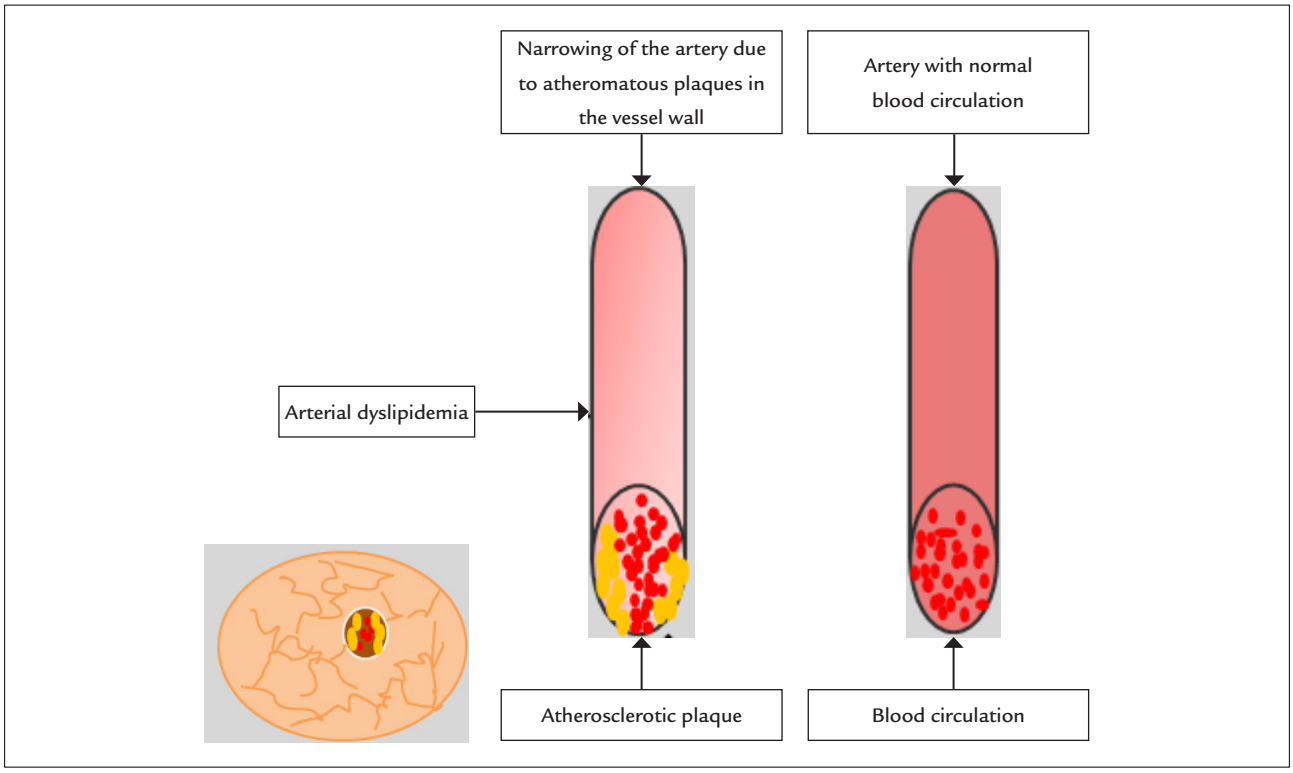

FIGURE 3 Schematic model of an artery with dyslipidemia.

lipid levels and the risk of premature birth complications. According to the authors, low TC, LDL-c and HDL-c values are associated with a moderately increased risk of medically indicated preterm deliveries, whereas high TC, LDL-c and triglycerides are associated with spontaneous preterm deliveries.

There is an established link between TNF-α and the release of lipids by adipocytes, i.e. TNF-α being induced by lipolysis. A study revealed that, midway through gestation, an increase in TNF-α and lipid levels can lead to the development of gestational hyperlipidemia. It also suggested an interrelationship involving TNF-α, hyperlipidemia and a preterm delivery.[24] Another study emphasized the rates of complications attributed to maternal obesity, such as hyperglycemia and hyperlipidemia, with complications in materno-fetal and neonatal outcomes. This leads us to deduce that obesity and dyslipidemic alterations may place a full-term pregnancy in jeopardy.[25] On the other hand, so researchers found an inconsistency in the association between obesity and preterm delivery, due to the fact that some pregnant women presented with obesity-related diseases.[26]

The relationship between dyslipidemia and risks of materno-fetal complications is significantly independent of maternal obesity. In the studies by Merzouk et al.,[27] the increase in fetal lipid levels showed an association with the metabolic levels of poorly-controlled diabetic mothers and consecutively their macrosomic newborns had increased values of all serum lipids and in their apolipoprotein and lipoprotein lipid levels.

Regarding the possibility of prematurity being caused by dyslipidemic and hyperglycemic changes and overweight during pregnancy, we must bear in mind that the association between maternal obesity and preterm birth is controversial, with particularities yet to be uncovered. In other words, while some studies reported high risks or a diminished relationship, other studies found no correlation at all.[22,25,26,28] Nevertheless, some researchers state that prematurity is independent of maternal hyperglycemia,[5] suggesting thus that it is more closely associated with maternal dyslipidemia.

Lipid and glycemic metabolism and placental transfers

The placenta plays a key role in transferring lipid radicals to the fetal compartment, which can be consecutively affected by maternal diseases associated with the impairment of lipid homeostasis.[29] Therefore, the role of long chain polyunsaturated fatty acids (LC-PUFA) becomes emphasized: the presence of lipoprotein receptors in the placenta promotes their uptake, which causes fatty acids to be metabolized and diffused to the fetus.[6]

A study deserving special mention is an observational epidemiological study on pregnant women indicating certain proteins that indirectly influence neonatal adiposity, such as leptin and adiponectin, two proteins that can be stimulated when there is maternal insulin resistance, thereby altering the mechanisms of placental transport.[30] According to the scientific literature, metabolism during pregnancy is related to the production of ketone bodies being consecutively used by the fetus for fatty acid synthesis. This emphasizes the fact that the contribution of maternal fatty acids to the fetus and the possible bioenergetic conversions can be either intensified or restricted, which can cause serious problems to fetal organs and tissues in either case.[6,31]

With regard to glycemic and lipid metabolism and placental transfer, a study showed that pathophysiological problems can be related to materno-fetal transport mechanisms. Similarly, the influence from the mother's lipid catabolism can also be involved, which can directly or indirectly favor or limit the transfer of lipids to the fetus.[32]

In this context, dyslipidemia during pregnancy and the parameters of lipid transfer from mother to fetus have been scientifically shown to be influenced by placental hormones affecting both glucose and lipid metabolism to ensure that the fetus has a sufficient supply of essential nutrients for its development.[5] However, as far as scientific results and/or parameters we surveyed are concerned, metabolic adaptations are notoriously less flexible among obese pregnant women than they are in normal-weight pregnant women, which may impair the materno-fetal transport mechanism.

Our systematic review has some limitations, such as difficulties in finding factors relating dyslipidemia to prematurity in the studies with the population defined according to the initial protocol, given that we aimed at investigating scientific studies of populations with human beings. Another limiting factor was the small number of epidemiological studies on the particularities involving causes and risks of prematurity and consecutively the abbreviated follow-up on the possible dyslipidemic outcomes among newborns. Conversely, one strength of our study was the number of studies with dyslipidemic obese pregnant women, which greatly allowed for comparative analyses and/or suggestions as to prognoses according to the statistical results.

Conclusion

There is a reduced adaptation of obese pregnant women to the metabolic changes of gestation. This favors dyslipidemic intercurrences in the mother, which, directly or indirectly, suggests the occurrence of premature births and high lipid transfer to the fetus. Therefore, preterm newborns, whose mothers were dyslipidemic during pregnancy, have greater risk of epicardial fat, both in early (first year of life) and in later (adult) phases of life.

Resumo

Dislipidemia e obesidade materna: prematuridade e prognóstico neonatal

Objetivo: Identificar as alterações provocadas pela dislipidemia e pela obesidade na gestação que sugerem causas de partos prematuros e o prognóstico para o recém-nascido.
Método: Revisão sistemática nas bases de dados Medline, Lilacs, Embase e da biblioteca Cochrane entre os anos de 1996 e 2016. O processo de seleção ocorreu a partir dos descritores dislipidemia, gravidez, obesidade, nascimento prematuro. Um protocolo foi programado, havendo uma etapa seletiva de inclusão/exclusão das pesquisas.
Resultados: Dentre os 5.789 artigos inicialmente selecionados entre março e julho de 2016, somente 32 estavam de acordo com os critérios estabelecidos. Desses, 28,12% focavam nos fatores de risco da prematuridade; 37,50%, em alterações metabólicas e dislipidemia gestacional; 21,87%, em intercorrências dislipidêmicas no parto prematuro; 12,50%, em metabolismo lipídico, glicêmico e transferências pela placenta.
Conclusão: Existe uma menor adaptação da gestante obesa às mudanças metabólicas da gestação, favorecendo intercorrências dislipidêmicas na mãe, o que, direta ou indiretamente, sugere a ocorrência de partos prematuros e uma elevada transferência de lipídios para o feto. Portanto, recém-nascidos prematuros de mães dislipidêmicas durante a gravidez apresentam maior risco de desenvolver gordura epicárdica tanto na fase precoce (primeiro ano de vida) quanto na tardia (vida adulta).

Palavras-chave: Dislipidemias. Gravidez. Obesidade. Nascimento Prematuro.

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Portuguese Primary Care physicians response rate in surveys: A systematic review

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Summary

Introduction: Surveys are a useful tool in primary care. However, low response rates can introduce selection bias, impairing both external and internal validity. The aim of this study was to assess the average response rate in surveys with Portuguese general practitioners (GPs).

Method: We searched the Medline, Web of Science, Scopus, Embase, PsychInfo, SciELO, IndexRMP, RCAAP, *Revista Portuguesa de Medicina Geral e Familiar, Acta Médica Portuguesa* and the proceedings of conferences of general practice from incepton to December 2016. We included all postal, e-mail, telephone and personal surveys to primary care physicians without language restrictions. We did not assess risk of bias of included studies, since the main outcome was survey response rate. We performed planned subgroup analyses of the use of monetary incentives, the use of non-monetary incentives, survey delivery modes and prior contact with participants.

Results: A total of 1,094 papers were identified and 37 studies were included in this review. The response rate in surveys done to Portuguese GPs was 56% (95CI 47-64%). There was substantial heterogeneity among included studies (I2=99%), but subgroup analysis did not explain this heterogeneity.

Conclusion: Consistent with other published studies, the average response rate in surveys done with Portuguese GPs was 56%, with substantial variation among studies. Use of monetary incentives, one of the most effective strategies to increase response rates, was not present in any of the included studies.

Keywords: Physicians. Family Practice. Primary Health Care. Surveys and Questionnaires. Portugal.

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Introduction

Surveys are useful in medical research.[1-3] They can provide insight on knowledge, attitudes and behaviors related to challenging conditions or complex patients. Furthermore, they can be used to assess needs, which can then guide interventions to improve care.[4,5] Surveys are used by a wide range of professionals in primary care research as a standardized tool which is easily applicable.[6]

Low response rates can introduce important selection bias into survey results due to the extent to which non-responders may differ from the study population.[7] Random sampling is done to ensure that the sample shares the same characteristics as the reference population. However, this may be compromised if there is a low number of non-respondents, as often non-respondents and respondents have different characteristics. For example, if respondents are more educated than non-respondents, the survey results may be representative of the most educated elements of the reference population, not the whole reference population. These differences can impair both external and internal validity.[8] International studies report an average response rate of 61% (95CI 59-63%)[9] for surveys in general practitioners (GPs).

GP survey response rates are influenced by monetary incentives, perceived value of the research, concerns about disrupting routine practice, time, confidentiality, volume of requests, questionnaire length and insufficient background information.[10] Furthermore, non-responders in surveys involving GPs seem to be older and less likely to possess a postgraduate medical degree or belong to a practice that is involved with post- or undergraduate training.[11]

Monetary incentives seem to be the most successful strategy to increase physicians' response rates to surveys.[12,13] Other effective approaches include non-monetary incentives, shorter surveys and pre-contact (defined as contacting participants before delivering the survey in order to explain the aim and clarify any doubts).[6,11,12] The survey delivery mode is also important, with postal surveys generally showing higher response rates when compared with telephone, e-mail, fax and online surveys.[11,14] Nevertheless, despite increasing evidence regarding strategies to improve participation, GP response rates to postal surveys over the past decades remain relatively unchanged.[9]

In Portuguese speaking countries, despite growing interest in primary care research, no data is currently available regarding average response rates in general practice surveys. Synthesizing response rates from prior surveys will help researchers adequately plan sample sizes for future projects. Thus, the aim of this study was to assess the average response rate in surveys done with Portuguese GPs, as well as identify its potential influencing factors.

Method

Selection criteria

We included studies that involved primary care physicians (family medicine specialists, non-specialists and residents), using all types of survey delivery modes (e.g., postal, e-mail, online, and telephone), and both validated and non-validated questionnaires, regardless of sponsor and knowledge field (e.g., clinical, public health, economics, management, marketing). Both published (journal article, report, thesis) and unpublished studies were considered. No language restriction was applied. Included studies needed to report the percentage of individuals contacted that completed the survey. Excluded studies included surveys directed mostly to public health specialists, physicians not involved with clinical practice (e.g., researchers or managers) or healthcare professionals other than doctors.

Search methods for the identification of studies

We searched international databases (Medline, Web of Science, Scopus, Embase, PsychInfo and SciELO) and Portuguese repositories (IndexRMP, RCAAP); the last search date was December 2016. The search combined free terms and, when supported, controlled vocabulary (full search strategy available in Supplement I). We handsearched the table of contents of the *Revista Portuguesa de Medicina Geral e Familiar* (RPMGF) (Portuguese Journal of General Practice with previous title: *Revista Portuguesa de Clínica Geral*) and the *Acta Médica Portuguesa* (AMP), as well as the reference lists of eligible articles. We also searched for grey literature in the conference proceedings of Portuguese family medicine conferences.

Study selection

Two authors (NB, SC) independently scanned titles and abstracts from the references retrieved. When the title or abstract did not provide sufficient data to rule out eligibility, full text was obtained and eligibility was assessed independently by the same two authors. Disagreements were solved through discussion with a third author (BH or LL). Reasons for excluding a study were recorded and added to the PRISMA flowchart (Figure 1).

Data extraction, synthesis and analysis

A standardized extraction form with all variables was developed and an identification tag was attributed to each publication. NB and SC abstracted the data for each study and both records were compared for data entry or coding errors; disagreements were solved through consensus. The following variables were collected: first/contact author, title, year when the first participant was recruited, type of publication and study research question. Our main outcome was survey response rate, defined as the number of physicians who provided valid data per number of physicians contacted. We also tried to identify potential explanatory variables to response rate: monetary and non-monetary incentive use, survey delivery mode (postal, telephone, e-mail, online, other) and existence of pre-contact (i.e., whether researchers contacted participants before the survey). Missing data was retrieved, when possible, through e-mail contact with the main author or the corresponding author of the study. As we were exclusively interested in survey participation rates, risk of bias assessment of individual studies was not assessed.

Categorical variables and participation rates were described as proportions. Categorical variables were described with frequencies and percentages. Assessment of publication bias was performed through visual inspection of funnel plots. Meta-analysis of the participation rates was performed using a random effects model (DerSimonian and Laird inverse variance method). Planned sub-

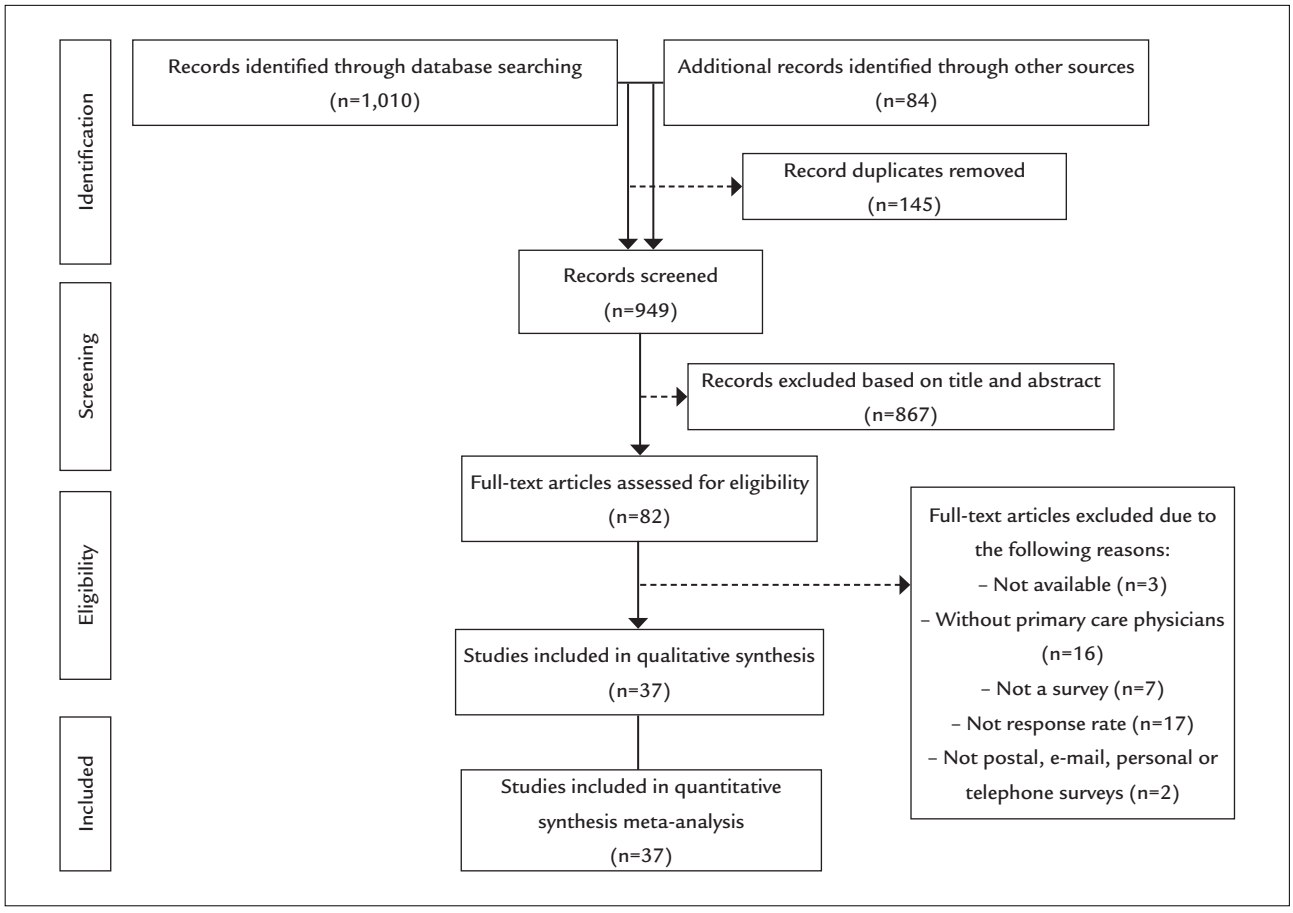

FIGURE 1 PRISMA flowchart of retrieved studies.

group analyses included use of monetary incentives, use of non-monetary incentives, survey delivery modes and contact with participants prior to the survey. Heterogeneity was assessed visually and using I^2.

Results

A total of 1,010 papers were identified through database searching and 84 through a manual search of Portuguese journals, as well as from grey literature sources (Figure 1). Study characteristics are shown in Table 1. The smallest study had a total of 13 participants[15] and the largest had 2,815[16] (mean number of participants approximately 473 per study). The majority of studies addressed clinical practice issues, such as clinical diagnosis or treatment, and work satisfaction. Half of the included studies were developed in primary healthcare units. We also retrieved studies from Portuguese academic institutions, regulatory institutions related to health and pharmaceutics. Twelve (12) studies involved a national sample of physicians; 13 studies were conducted in the region of Lisbon and nine in the northern region of Portugal.

On average, the response rate in surveys done with Portuguese GPs was 56% (95CI 47-64%). There was substantial heterogeneity among included studies (I^2=99%) (Figure 2) and subgroup analyses did not explain this heterogeneity.

Four different delivery modes were used in the included studies: e-mail,[17-22] postal,[16,23-36] personal contact (i.e., researchers delivered the questionnaire directly to the potential respondent)[15,37-50] and telephone-based surveys.[51] Subgroup analysis suggests that response rates differed in studies which used different survey delivery modes (interaction test p<0.0001). The highest response rate (96%) was seen in the single study that was based on a telephone survey[51] (95CI 92-98%) and, on average, studies in which researchers handed out survey forms personally had higher response rates than those using e-mail or postal surveys. Nevertheless, study heterogeneity among subgroups defined by survey delivery mode remained high (I^2=99% for e-mail surveys, I^2=98% for personal delivery, and I^2=99% for postal surveys). Subgroup analysis also suggests that response rates differ in studies using non-monetary incentives (interaction test p=0.04). Only two studies used this kind of

incentive and both with postal reply-paid surveys,[32,50] but response rate was lower compared to no use of incentives. In both subgroups, heterogeneity remained high (I^2=85% and 99%, respectively). We found no evidence of an interaction between contacting study participants beforehand and response rates (interaction test p=0.27). We were unable to perform one of our main pre-specified subgroup analyses, since we found no studies using monetary incentives.

We also performed two non-pre-specified subgroup analyses to further explore the sources of heterogeneity. Firstly, we divided studies into small and large studies using an arbitrary cutoff of 500 participants, adjusted to our mean number of participants per study. Larger studies had lower response rates compared with smaller studies (interaction test p<0.0001), although there was still substantial heterogeneity in the two subgroups (I^2=95.1% for smaller studies, and I^2=99.3% for larger studies). We also analyzed the impact of different affiliations on response rate but we found no evidence supporting this influence (interaction test p<0.01). Twenty-one (21) studies were affiliated to healthcare provider,[15,17-19,22-26,28,31,34,35,37-39,41,42,44,46,48] fourteen to academic institutions,[21,27,29,30,32,33,36,40,43,45,47,49-51] one related to regulatory institution[16] and other to the pharmaceutical industry.[20] Heterogeneity could not be explained by this subgroup analysis (I^2=99% for academic institution affiliation and I^2=98% for healthcare provider affiliation).

Discussion

On average, the response rate in surveys done to Portuguese GPs was 56%, but we found substantial heteroge-

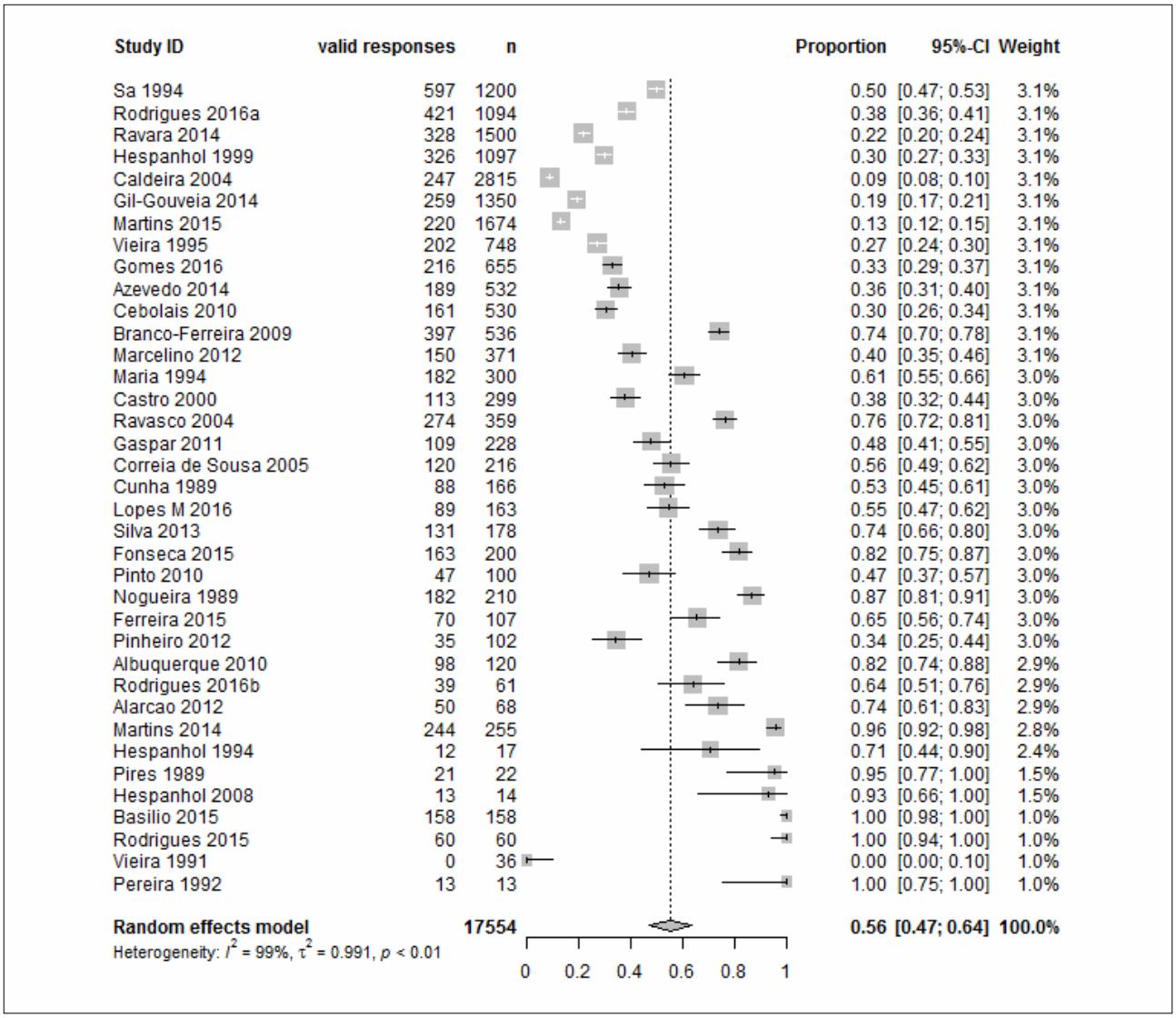

FIGURE 2 Forest plot of main results.

TABLE 1 Characterization of the studies.

Study ID	Aim of study	Study sample	Sample size	Incentives	Delivery mode	Previous contact	Affiliation
Cunha et al.[37]	To characterize primary and secondary care communication	GPs working on PHCU of Viseu region	166	No	Presential	Yes	Healthcare provider
Nogueira[38]	To determine GPs stress levels and exhaustion	GPs working of PHCU of Oporto region	210	No	Presential	No	Healthcare provider
Pires and Cerdeira[39]	To characterize professional satisfaction in a healthcare unit	GPs working on a PHCU	22	No	Unavailable	No	Healthcare provider
Vieira and Viegas[23]	To determine family doctors professional satisfaction	GPs working on a PHCU	36	No	Postal	No	Healthcare provider
Pereira[15]	To characterize home visits to patients of an healthcare center	GPs working on a PHCU	13	No	Presential	No	Healthcare provider
Hespanhol[40]	To evaluate GPs daily stress levels	GPs working on a PHCU	17	No	Presential	No	Academic institution
Maria et al.[24]	To evaluate knowledge and attitudes of GPs towards HIV infection	GPs working on PHCU of Lisbon region	300	No	Postal	No	Healthcare provider
Sá et al.[25]	To describe attitudes and habits of GPs towards tobacco use	GPs working on PHCU around the country	1,200	No	Postal	No	Healthcare provider
Vieira et al.[26]	To determine job satisfaction in physicians with a career in general clinical medicine	GPs working on PHCU around the country	748	No	Postal	No	Healthcare provider
Hespanhol et al.[27]	To evaluate professional satisfaction in family medicine	GPs working on northern region of Portugal	1,097	No	Postal	No	Academic institution
Castro[28]	To identify reasons to choose family medicine	GP residents on the northern region	299	No	Postal	No	Healthcare provider
Caldeira et al.[16]	To characterize antibiotics prescription on respiratory diseases	GPs around the country	2,815	No	Postal	Yes	Regulatory institution
Ravasco et al.[29]	To determine current practice of nutritional therapy in Portugal	GPs working on PHCU around the country	359	No	Postal	No	Academic institution
Correia-de-Sousa and Mateus[41]	To address family medicine residents and specialists reading habits and needs	GP residents and specialists working on the northern region of Portugal	216	No	Presential	No	Healthcare provider
Hespanhol[30]	To characterize professional satisfaction in a healthcare unit	GPs working on a PHCU	14	No	Postal	No	Academic institution
Branco-Ferreira[42]	To investigate therapeutic options in allergic rhinitis	GPs working on PHCU around the country	536	No	Presential	Yes	Healthcare provider
Albuquerque and von Hafe[17]	Translation of hypertension guidelines into practice	GPs working around the country	120	No	E-mail	No	Healthcare provider
Cebolais et al.[31]	To define reasons why family doctors take, or do not take, flu vaccine	GPs working on the south region of Portugal	530	No	Postal	No	Healthcare provider
Pinto and Corte-Real[18]	To determine the use of the international classification of primary care among family medicine residents	GP residents from south of Portugal, Azores and Madeira	100	No	E-mail	No	Healthcare provider

(*Continues*)

TABLE 1 (Cont.) Characterization of the studies.

Study ID	Aim of study	Study sample	Sample size	Incentives	Delivery mode	Previous contact	Affiliation
Gaspar et al.[32]	To determine professional motivation during family medicine residency	GP residents around the country	228	No	Postal	No	Academic institution
Alarcão et al.[43]	To identify general practitioners' knowledge, attitudes, beliefs, and practices in the management of sexual dysfunction	GPs working in PHCU in the Lisbon region	68	No	Presential	Yes	Academic institution
Marcelino et al.[33]	To investigate burnout levels among Portuguese family doctors	GPs working on PHCU around the country	371	No	Postal	No	Academic institution
Pinheiro et al.[34]	To determine who recommends the adult cervical cancer vaccination	GPs working on PHCU of east Lisbon region	102	No	Postal	No	Healthcare provider
Silva et al.[44]	To determine expectations and difficulties perceived by GPs in mental health	GPs working on Portuguese northern region	178	No	Presential	No	Healthcare provider
Azevedo et al.[19]	To determine residency satisfaction among general practice residents	GP residents of the northern region of Portugal	532	No	E-mail	No	Healthcare provider
Gil-Gouveia[35]	To evaluate doctors' perspective about headache	GPs visited by representatives of study sponsor	1,350	No	Postal	No	Healthcare provider
Martins et al.[51]	To investigate preventive health services implemented by family physicians in Portugal	Portuguese GPs working on PHCU around the country	255	No	Telephone	Yes	Academic institution
Ravara et al.[45]	To characterize smoking behavior among Portuguese physicians	GPs attending two medical conferences	1,500	No	Presential	No	Academic institution
Basílio et al.[46]	To determine the perception of depression and anxiety among family physicians according to patient gender	GP residents and specialists attending to a primary care formation	158	No	Presential	No	Healthcare provider
Ferreira et al.[47]	Detection and intervention strategies by primary health care professionals in suspected elder abuse	GPs working on Coimbra region	107	No	Presential	No	Academic institution
Fonseca and Martins da Silva[20]	The diagnosis and treatment of LUTS due to benign prostatic hyperplasia by primary care family physicians	GPs working around the country	200	No	E-mail	No	Pharmaceutics
Martins et al.[21]	Career satisfaction of medical residents in Portugal	GP residents working around the country	1,674	No	E-mail	No	Academic institution
Gomes[22]	Depressive disorder prevalence in GP residents	GP residents of Portugal south region	655	No	E-mail	No	Healthcare provider
Lopes et al.[48]	Family evaluation tools use among GPs	GPs working on Lisbon region	163	No	Presential	No	Healthcare provider
Rodrigues et al.[49]	To define therapeutic options among family doctors in hypertension	GP residents and specialists working on PHCUs of Lisbon region	60	No	Presential	Yes	Academic institution

(*Continues*)

TABLE 1 (Cont.) Characterization of the studies.

Study ID	Aim of study	Study sample	Sample size	Incentives	Delivery mode	Previous contact	Affiliation
Teixeira Rodrigues et al.[50]	To develop and validate an instrument to assess the attitudes and knowledge underlying physician antibiotic prescribing	GPs working on Lisbon region	61	No	Presential	No	Academic institution
Teixeira Rodrigues et al.[36]	To assess the influence of the determinants of physician prescribing on the quality of antibiotic use	GPs working on Lisbon region	1,094	No	Postal	No	Academic institution

ID: identification; GPs: general practitioners; PHCU: primary healthcare unit; LUTS: lower urinary tract symptoms.

neity (I^2=99%). Our search did not retrieve any studies using monetary incentives, which is a strategy known to increase response rates.

The funnel plot is very asymmetric, suggesting that smaller studies were more likely to be published or presented at conferences if they had higher response rates.

Strengths and limitations

The main strength of this study is our attempt to reduce bias by following systematic review guidelines.[52] Given that survey response rates may be related to publication status, we have made an effort to identify other surveys through conference proceedings, databases of MSc and PhD theses, and by contacting relevant authors. Yet, it is likely that small studies with low response rates were never published or presented at conferences, which means that the estimated average of 56% for response rates may be optimistic.

The major weakness of the study was the substantial heterogeneity that remains largely unexplained. It is reasonable to question whether a summary measure should be obtained when heterogeneity is high. However, we agree with the view that researchers and clinicians still need a best estimate to inform their decisions[53] and that it is licit to pool the primary studies' estimates together as long as their limitations are acknowledged. In our main meta-analysis, heterogeneity was very high (I^2=99%), and within our pre-specified and post-hoc subgroup analyses heterogeneity was also high (I^2>75.0%). The main factors described in the literature as having an influence in response rates do not explain the variation we found between studies.[11] In hindsight, we could have explored the topic of the survey or its length. Clinicians may be more inclined to reply to a survey if they think the topic is more interesting and if the questionnaire is short.[11]

Interpretation in the context of the available literature

So far, surveys in Portugal have not used monetary incentives to increase GP participation rates. According to the international literature,[11,12] monetary incentives are the most effective method to increase survey participation. However, most of the studies we found were conducted by family medicine residents and the vast majority seemed to be self-funded. Yet, it shows that there is potential for increasing participation rates in Portuguese studies if there is more funding for research in general practice.

Our estimate of 56% response rate is consistent with the average response rate of 61% (95CI 59-63%) found in international studies.[8] We were surprised to find that pre-contact strategies were not associated with increased response rates (75% vs. 52%, p=0.27 for the interaction test), contrary to what has been previously described.[8] It is possible that this result is due to the small number of studies which described contacting participants before sending the questionnaires (n=6). We found that there were differences according to delivery mode. There was a single study surveying GPs by telephone,[51] which yielded the highest response rate in our review. However, it is impossible to say whether such high response rate is associated with this specific delivery mode or if it was due to other characteristics of this particular study. Personal delivery also seems to produce higher response rates (75%) compared to postal questionnaires (37%); e-mail questionnaires seem to have intermediate response rates (48%). A possible explanation is that in small surveys it is feasible to hand-in questionnaires personally, and that there is often some sort of personal relationship with the researcher (often a co-worker) that may contribute to increase the participation rate. In fact, it is clear in our data that smaller studies have higher response rates than larger studies. Whether this is a true association or just an artifact of publication bias (small

studies with low response rates not being considered for publication or presentation) is unclear to us.

Conclusion

Researchers wanting to conduct surveys with Portuguese general practitioners should anticipate response rates of 56% or lower. There is substantial variation in response rates in this target population, which remains unexplained. Monetary incentives should be considered by researchers in future studies, as this has been shown in the international literature to be an effective strategy in increasing response rates.

Resumo

Taxa de respostas dos médicos de família portugueses a questionários: uma revisão sistemática

Introdução: Questionários são úteis na investigação em cuidados de saúde primários. Contudo, baixas taxas de resposta podem introduzir um viés de seleção, prejudicando a validade externa e interna. O objetivo deste estudo foi identificar a taxa de resposta média a questionários aplicados a médicos de família (MF) portugueses.
Método: Foram pesquisadas as bases de dados Medline, Web of Science, Scopus, Embase, PsychInfo, SciELO, IndexRMP, RCAAP, *Revista Portuguesa de Medicina Geral e Familiar*, *Acta Médica Portuguesa* e resumos em conferências de medicina familiar do início até dezembro de 2016. Incluiram-se estudos realizados a médicos de família portugueses independentemente de sua tipologia, do tipo de entrega (correio, e-mail, pessoalmente e por telefone) e do idioma do artigo. Não foi avaliado o risco de viés dos artigos porque o principal resultado considerado foi a taxa de resposta. Foram efetuadas análises de subgrupos sobre a utilização de incentivos monetários, de incentivos não monetários, o modo de entrega e o contato prévio com os participantes.
Resultados: Foram identificados 1.094 artigos e incluídos 37 estudos. O número de participantes em cada estudo variou entre 13 e 2.815 participantes. A taxa de resposta média foi de 56% (IC95% 47-64%). Identificou-se uma heterogeneidade substancial (I^2=99%) não explicável pela análise de subgrupos.
Conclusão: A taxa de resposta média a inquéritos realizados a MF portugueses foi de 56%, o que corresponde aos valores identificados em revisões internacionais, apesar da variação significativa entre os estudos englobados nesta revisão. O uso de incentivos monetários, uma das estratégias mais eficazes para aumentar as taxas de resposta, não foi identificado em qualquer dos estudos incluídos.

Palavras-chave: Médicos. Medicina de Família e Comunidade. Atenção Primária à Saúde. Inquéritos e Questionários. Portugal.

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Human leishmaniasis in Brazil: A general review

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Summary

Leishmaniasis is a disease with ample clinical spectrum and epidemiological diversity and is considered a major public health problem. This article presents an overview of the transmission cycles, host-parasite interactions, clinical, histological and immunological aspects, diagnosis and treatment of various forms of the human disease.

Keywords: Leishmaniasis. Protozoan Infections. Review.

Introduction

Leishmaniasis is caused by several species of digenetic protozoa of the order Kinetoplastida, family Trypanosomatidae and genus *Leishmania*, which affect humans and many animals.[1] This parasite is endemic in at least 98 countries and approximately 0.2-0.4 and 0.7-1.2 million new cases of visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL) occur every year, respectively.[2]

More than 90% of worldwide cases of VL occur in six countries (India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil) and despite a wide distribution, around one third of CL cases occur in the Americas, the Mediterranean basin and western Asia, mainly in Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru. Mortality data is extremely scarce and generally only represents hospital deaths. However, using an overall mortality rate of 10%, we can conclude there are an estimated 20,000 to 40,000 annual deaths resulting from this parasitic disease.[2]

Due to the significant overall increase in its incidence, there has been growing interest in leishmaniasis in recent decades. In addition to reporting recent epidemics in endemic areas, there is evidence of dissemination of leishmaniasis to previously non-endemic areas. Such increases can be explained in part by improved diagnosis and reporting of cases, but they also result from factors associated with increased population migration, increased detection of leishmaniasis associated with opportunistic infections, the emergence of resistance to drugs used in treatment, and the adaptation of the transmission cycles to peridomiciliary environments due to urbanization and deforestation.[3]

In Brazil, autochthonous cases of CL have already been reported in all states and cases of VL have been recorded in 21 of the states, with approximately 1,600 cities showing autochthonous transmission.[4,5]

Development

Transmission

The transmission cycles of leishmaniasis vary according to geographic region, involving a wide diversity of species of *Leishmania*, vectors (invertebrate hosts) and reservoirs (vertebrate hosts). More than 50 species of *Leishmania* have been identified worldwide, and at least 21 of these species have significant medical importance.[6] Particularly in Brazil, eight species have already been isolated from patients with the disease (Table 1).[3,4]

Vertebrate hosts of the various species of *Leishmania* include a wide variety of mammals such as rodents, canines, marsupials, edentates, carnivores, primates and, among these, humans.[3] The vectors are the females of the insects called phlebotomine sand flies belonging to the order Diptera, family Psychodidae, subfamily Phlebotominae and genus *Phlebotomus*, in the Old World, and *Lutzomyia*, in the New World. Approximately 700 species of phlebotomine sand flies have been described, of which about

TABLE 1 *Leishmania* species that cause leishmaniasis in Brazil.[3,4]

Tegumentary leishmaniasis				Visceral leishmaniasis
Localized cutaneous	**Disseminated cutaneous**	**Mucosal**	**Diffuse cutaneous**	
L. (V.) braziliensis	*L. (V.) braziliensis*	*L. (V.) braziliensis*	*L. (L.) amazonensis*	*L. (L.) infantum* (syn. chagasi)
L. (V.) guyanensis	*L. (L.) amazonensis*	*L. (L) amazonensis**		
L. (L.) amazonensis		*L. (L.) guyanensis**		
*L. (V.) lainsoni**				
*L. (V.) naiffi**				
*L. (V.) shawi**				
*L. (V.) lindenbergi**				

*Less frequent species.

30 species are proven vectors of leishmaniasis and more than 40 additional species are suspected vectors.[6]

Transmission of the disease occurs through the infected insect's bite at the time of hematophagy, and non-vector transmission (for example, an accident in the research laboratory) is rare. However, in the case of VL, other possible routes of transmission have also been reported, such as congenital transmission, blood transfusion and syringe sharing among drug users.[3]

Host-parasite interactions

Protozoa of the genus *Leishmania* alternate between two main morphological forms during their life cycle: amastigotes and promastigotes, which are found in vertebrate hosts and phlebotomine vectors, respectively (Figure 1).[7]

The immobile amastigote forms are spherical or oval and measuring about 2.5-5.0 µm in diameter. They have a kinetoplast located close to the nucleus and must be multiplied within the cells of the vertebrate host's mononuclear phagocytic system. Thus, phlebotomine females become infected during blood feeding on a vertebrate host by ingesting blood and/or interstitial lymph containing macrophages parasitized by amastigote forms of *Leishmania*.[8]

In the insect's digestive tract, the amastigotes differentiate into promastigotes, which are elongated, flagellated, mobile forms around 5-15 µm in length and with kinetoplasts located between the nucleus and the anterior extremity. While still in the vector's digestive tract, the promastigote forms go through several stages – procyclical, nectomonate, leptomonate, haptomonate – until they become metacyclic promastigotes, which are infectious to the vertebrate host.[8]

Highly adapted for successful transmission, the metacyclic promastigotes migrate to the insect's mouthparts (proboscis). Consequently, the vertebrate hosts are infected when female sand flies inoculate the metacyclic promastigote forms together with saliva during hematophagy.[9]

Once within the vertebrate host, the promastigotes are internalized by macrophages and, within the phagocytic vacuole, they are transformed into amastigotes, which replicate intensely until they rupture the parasitized cell. The released amastigotes infect other macrophages and the cycle starts again.[10]

Several adaptation mechanisms have been developed by parasites of the genus *Leishmania* in order to ensure their survival in the different hostile environments faced throughout their entire life cycle. These parasites not only deal with the aggressive digestive conditions found within phlebotomine sand flies, but must also prevent destruction by the immune system of the vertebrate host and ensure their survival within the macrophages.[11]

Regarding development in the vector, some of the adaptation strategies include: (1) expression of molecules on the cell surface such as LPG (lipophosphoglycan) and metalloprotease gp63, which protect the parasite from the hydrolytic enzymes present in the insect's intestine; (2) adherence of the nectomonate promastigote forms to the intestinal epithelial cells in order to avoid elimination with the vector's feces after digestion of the ingested blood; (3) structural modifications in the LPG molecules of the metacyclic promastigote forms, enabling their migration to the insect's mouthpiece; and (4) secretion of promastigote secretory gel (PSG) produced by the leptomonate forms, which favors transmission to the vertebrate host through regurgitation of the parasites.[9,12]

Transiently in the vertebrate host's bloodstream, before infecting the macrophages, the first immune system barrier encountered by the parasites after transmission is the complement system. Molecules present on the surface of the metacyclic promastigote forms, such as LPG and gp63, confer resistance to complement-mediated lysis. LPG prevents insertion of the C5b-9 complex into the membrane and gp63 promotes C3b cleavage at C3bi on the surface of the parasite, preventing the formation

of C5 convertase. Thus, both molecules prevent the formation of the membrane attack complex.[13]

After escaping from the extracellular environment, the parasites penetrate the phagocytic cells through interactions between their surface molecules and the receptors of the macrophages. Metacyclic promastigotes not only resist complement-mediated lysis, but also use it in their favor for entry into macrophages. Indeed, the main internalization mechanism of leishmaniasis depends on the interaction of C3b and C3bi molecules, which bind to the surface of the parasite with their respective receptors present in the macrophages, CR1 and CR3.[11] The internalization of the parasites through CR3 receptors is an important escape mechanism, given that in this process the microbicidal respiratory explosion mechanism is not activated and IL-12 production induced by cell-mediated immunity is inhibited.[13]

Several other receptors present on macrophages are described as facilitators of the internalization of the promastigote forms of different species of *Leishmania*. For example, metacyclic promastigote forms can also be opsonized with IgG molecules and internalized by binding to Fc receptors. Furthermore, they can be phagocytosed by the interaction of the LPG molecules with mannose-fucose receptors.[11] In addition, LPG molecules may also interact with C-reactive protein (CRP), one of the first products of inflammatory response, and cause phagocytosis by means of CRP receptors.[14] Furthermore, the gp63 and LPG molecules may also interact with fibronectin and CR4 receptors, respectively.[15]

After binding to the cell surface of the macrophages, the promastigote forms of the parasite are endocytosed in a phagosome, which after a series of fusion events becomes a phagolysosome. Unlike amastigote forms, promastigote forms are vulnerable to the acid and hydrolytic degradation of the phagolysosome. Thus, the first defense mechanism of the parasite inside the macrophages consists of the delay in the formation of the phagolysosome, with this process dependent on the LPG surface molecules, the presence of calcium and the inhibition of the protein kinase C (PKC).[16,17]

Once the phagolysosome is formed, the promastigotes become amastigotes, which are more resistant to the microbicidal activity of the macrophages, since they can inhibit the hydrolytic enzymes, the production of nitric oxide and also the metabolites of the oxidative burst.[12] In addition, *Leishmania* have developed several strategies to escape the host's immunological defense, including: (1) inhibition of the host cell's ability to present antigens of the parasite to other components of the immune system, by means of interference in the expression of MHC class II molecules and lower expression of costimulatory molecules, such as B7-1 and CD40; (2) inhibition of the production of the cytokines involved in the proinflammatory response (IL-1, TNF-α, IL-6) and activation of T lymphocytes (IL-12); and (3) induction of immunosuppressive molecules, such as prostaglandin E2 (PGE2), TGF-β and IL-10.[11,18]

In recent decades, it has been found that even the saliva of vectors has biomolecules such as maxidilan which, in addition to facilitating the hematophagy process, also favor the transmission of the parasite. These biomolecules have immunomodulatory properties that interfere in the presentation of antigens by the macrophages and in the production of cytokines, increasing the production of IL-4 and IL-6 and inhibiting TNF-α, IFN-γ and IL-12.[19]

The intracellular location of the amastigote forms of *Leishmania* causes infection control to be dependent on the cell-mediated immune response, characterized by increased CD4+ T lymphocytes. As with other infectious and parasitic diseases, numerous studies in experimental models establish a "Th1/Th2 paradigm" in leishmaniasis, in which resistance to disease is conferred by a Th1 response with elevated levels of IFN-γ, IL-12, IL-2 and TNF-α. This stimulates the microbicidal function of macrophages and promote the death of intracellular parasites – while susceptibility is linked to a Th2-type response, with an increase in the production of IL-4, IL-5, IL-10 and IL-13, inhibiting the activation of macrophages and contributing to parasite growth in the lesions.[20] However, resistance or susceptibility to disease in humans is not explained exclusively by the Th1 or Th2 response pattern, and the immune response may be strongly influenced by factors such as malnutrition, immune suppression (e.g. HIV) and, inevitably, the host's genetic components.[21]

At the same time that the Th1 response plays a clearly immunoprotective role, the high production of cytokines such as IFN-γ, TNF-α and IL-12 can be toxic and contribute to the pathogenesis of leishmaniasis. Thus, the Th1 response formed after infection is often accompanied by the response of CD4+CD25+ regulatory T cells (Treg) that produce IL-10 and TGF-β, which, in turn, block the excessive activation of Th1 cells and, consequently, prevent tissue damage.[22]

Recently, special attention has been given to the role of Th17 cells in the immune response against leishmaniasis. These cells differentiate from naïve CD4+ T lymphocytes in the presence of TGF-β and IL-6, and secrete cytokines such as IL-21, IL-17 and IL-22, which operate in the inflammatory process. However, the specific role of these cells in leishmaniasis still remains inconclusive, given that the studies are controversial as to their contribution in the resistance or susceptibility to infection.[23,24]

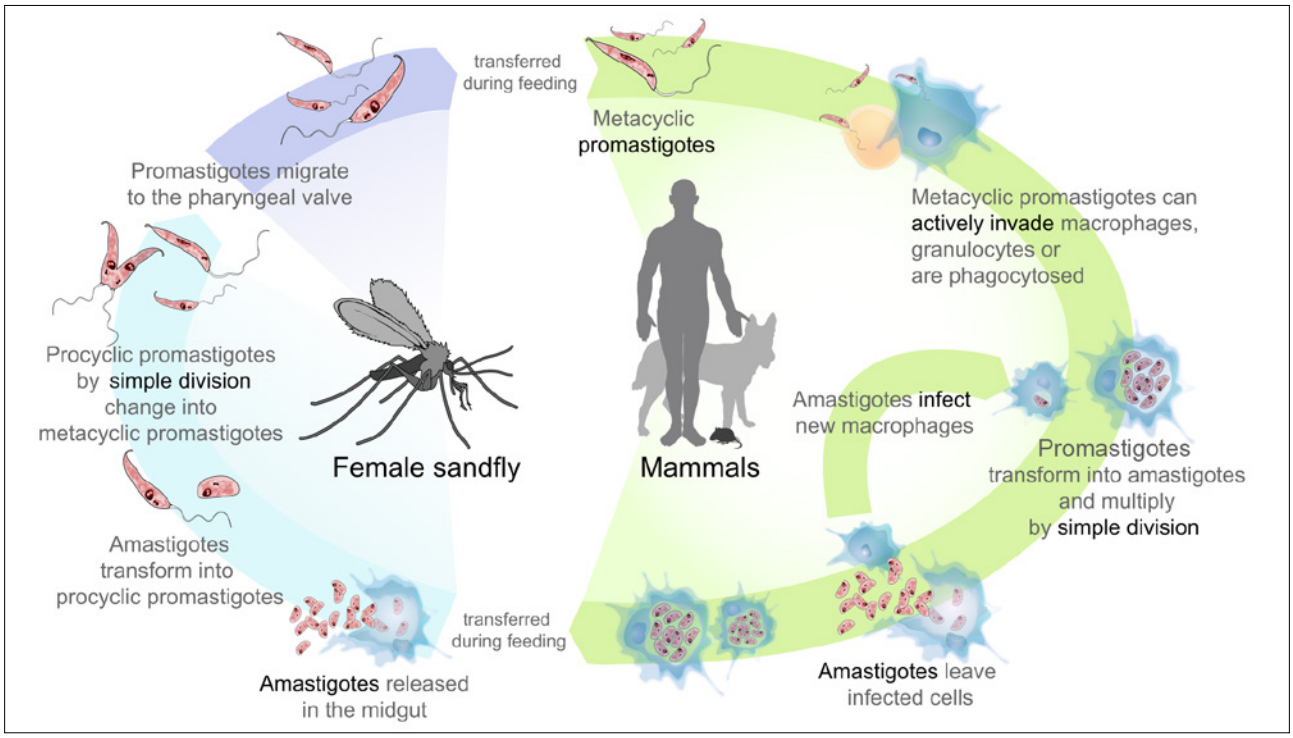

FIGURE 1 Life cycle of the parasites from the genus *Leishmania*, the cause of the disease leishmaniasis.
Source: Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Leishmaniasis_life_cycle_diagram_en.svg)

Clinical, histopathological and immunological aspects

In fact, the great variety of *Leishmania* responsible for CL and VL combined with the immune mechanisms of the host facilitates the existence of different clinical, histopathological and immunopathological manifestations. Considering the host's forms of response, the location of the lesions from the vector bite site and the clinical evolution, CL can be further classified as localized cutaneous leishmaniasis (LCL), disseminated cutaneous leishmaniasis (DL), diffuse cutaneous leishmaniasis (DCL) and mucosal leishmaniasis (ML) (Figure 2).[4]

LCL, the most frequent clinical manifestation, is characterized by the presence of an exclusively cutaneous lesion at the site of the phlebotomine sand fly bite, usually on exposed areas of the skin such as the face, hands and legs. The lesion begins with redness and swelling, increases in size progressively and, after a variable incubation period that usually lasts from 10 days to 3 months, develops into a typical ulcer with a rounded or oval shape and erythematous base. It is infiltrated and of firm consistency, well delimited and has elevated borders and a reddish background with coarse granulations. The lesion is usally painless; however, if there is an associated bacterial infection, local pain and the production of seropurulent exudate may occur.[25]

In general, LCL ulcers have few parasites and the patient's cellular immunity is preserved, including a strong T-cell response, with a predominance of Th1-type cytokines (IFN-γ and IL-12).[26] If left untreated, depending on the species of the parasite and the host's immune response, the lesion tends to heal spontaneously over a period of a few months to a few years, and may also remain active for a long time.[4]

DL, which is the disseminated form of CL, is a relatively rare expression that probably occurs due to hematogenous or lymphatic dissemination of the parasite. In these cases, the skin lesions are numerous, and are generally small and ulcerated, and distributed over several areas of the body. Parasites in the lesions are rare or absent and the immune response is quite varied. There appears to be incomplete inhibition of T cells, yet there is an evident supremacy of the Th1 response over Th2.[27]

ML is clinically expressed by destructive lesions located in the mucosa of the upper airways, possibly due to the spread of parasites to these areas, usually after LCL with chronic evolution, due to lack of treatment or inadequate treatment. In general, the initial clinical manifes-

tations include nasal obstruction, hyperemia, formation and elimination of crusts by nasal mucosa and epistaxis. The nasal mucosa is involved in almost all cases, mainly affecting the cartilaginous septum, lateral walls, vestibule, and head of the inferior turbinate and, secondarily, the palate, lips, tongue, pharynx and larynx. There may be a progressive increase in the volume of the nose, destruction of the nasal septum cartilage with collapse of the tip of the nose, complete destruction of the nose and surrounding areas (with swallowing and speech disturbances), and significant mutilation of the face, leading to death due to complications from secondary infections.[25]

Immunologically, ML is characterized by a high specific cellular immune response, both Th1 and Th2. In these cases, there are high levels of proinflammatory cytokines (TNF-α and IFN-γ) and IL-4, and decreased levels of IL-10 and TGF-β, which explains the chronic and severe tissue destruction and the scarcity of parasites in the lesions.[28] Untreated mucosal lesions are normally progressive and, even when treated, may leave behind sequelae such as nasal pyramid retraction, septum or palate perforation and destruction of the uvula, among others.[4]

DCL is a rare and severe clinical form of CL, which occurs in patients considered as being anergic, with deficiency in the cellular immune response to *Leishmania* antigens. Initially insidious, with a single lesion, it evolves in a chronic manner, with the formation of infiltrated plaques and multiple non-ulcerated nodulations that cover large cutaneous extensions. Generally, many parasites are found in the lesions and the cytokine profile of the patients is predominantly of the Th2-type, with low IFN-γ production and high levels of IL-4 and IL-10. As a rule, the nodular lesions do not heal spontaneously and are resistant to available treatments.[29]

VL, also known as kala-azar, is a chronic, systemic disease that mainly affects the lymph nodes, spleen, liver and bone marrow, and, less commonly, the kidneys, Peyer's patches in the intestine, the lungs and skin. The incubation period of the disease is quite variable, ranging from 10 days to 24 months (with an average between 2 to 6 months), and the main discrete or marked clinical manifestations include fever, hepatomegaly, splenomegaly, cutaneous/mucosal pallor, diarrhea and weight loss. Often, complementary tests show different degrees of anemia,

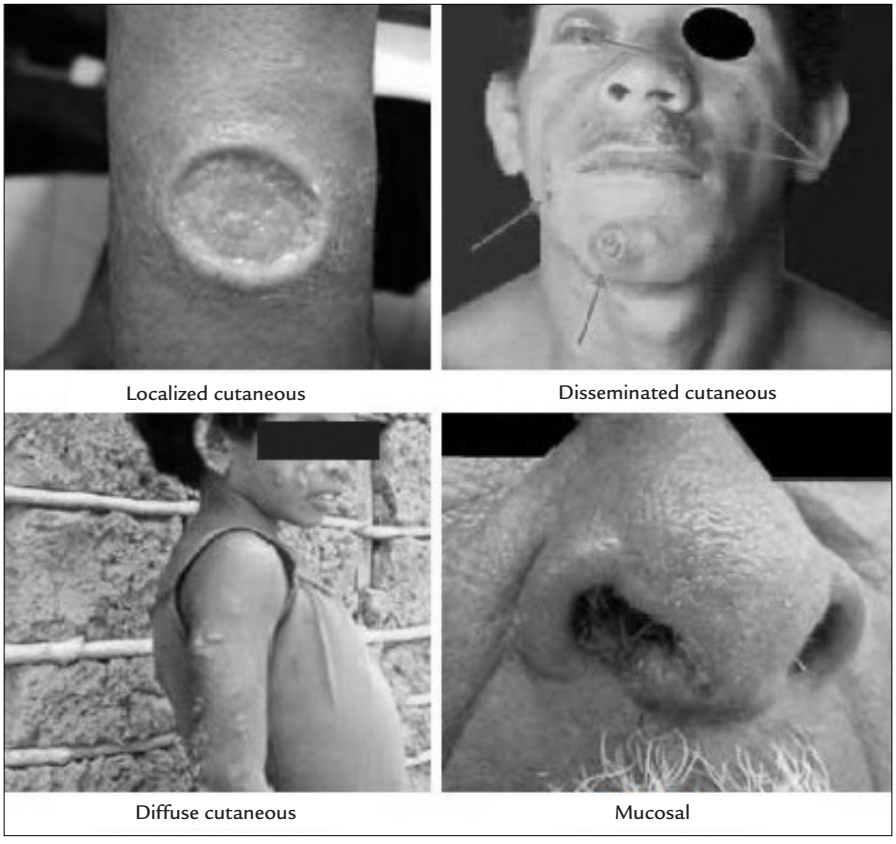

FIGURE 2 Clinical classifications of tegumentary leishmaniasis.
Modified from: Ministério da Saúde.[4]

thrombocytopenia, and leukopenia with marked predominance of lymphomonocyte cells, hypoalbuminemia and hypergammaglobulinemia.[5,30]

As for the immunological aspects of VL, these have not yet been clearly defined. In these cases, the Th1-resistance and Th2-susceptibility paradigm may be a banalization of a much more complex network of interactions, given that high levels of specific antibodies are also observed in this form of the disease.[31] Left untreated, VL almost always progresses to death and, even when treated, the disease can result in rates of fatal cases of around 10-20%, with death often being caused by bacterial infections and/or bleeding.[32]

Diagnosis

The diagnosis of leishmaniasis involves the association of the clinical, epidemiological and laboratory aspects of the disease, and the application and sensitivity of each method may vary according to the clinical forms, the time of evolution of the lesions and the different species of *Leishmania* involved.[3]

The techniques that enable the demonstration of microscopic parasites constitute the "gold standard" in the diagnosis of the disease due to their specificity. In CL, investigation of the parasite can be done by scarification, biopsy, imprint and puncture aspiration, usually performed at the edge of the lesion. These are fast and inexpensive techniques, although they have limited sensitivity, especially in chronic lesions. In the case of VL, viewing of the parasites in tissue samples requires invasive procedures, and therefore has limited indications. Bone marrow aspirate is the most used method and its sensitivity is between 60% and 85%. Splenic aspiration has a sensitivity level higher than 95%, but is usually not conducted due to the risk of bleeding. Although less risky, liver and lymph node punctures show very low sensitivities of approximately 45%. In vitro cultivation and the inoculum of the material obtained from clinical samples in animals may improve the positivity of the result and the safety of the diagnosis. However, these methods are rarely used in clinical practice, since, in addition to the complexity and high cost, the parasites' growth can take weeks or months.[33]

Polymerase chain reaction (PCR) has shown promising results in the diagnosis of leishmaniasis. In addition to presenting high sensitivity, PCR can be performed from different clinical samples, including peripheral blood in cases of VL, and enables the characterization of the *Leishmania* species involved, depending on the technique employed. Despite being widely used for research purposes, it is not used often in the diagnostic routine, as in addition to the high cost the technique requires standardization, laboratory infrastructure and technical rigor.[29]

Serological techniques – such as indirect immunofluorescence (IFAT), direct agglutination (DAT) and enzyme-linked immunosorbent assay (ELISA) –, which are standardized for the detection of anti-*Leishmania* antibodies, are important tools for the diagnosis of cases of VL. These are usually associated with a prominent humoral response. However, they are not commonly used in cases of CL, due to variable sensitivity and specificity rates and reduced levels of antibodies, especially in cases of LCL.[33] As such, immunochromatographic assays have been evaluated in different endemic regions aimed at diagnosing VL in the field. In Brazil, the test used the most and recommended by the Ministry of Health is the rapid test with the recombinant antigen k39, which has shown sensitivity ranging from 86-100% and specificity of 82-100%.[34] It is worth noting that serological tests also present important limitations: (a) individuals in endemic areas with positive serology, without signs and symptoms, may or may not develop the disease; (b) positive serology is not necessarily related to active disease, as elevated levels of antibodies may remain in the patient's serum for a long period after clinical cure; (c) in cases of HIV coinfection, serological tests are often negative, due to the lower level of circulating antibodies resulting from immunosuppression.[35]

In general, a differential diagnosis should always be considered. In CL cases, numerous skin lesions resulting from other diseases may mimic clinical and epidemiological aspects common to leishmaniasis, such as syphilis, leprosy, tuberculosis, paracoccidioidomycosis, histoplasmosis, chromoblastomycosis, sporotrichosis, pyoderma, discoid lupus erythematosus, psoriasis, Jessner lymphocytic infiltrate, vasculitis and cutaneous neoplasias, among others.[4] As for VL, diseases that also cause febrile hepatosplenomegaly, such as malaria, brucellosis, typhoid fever, schistosomiasis and the acute form of Chagas disease are also prominent, as well as hematological disorders such as lymphoma, multiple myeloma and sickle cell anemia.[5]

Treatment

Successful treatment involves several factors, such as: (1) host factors such as genetics, immune response and clinical presentation of the disease; (2) treatment resources, such as quality of the drug, dosage, and duration and completion of the therapy; and (3) characteristics of the parasite, such as intrinsic sensitivity of the species and lack of resistance to the medication.[36]

The drugs of first choice in the treatment of all clinical forms of leishmaniasis are pentavalent antimonials

(Sb + 5), sodium stibogluconate (Pentostan®) and N-methylglucamine antimoniate (Glucantime®), with the latter marketed and distributed solely by the Ministry of Health in Brazil.[4,5] Both are administered parenterally and interfere with the bioenergetics of the amastigote forms of the parasite, inhibiting the glycolytic activity and oxidative pathway of fatty acids, with consequent reductions in ATP production and molecular biosynthesis.[37]

Despite pentavalent antimonials showing an effectiveness of approximately 90% in most studies (with the exception of cases of DCL), these drugs have toxic side effects on the cardiac, kidney and liver systems.[38] Therefore, they are contraindicated for patients suffering from heart, kidney and liver diseases, and also for pregnant women, as they are able to cross the transplacental barrier and affect the fetal nervous tissue, leading to severe mental retardation syndromes.[4,5]

In recent years, the emergence of resistance to pentavalent antimonials in the parasite has limited treatment in various countries. In some parts of India, for example, failure rates of more than 60% have been observed in the treatment of VL caused by *L. (L.) donovani*.[36] In Latin America, the rates also vary, even in LCL cases.[39] One of the factors that has certainly contributed to increased resistance is the generalized misuse of the drug (such as insufficient dosages, irregular and incomplete therapies).[40]

If there is no satisfactory response to therapy with pentavalent antimonials or if it is not possible for them to be used, the drugs of second choice in the treatment of leishmaniasis are amphotericin B and pentamidine.[4,5]

Amphotericin B deoxycholate (Fungizone) is an antibiotic normally used for the treatment of systemic fungal infections. It has good activity in the destruction of leishmaniasis, with cure rates of over 97% for both CL and VL (depending on the species involved).[38] Said drug acts selectively on the amastigotes and promastigotes forms of the parasite, through preferential attachment with esters present in the plasma membrane. In addition, it causes an increase in the synthesis of nitric oxide by the macrophages.[41] However, treatment with amphotericin B is quite arduous and can only be performed in a hospital environment (intravenous). Adverse effects are numerous and frequent, including fever, headache, nausea, phlebitis, cyanosis, anemia, leukopenia, hypotension, hypokalemia, hypomagnesemia, cardiovascular alterations and renal complications.[38] In 1997, a new formulation of amphotericin B became commercially available – liposomal amphotericin B (AmBisome). This new drug, which is also administered intravenously, achieves high concentrations in the liver and the spleen and low concentrations in the lungs and kidneys. Therefore, it is less toxic and induces fewer side effects.[42] Thus, it is recommended for patients with VL and renal and/or cardiac complications, and also for patients considered vulnerable, such as pregnant women and HIV-positive people.[5] However, there are limitations that restrict its use, including its high cost, efficiency variations between regions, slow intravenous administration, thermal instability and adverse reactions related to the infusion.[42] Additionally, in the treatment of CL, there are still no controlled clinical trials that support the use of liposomal amphotericin[4] and the few isolated studies that exist demonstrate varied cure rates.[43]

Pentamidine comes in the form of two salts: mesylate and isethionate (available in Brazil). Such drugs are used primarily in regions where the failure of treatment with pentavalent antimonials is common – especially in India, French Guiana and Suriname – and in individual cases of resistance to the first therapy of choice.[38] The main limitations involving the use of pentamidine are related to its side effects such as headache, nausea, abdominal pain, hypoglycemia, tachycardia, kidney failure in 25% of patients (usually reversible) and pancreatitis that can lead to the onset of diabetes mellitus, in 10 to 15% of cases. Therefore, pentamidine is contraindicated in cases of pregnancy, diabetes mellitus, kidney failure, liver failure, heart disease and for children weighing less than 8 kg.[4,5] Another factor that has made the use of these drugs unfeasible is the emergence of parasitic resistance, meaning that efficacy has decreased over the years and cure rates below 70% have been reported.[40]

In recent decades, many researchers have focused their studies on the search for alternative treatments. Paromomycin (aminosidine), an aminoglycoside antibiotic administered parenterally, began to be used in the treatment of VL initially in India.[44] Due to its low cost and infrequent side effects, which may include nephrotoxicity and ototoxicity, paromomycin represents an alternative for cases of resistance to the drugs of the first choice.[38] However, wide inter- and intra-regional efficacy variations are observed in the treatment of VL with paromomycin[45] and the cure rates reported in CL treatment are often lower than those observed with the use of pentavalent antimonials.[46]

In 2002, the first oral drug in the treatment of VL – miltefosine – was introduced in India. Despite the frequent gastrointestinal side effects, such as vomiting and diarrhea, and possible transient elevations of hepatic transaminases, miltefosine represents a major advance in the treatment of the disease because it appears to be well tolerated and exhibits cure rates above 90% in cases of VL.[47] However, in recent years, the relatively high cost, concerns about tera-

togenicity and the potent development of resistance have limited the use of miltefosine in several countries.[48]

Currently, high expectations have now been raised about drug combination therapy in order to reduce the dosage and duration of treatment and thereby improve the tolerance and conformity of the medication already available on the market.[36] Therefore, the search for new therapies or alternatives against the different forms of leishmaniasis remains a clinical priority.

Conclusion

Despite advances in scientific knowledge, leishmaniasis remains a major public health problem in several countries, with the disease spreading to areas that were previously non-endemic. Many challenges still have to be overcome in combating this pathology, emphasizing actions that are focused on early diagnosis, the formulation of new drugs and therapeutic regimes, as well as flexible, distinct and adequate control strategies for each transmission pattern, considering local environmental, social and economic characteristics.

Resumo

Leishmaniose humana no Brasil: uma revisão geral

A leishmaniose representa um complexo de doenças com amplo espectro clínico e diversidade epidemiológica, sendo considerada um grande problema de saúde pública. O presente artigo apresenta uma revisão geral sobre os ciclos de transmissão, as interações parasito-hospedeiro, os aspectos clínicos, histopatológicos e imunológicos, o diagnóstico e o tratamento das diversas formas da doença humana.

Palavras-chave: Leishmaniose. Infecções por Protozoários. Revisão.

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Current guidelines for prostate cancer screening: A systematic review and minimal core proposal

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Summary

Objective: Considering the importance of screening for prostate cancer, the possibility of damage resulting from indiscriminate screening and the difficulty of disclosure and adherence to the main guidelines on the subject, we aimed to identify current guidelines, look for common approaches and establish a core of conducts.
Method: Systematic review of the literature on screening practice guidelines for prostate cancer searching the databases PubMed, Lilacs and Google Scholar and active search in the sites of several national health entities.
Results: Twelve (12) guidelines were selected, whose analysis resulted in the identification of six common points of conduct, with the following minimum core of recommendations: (1) screening indication or not: must be individualized, and preceded by an informed decision; (2) tests used: PSA with or without rectal digital examination; (3) age at which initiate testing in men in general risk: 50-55 years; (4) age at which to initiate testing in men at increased risk: 40-45 years; (5) the interval between screening: annual or biennial; and (6) age at which to discontinue testing: 70 years-old or life expectancy less than 10 years.
Conclusion: Although there are differences between them, it was possible to establish a minimum core of conducts that may be useful in the daily practice of the physician.

Keywords: Mass Screening. Prostatic Neoplasm. Practice Guideline.

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Introduction

Prostate cancer (PCa) is one of the leading causes of mortality among men worldwide.[1] In Brazil alone, 70.42 new cases per 100,000 men are estimated per year.[2]

For many years, screening for early detection of prostate cancer relied solely on digital rectal examination. During that period, most cancers were diagnosed in advanced stages, with no effect on mortality reduction. With the introduction of prostate-specific antigen (PSA) determination as a screening test, there was a dramatic increase in PCa diagnosis, especially in the early stages, followed by a reduction in mortality.[3] These figures stimulated the use of PSA testing for the early diagnosis of PCa, thanks also to the recommendation of several scientific societies.

Nevertheless, the publication of two large randomized trials has shown conflicting results on the ability of such screening for PCa to reduce mortality.[4,5] For these reasons, and due to the possibility of causing harm, screening for prostate cancer (SPCa) is one of the most controversial medical topics.

In an effort to maximize benefits and minimize harm, several government and scientific entities have issued recommendations for the screening of prostate cancer.[6-17]

Two problems, however, reduce the potential benefit that might derive from the issuing of these guidelines: any existing contradictions among them,[18] or insufficient disclosure or adoption thereof.[19] By means of a systematic review, our study aimed at (1) identifying the most up-to-date guidelines for PCa screening from the main national and international medical and governmental entities; (2) comparing the main recommendations of each one; and then (3) proposing a minimum core set of recommendations representing the majority of the overall recommendations that can be easily assimilated and implemented by the clinician.

Method

We conducted a systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations.[20]

Search strategy

We employed three survey strategies. (1) Medical articles surveyed in the PubMed and Scielo databases. The terms we searched in the former were: (((cancer of prostate[MeSH Terms]) AND guideline[Title]) OR recommendation[Title]) AND screening[Title/Abstract]; whereas the terms we searched in the latter were "rastreamento" AND "cancer" AND "prostata;" (2) Complementary search of articles in the Google Scholar database. Search terms: Prostate cancer screening guidelines recommendations; (3) Active search on the websites of several national scientific entities for recommendations or practical guides. We surveyed the following websites: the Brazilian Association of Preventive Medicine (Associação Brasileira de Medicina Preventiva), the Brazilian Medical Association (Associação Médica Brasileira), the National Cancer Institute (Instituto Nacional do Câncer), the Ministry of Health (Ministério da Saúde), the Brazilian Society of Cancerology (Sociedade Brasileira de Cancerologia), the Brazilian Society of Clinical Medicine (Sociedade Brasileira de Clínica Médica), the Brazilian Society of Geriatrics and Gerontology (Sociedade Brasileira de Geriatria e Gerontologia), the Brazilian Society of Clinical Oncology (Sociedade Brasileira de Oncologia Clínica) and the Brazilian Society of Urology (Sociedade Brasileira de Urologia).

Characteristics of the studies

We selected published studies with the endorsement from different scientific societies (urology, oncology, internal medicine, preventive medicine) and from government regulatory agencies, and encompassing different study type, namely consensus, recommendations and practical guides on prostate cancer screening.

Delimitation

We narrowed our study by publication date (2010-2016) so as to include recommendations that had the opportunity to evaluate the two major randomized prostate cancer screening trials.[5,4] We limited the publication languages to English, Portuguese and Spanish, and the population to adult men.

The last search date was March 10, 2017.

After we chose the articles, we proceeded to identify the common discussion points in order to establish a minimum core set of recommendations commonly shared by most of the studies selected.

Results and Discussion

By following the survey strategy, we initially found 110 articles on PubMed and another 20 on Scielo. After reading the title and abstract, we excluded 124 articles because they did not meet our study's goals. Of the six pre-selected articles, we excluded one because it was the previous version of an existing recommendation among the remainder of the articles. We included four new articles from searching Google Scholar and another two from searching the national entities' websites, which resulted in a total of eleven analyzed recommendations.[6-16]

After the date of the systematic review, a US Preventive Service Task Force draft recommendation[17] was published for public consultation, suggesting a change in its recommendation in force.[16] We considered both, though, which increased to twelve the number of recommendations we analyzed.

The analysis of the recommendations allowed us to identify six common points in our analysis: (1) whether there was an indication for screening or not; (2) examinations used; (3) age of onset for screening in men at general risk; (4) age of onset in men at increased risk; (5) interval between screenings; and (6) age of screening discontinuation (Chart 1).

Should screening for prostate cancer be indicated?

Currently, only one entity recommends against screening any given patient – the European Society for Medical Oncology (ESMO).[12] Until not long ago, this was also the recommendation from the US Preventive Services Task Force (USPSTF).[16] However, they recently published a draft recommendation for public consultation where they admit to offering screening for men aged 55-69 years.[17]

The Canadian Task Force (CTFPHC) and Brazil's National Cancer Institute (Inca, Instituto Nacional de Câncer) advise the physician not to offer the screening, so that it is performed only on the patient's demand for those aged 55-69 years or those at increased risk of prostate cancer.[6,13] The stand of these entities, as well as that of all others, is that the current state of knowledge on the early detection of prostate cancer cannot support a definitive decision either to indicate or to contraindicate the screening. The decision must be made by the patient himself, through an informed decision process, or shared with his physician. If the patient still does not feel able to make a decision even after receiving the information, his doctor may make the decision instead, based on what she or he knows of her/his patient's values and preferences. These recommendations indicate not only the need

CHART 1 Summary of the guidelines from the entities recommending the screening for prostate cancer.

Entity and reference	American Cancer Society[7]	American College of Physycians[8]	American Urological Association[9]	Canadian Urological Association[10]	European Association of Urology[11]	Sociedade Brasileira de Urologia[15]	National Comprehensive Cancer Network[14]
Year	**2010**	**2013**	**2013**	**2011**	**2014**	**2011**	**2015**
Should SPCa be performed?	Yes, for men with a life expectancy greater than 10-15 years, who require it following an informed decision process						Yes, after a discussion about risk and benefit
Mass campaigns	Recommends against	Recommends against	Recommends against	NC	Recommends against	NC	Recommends against
Mode	PSA alone or PSA+DRE	PSA with or without DRE	PSA	Total PSA and total/free ration, and DRE	PSA and DRE	PSA and DRE	PSA with or without DRE
Age of onset, no additional risk	General ≥ 50 years	General 50-69	General 55-69 years	General ≥ 50 years	General ≥ 50 years	General ≥ 50 years	45 years
Age of onset for increased risk	High risk ≥ 45 years Highest risk ≥ 40 years	Same as above	Higher risk: 40-54 years	Higher risk ≥ 40 years	Higher risk ≥ 45 years	Higher risk ≥ 45 years	NC
Interval between screenings	Annual if PSA ≥ 2.5 ng/mL Biennial if PSA < 2.5 ng/mL	Annual if PSA > 2.5 ng/dL Does not define it for other values	Biennial	Annual	2-8 years	NC	1-2 years if PSA ≥ 1 ng/mL 2-4 years if PSA < 1 ng/dL
Age of discontinuation	Life expectancy less than 10 years	Life expectancy less than 10-15 years Age > 70 years	Life expectancy less than 10-15 years Age > 70 years	Life expectancy less than 10 years	Life expectancy less than 15 years	Life expectancy less than 10 years	Life expectancy less than 10 years or age > 75 years*

SPCa: screening for prostate cancer; DRE: digital rectal examination; PSA: prostate-specific antigen; NC: not commented or addressed. (*) Patients over 75 years of age with excellent health and no comorbidities can continue to be screened. The guidelines from CTFPHC,[6] ESMO,[12] INCA[13] and the USPSTF[16] are not depicted in the chart because they do not contribute to the above recommendations given that they do not recommend screening.

for a visit to a doctor, but also prior and reasonable knowledge of the doctor about his patient. For this reason, all the entities engaged in discussing this matter are against community screening campaigns.[7-9,11,16]

Regarding the patient's values, the physician should differentiate (a) those who value an early finding of cancer, even if that might put him at the risk of undergoing unnecessary treatment and sustaining collateral harm; from (b) those who value avoiding potential harms from the screening and treatment, even if that might put him at the risk of finding an aggressive cancer for which there is no further treatment in the future.

This conversation with the patient on the possible benefits and harms from screening is the most important – and also the most difficult – topic on this subject. Its complexity and the lack of time during visits are the most commonly encountered difficulties.[21] Furthermore, it is very difficult for the doctor to be truly impartial. There is evidence that these conversations tend to value benefits and minimize harm.[22]

The American Cancer Society (ACS),[7] the American College of Physicians (ACP)[8] and the Canadian Task Force on Preventive Health Care (CTFPHC)[6] all suggest a set of information that should be shared with the patient so that he can reach an informed decision (Chart 2). The USPSTF provides a flow chart (as supplementary material to the article) that facilitates the patient's understanding of the figures involved in his decision.[17]

Which screening tests should be used?

Although there are currently several new markers proposed for PCa screening,[23] the revised guidelines recommend that only PSA be used either alone or in association with digital rectal examination (DRE).

The role of DRE is controversial. As far as screening is concerned, DRE appears to have little[7] or nothing[10] to add to PSA testing, and cancers detected by DRE alone tend to be low-grade tumors with a low potential for lethality. Therefore, the ACS recognizes its aiding role in assessing patients

CHART 2 Points for discussion with the patient to facilitate an informed decision.

Screening for prostate cancer is still a controversial subject, and there is no consensus among experts
Screening (PSA either alone or combined with digital rectal examination) can detect prostate cancer before it would be detected without screening; however, the PSA test cannot differentiate whether a cancer is severe or not, or whether the examination result is increased even without the presence of cancer. Still, in men with PSA > 10 ng/dL, treatment will have a greater chance of reducing the possibility of death
The PSA test is not "just a blood test." It may trigger the beginning of a process of further examinations and treatments for which the person must be alert and prepared. In this process, there is more chance of harms than benefits, and the patient should be quite sure about what he wishes to do. For this reason, it is necessary to discuss any findings with his physician before deciding whether to undergo screening for prostate cancer
Of every 1,000 men who choose to take the screening test, five will die from prostate cancer. Among those who choose not to, 6:1,000 die from prostate cancer. Hence, screening for prostate cancer saves one man from death for every 1,000 men screened
Most men who choose not to be screened will not have a prostate cancer diagnosed and will die from another cause. This occurs because the clear majority of prostate cancers are slow-growing and do not lead to death
Depending on the treatment chosen, it can lead to urinary, intestinal, sexual and other disorders. These problems can be minimal or significant, temporary or permanent. For every 1,000 men who are treated for prostate cancer, about 280 will have erectile dysfunction, up to 170 will have urinary incontinence, whereas another 4 to 5 will die from the treatment
PSA and digital rectal examination may produce false-positive and false-negative results, which means that men without cancer may have abnormal results and thus undergo other tests unnecessarily or have clinically significant cancers but still get normal test results. False-positive results may lead to permanent anxiety about the possibility of having prostate cancer
Abnormal PSA or DRE results do require prostate biopsy. The procedure can be painful, lead to complications such as infection and bleeding, and may not indicate the presence of significant cancer. One study showed that the chance of dying after a biopsy is 2/1,000 (0.2%)
Not all men who have a cancer detected by screening require immediate treatment, but they may require periodic blood tests and prostate biopsy for future decision-making
There are several ongoing studies that could modify current ideas and recommendations on prostate cancer screening. The patient can, at any given time, change his opinion on screening, starting it or interrupting it when he so wishes

Adapted from Wolf et al.,[7] Qassem et al.[8] and Bell et al.[6]
DRE: digital rectal examination; PSA: prostate-specific antigen.

with PSA in the so-called "gray range" (2.5-4.0 ng/dL) and emphasizes that the examiner should be experienced.[7]

The Canadian Urological Association (CUA) was the only entity to recommend the use of the total PSA/free PSA ratio as an instrument for SPCa because they consider that using the ratio improves specificity.[10] The National Comprehensive Cancer Network (NCCN) panel group mentions several other markers (free PSA, 4Kscore, PCA3) that could be used: not for screening, but rather as ancillaries in the decision-making as to whether or not perform a biopsy in those with high PSA values.[14]

At what age should screening start among men at general risk?

This is the topic with the least dispersion across the guidelines, which recommend starting at 50[7,8,10,11,15] or 55 years.[6,9,17] The NCCN is the only entity that recommends screening at age 45, irrespective of the presence of increased risk factors. They justify their stance by demonstrating that the studies on which others were based to define an age of onset did not investigate other age groups. They also show evidence that altered PSA results, even at very early ages, may predict PCa in the future.[24,25]

At what age should screening start among men at increased risk?

Increased risk is reported for men of African descent and those with first-degree relatives (father or siblings) with PCa before 65 years.[6,7,9-11,15] For those men, the recommendation is that screening should start at 40[9,10] or 45 years.[7,11,15] The ACS, which recommends starting at age 45 in patients at increased risk on the one hand, recommends starting at age 40 on the other hand in those ranked as at "higher risk," i.e. those having more than one first-degree relative with PCa.[7]

What is the interval between screenings?

This, in turn, is the topic of greatest dispersion among recommendations, varying from 1- to 8-year intervals.

The ACS uses PSA values for defining the time interval until the next scan, recommending that it occurs within one year if PSA is greater than or equal to 2.5 ng/dL, or after two years if PSA is less than 2.5 ng/dL.[7] The ACP also uses PSA values and recommends annual intervals if PSA > 2.5 ng/dL.[8]

The AUA recommends a biennial interval, highlighting it as the one preserving most of the advantages of the annual interval, while minimizing it harms.[9]

The UAE recommends the largest time interval between scans, which ranges from biennial, for those at highest risk, to up to 8 years, for those who are "not at risk," although they do not define who these patients are.[11]

Regardless of the time interval, and considering that medical knowledge is continuous and concepts can change, it is recommended that the physician should reassess the patient's life expectancy with each new screening. They should also discuss the potential benefits and harms with him again in light of the new data and knowledge.[7]

At what age should screening be discontinued?

In general, the entities recommend that screenings should not be performed or should be discontinued altogether in men with a life expectancy of less than 10 or 15 years. The problem is that determining life expectancy is not a natural or habitual calculation for the physician, who tends to overestimate it and underestimate comorbidities.[26,27] To assist the physician with her/his decision, entities bring examples of conditions that reduce life expectancy to levels below those cutoff points. The ACS mentions those patients having class IV (NYHA) heart failure, moderate to severe COPD, chronic renal failure, moderate to severe dementia, advanced cancer and other life-limiting comorbidities.[7] For a more complete listing of comorbidities with an impact on survival rates, we refer to the Charlson Comorbidity Index.[28]

The entities that do define a point to discontinue screening, though, suggest doing so from the age of 70 years.[6,8,9,12] The AUA[9] considers that, in people aged 70 years or older, even when in good health, screening should be discouraged and even suspended if PSA levels are equal to or less than 3.0 ng/dL. In contrast, the NCCN,[14] once again in disagreement with the others, recommends that men older than 75 years should be screened provided they are in excellent health and have no comorbidities.

What should the cutoff value for "altered" PSA be?

Classically, the cutoff value for considering an altered PSA has been 4 ng/dL. Among large randomized trials, the PLCO[4] uses 4 ng/dL, and the ERSPC[5] uses 3 ng/dL as a cutoff value to indicate biopsy. Most urologists prefer to use a 2.5 ng/dL cutoff value, while there are those who advocate different cutoff values according to age, although no cutoff value entirely satisfies the criteria for including all those who would benefit from being screened, which thus minimizes the number of overdiagnoses.[7] In fact, the best course of action against an increased or unexpected PSA result is repeating the test. The CUA recommends that no course of action should be taken based on a PSA result alone, since conditions other than cancer can cause it to fluctuate.[10] The NCCN also recommends repeating all PSA tests > 3 ng/dL.[14] Simply repeating the test before any other course of action is decided upon could reduce overdiagnosis and its consequent harms.

The ACS recommends that men with PSA ≥ 4 should be referred for further evaluation and biopsy. Those at increased risk (Afro-descendants, family history, older age or abnormal DRE findings) may be referred if PSA > 2.5 ng/dL.

The EUA considers that men with PSA > 1 ng/dL at age 40 and those > 2 ng/dL at age 60 are at higher risk of presenting with PCa.

Conclusion

Considering that all the guidelines analyze the same problem (screening for PCa) and have the same goal (reducing mortality), it would be expected that there were no disparities across them. Yet, the problem was bigger in the past. By using an evidence-based perspective and multiprofessional analysis groups (epidemiologists, clinicians, urologists), the new guidelines are increasingly in tune. However, adherence to them remains very low, which increases the risk of overdiagnosis and harm to patients.[19]

When analyzing the most relevant points for the clinician's practice, we identified six recommendations that sum up the majority thereof and, for the sake of simplicity, facilitate their routine use:

1. Recommendation: Screening should be discussed with the patient, after he has been made aware of the limitations and harms caused by the procedure. This discussion, and the patient approval, must be considered a *sine qua non* condition to screening. The clinician should use the educational material produced by the entities, or any other reliable sources, matching the patient's level of understanding.
2. Tests to be used: PSA dosing, either coupled with the digital rectal examination or not.
3. Age of onset for screening in individuals at general risk: 50-55 years, at the discretion of the physician and the patient.
4. Age of onset for screening in individuals at increased risk: 40 or 45 years, at the discretion of the physician and the patient.
5. Interval between screenings: Annual or biennial, at the discretion of the physician and the patient.
6. Discontinuation of screening: 70 years or when life expectancy is less than 10 years.

With respect to PSA cutoff values, given the great divergence found in the literature and the fact that the subject has been approached by few entities, there is no common ground. It is prudent to repeat the test to confirm any changes and refer the patient to a specialist with experience in diagnosing and treating prostate cancers.

We believe that this minimal set of recommendations can aid in disseminating and promoting adherence to evidence-based practices for such an important male health problem like prostate cancer.

Resumo

Guias de conduta vigentes para o rastreamento do câncer de próstata: uma revisão sistemática e proposta de núcleo mínimo

Objetivo: Considerando a importância do rastreamento de câncer de próstata, a possibilidade de dano decorrente do rastreamento indiscriminado, a dificuldade de divulgação e adesão às diretrizes sobre o assunto, objetivamos identificar as principais diretrizes vigentes, procurar pontos de abordagem comuns e estabelecer um núcleo mínimo de condutas.
Método: Revisão sistemática da literatura sobre guias de prática de rastreamento para câncer de próstata nas bases Pubmed, Lilacs e Google Scholar, além de busca ativa nos sítios de diversas entidades de saúde nacionais.
Resultados: Foram selecionadas 12 diretrizes, cuja análise resultou na identificação de seis pontos comuns de conduta, com o seguinte núcleo mínimo de recomendações: (1) a indicação ou não de rastreamento: deve ser individualizada e precedida de uma decisão informada; (2) os exames utilizados: PSA com ou sem exame digital retal; (3) a idade de início geral: 50-55 anos; (4) a idade de início em homens com risco aumentado: 40 anos; (5) o intervalo entre os rastreamentos: anual ou bienal; e (6) a idade de suspensão do rastreamento: 70 anos ou expectativa de vida menor que 10 anos.
Conclusão: Embora existam divergências entre elas, foi possível estabelecer um núcleo mínimo de condutas que podem ser úteis na prática diária do médico.

Palavras-chave: Programas de Rastreamento. Rastreamento. Neoplasias da Próstata. Câncer de Próstata. Guias de Prática Clínica.

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