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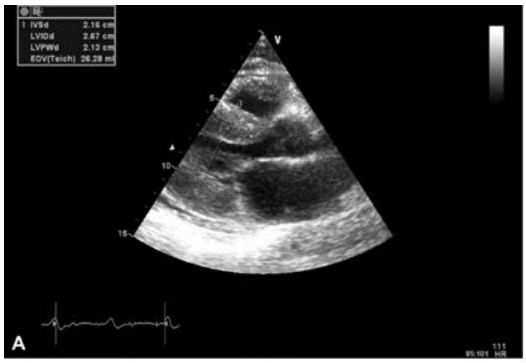

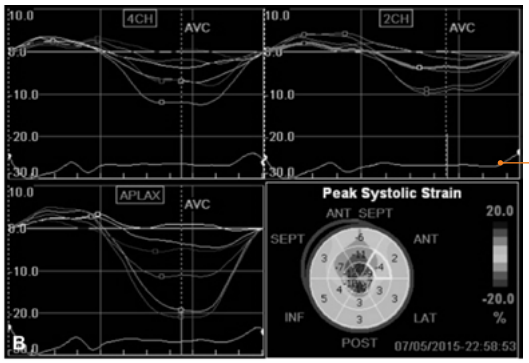

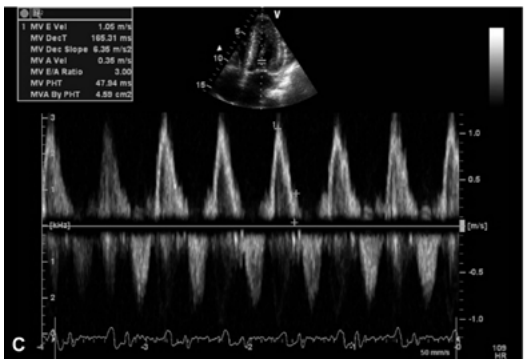

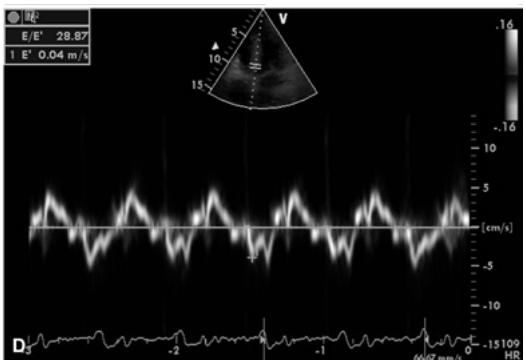

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Phytotherapy: yesterday, today, and forever?

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Since before we can remember, humans used natural resources at hand to fight whatever jeopardized their well-being. The earliest reference to this was found in China, in the writings of Emperor Cho Chin Ken, from around 3,000 B.C. There are references to approximately 1,700 medicinal plants in a papyrus from Egypt, and also data from peoples such as the Assyrians, Greeks, and others.[1] Some places around the world, especially those with fewer economic resources, still adopt the same practices used back then. So much so, that the World Health Organization acknowledges phytotherapy as an important factor in primary health care. Much is achieved through traditional knowledge, which is usually passed from generation to generation. But the search to understand mechanisms of action, active principles, and scientific basis has been placed on the foreground.

The advance of chemistry and pharmacology, in the early 19th century, allowed for the first molecules to be isolated in a laboratory. Plants produce several substances that affect their metabolism, defense, adaptation to their environment, and even competition between species. These phytochemicals, which can act as agents to combat human diseases, started being identified and became increasingly known.

An important milestone in establishing phytotherapy as science was the creation, in 1976 Germany, of the Komission E, who sought to gather as much information as possible on plants that were considered medicinal, developing studies on each of them[2]. The importance of these studies is internationally recognized to this day. At the same time, the safeness and effectiveness of phytotherapics began to be demanded by the market. Furthermore, in order to normalize their offering, a means for standardizing the extracts was established.

To understand how that standardization works, it is necessary to know that the extract of any given plant is composed of several substances, some of which are biologically active, others that are secondary, all of which can have synergistic, or even antagonistic, actions. These components, in general, have a constant proportion. Thus, when a substance is identified, among all (ideally the active substance), its percentage in the extract will determine the others. And it is only possible to consider an extract similar to another when the amount of that marker is the same in both[3].

As chemicals from plants were further studied, molecules were isolated – and also modified in lab-

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oratories –, and new highly effective compounded medications synthesized (although plant substances were often used as a base for the synthesis). For example, acetylsalicylic acid was synthesized from salicylic acid extracted from willows; it had fewer adverse effects and started to be widely used, with a patent and brand registration. These new compounds took over the market. Small pharmacies became the large industrial conglomerates we are familiar with today. Phytotherapy began to lose credibility, and its use decreased.

Evidence-Based Medicine started being developed, seeking to scientifically prove if certain products were safe, what were their effects, mechanisms of action, all of which gave more credibility to medications. Phytotherapics were often attacked as ineffective, and people saw them with doubt or suspicion. That motivated legislation in several countries. However, people continued to use phytotherapics. Research conducted in 2010 showed that around 70% of Germans used them, acknowledging, thus, its effectiveness but also demanding scientific confirmation[4].

Currently, products derived from plants, overall, are not the primary option for emergencies. They can be complementarily used in cases of acute disease, are useful for several chronic diseases of mild to moderate intensity, and can be used in preventive care. However, they seem to be often used with no medical prescription and that are still many myths surrounding its use, such as "It can't hurt to try", "I don't need to tell my doctor that I used a phytotherapic because it is a natural product", and "It doesn't matter where the raw material comes from, it's all the same." Indeed, they usually do have fewer adverse effects and, in general, research shows that people who make use of phytotherapics are often those with greater concern for their health.

On the other hand, legislation on them varies from country to country. In the United States, for example, they are considered supplements and are not regulated by the FDA, despite their increasing use by the population. However, they face severe contamination and adulteration problems in the country, especially those of Chinese and Indian sources, which can cause adverse effects, serious ones included, and even death[5]. This has led three American non-governmental organizations – American Botanical Council-ABC, American Herbal Pharmacopea-AHP, and National Center for Natural Products Research – to start a wide-scale program to educate employees in the phytotherapics and supplements industries. The program intends to act as a self-regulating mechanism. Adulteration can happen accidentally, due to ineffective quality control , or intentionally aiming at financial gain.

Nowadays, a quality phytotherapic production process includes several stages. Cultivation must be controlled to ensure plants with constant quality levels. The raw material obtained at harvest must be pressed and dried for transport and storage, the storage location must be extremely clean and well-ventilated, and packages must be stored separately from other plants stored in the same facilities and away from the floor. The extracts obtained must be analyzed for their purity and dose of active principles.

The preparation of an extract also includes many careful stages. Firstly, the raw materials are turned into powder. Then, the powder is dissolved into an extracting solution (for each plant the most appropriate solvent is used: water, alcohol, ether, etc.). Next, the liquid is filtered , and an extract is obtained through the evaporation of the solvent and vacuum drying (the temperature is usually raised to 40°C or 50°C). The extract is then used to produce the end product in the form of capsules, tablets, and others.

In emerging countries, it is estimated that 75% of the population uses natural products, while in developed countries that number is around 50% and mostly linked to lifestyle-related diseases. The traditional forms of use, such as in integrative medicine, Ayurveda, traditional Chinese medicine, homeopathy, acupuncture, and all other types of practice considered "alternative," have been increasingly adopted.

In Brazil, indigenous peoples already used plants to treat diseases, and the arrival of Africans and European Jesuits added to their knowledge[1]. There are historical, scientific sources on the use of medicinal plants, such as *Flora Fluminensis*, by Friar Mariano da Conceição Veloso (1742-1811); *Systema Materia Medicae Vegetabilis Brasiliensis* (1843), by Karl Friedrich Von Martius; *Matéria* Médica Brasileira (1862), by Manuel Freire Allemão Cysneros; and the *Dicionário das Plantas* Úteis *do Brasil e das Plantas Exóticas Cultivadas*, by Pio Correia, a collection of six volumes, published from 1926.

Brazilian legislation is stringent. However, despite this being an advantage, it makes it more difficult to launch new phytotherapics due to the severe requirements in quality and reference for clinical studies. Yet, most phytotherapics used in Brazil are produced using plants from other countries[6].

There are the traditional phytotherapics used as infusions or concoctions, tincture, syrups, or ointments, which include living pharmacies and the use of medicinal plants as a vegetable drug (the plant *in natura*). There are also the phytotherapics produced by the industry with different levels of technology and based on well-documented clinical evidence. That last category could use some innovation. Some phytotherapics are used in SUS (Brazilian Single Health System). Traditional products are exempt from prescription, unlike phytotherapic medications (also known as phytomedications), and the main difference between both categories is in the requirement for scientific proof.

For over a decade, there was a massive loss in the development and innovation of Brazilian phytotherapics due to the CGEN (Council for the Management of Genetic Heritage), which regulated research into Brazilian plants and set requirements that were often impossible to comply with, such as defining a legal representative in the community where a sample from a particular plant was collected. Several pieces of research were hampered due to legal uncertainty. In 2015, another law (Law 13.123/2015) was created to regulate the genetic access in the country, apparently improving the conditions for research and the equal distribution of the benefits derived from the economic exploitation of plant resources. The previous authorization by the CGEN is no longer necessary.

The first phytotherapic fully developed in the country and using exclusively Brazilian plants was an anti-inflammatory based on *Cordia verbenacea*, a bush from the Amazon Forest traditionally used for reducing inflammation. It was launched in 2005 and soon became a leader in medical prescriptions.

State policies are now favorable. The industry seems to be aligning themselves, and the academia has been developing studies that still lack cohesion. There still the need to perfect the several elements involved. There is a demand, not only from the industry but from the government (SUS) and the academia (scientific production). It is necessary to implement a food network of producers for the extracts, including family farming and sustainability. We need to develop studies of basic research, pharmaceutical analytics, and techniques, followed by clinical trials so that finally the medication can be included in the Anvisa records and registered to be marketed. It is a long road, and everything depends on its harmonic balance.

In 2007, the PNPMF (National Program of Medicinal Plants and Phytotherapics) was implemented with the purpose of ensuring the Brazilian population access to the secure and rational use of medicinal plants and phytotherapics, promoting the sustainable use of biodiversity, developing the production chain and national industry. The PNPIC (National Program of Integration and Complementary Practices) was instituted and included several so-called "alternative" approaches, including the phytotherapy. As part of the program, medications based on 12 plants were approved and distributed by the Ministry of Health to the municipalities, who then forward them to the Basic Health Units. Unfortunately, the program is still unknown by many, so it is underused. There is also a list of 71 plants in which the government is interested in studying so that they can, in the future, be included in the Rename (National List of Medications).

Although phytotherapy is not a subject included in the curriculum of most medical schools in the country, it has been widely studied in pharmacy faculties. In post-graduate programs, however, thousands of dissertations have been developed and presented throughout Brazil on the subject of medicinal plants[8-11]. Unfortunately, once they are defended, they are published but not put into practice, with few exceptions.

Brazil has incredible biodiversity (15-20% of the world's biodiversity), with about 60,000 varieties of plants. Nonetheless, only approximately 1,500 of those are documented. In the words of the American biologist Thomas Lovejoy: "It is counterintuitive that this potential is completely understudied and underused in programs for the discovery of natural substances for the most diverse applications."

Many health professionals are interested in phytotherapics, especially pharmacists and nutritionists. But dentists, veterinarians, and physical therapists also find uses for its application. Doctors, however, often still have restrictions regarding them. In research conducted with doctors in Brazil, 95% declared that they would prescribe them more often if there were studies to prove their security and effectiveness. They would also like more information (since there is no subject on phytotherapy in medical school) and claim to prescribe them when there are restrictions for treatment with synthetics. Only 5% declared having no intention of prescribing phytotherapics.

On the other hand, there is an increase in interest by the population in this type of medication[12], which is linked to an increasing interest in improving life-style conditions. All of that leads us to believe that the adoption of measures is of the essence, not only to educate the population and the professionals, but also to increase quality in raw materials, research, and innovation.

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Homeopathy: scientific or not?

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Dear Editor

We read the publication on "Special Dossier: Scientific Evidence for Homeopathy" with great interest [1] and would like to share ideas on this issue. In fact, homeopathy becomes an alternative medicine system that is presently used worldwide but there are several comments on its scientific reliability. It is usually mentioned that homeopathy's effect is a type of placebo effect [2]. Although there are many publications on homeopathy, the proof of scientific merit is still a controversial issue and some medical scientists point to the "hoax" problem in those homeopathy reports [3]. Regardless of its actual biological effect, if we consider homeopathy as a type of alternative medicine, it might at least psychologically support the patients. In addition, there are some new findings that homeopathy might be useful in preventive medicine as prevention of tropical epidemic disease such as dengue [4]. This becomes a new hope for several poor countries. In our experience in Thailand, a tropical country in Indochina, some local physicians already use the homeopathy technique for dengue prevention but there is much criticism from others. Regarding the present status of homeopathy, the important question is where this alternative medicine system should be set and how to improve the quality management system for this alternative medicine practice.

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Recommendations for hypofractionated whole-breast irradiation

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SUMMARY

This recommendation consensus for hypofractionated whole-breast radiotherapy (RT) was organized by the Brazilian Society of Radiotherapy (SBRT) considering the optimal scenario for indication and safety in the technology applied. All controversies and contraindication matters (hypofractionated RT in patients who underwent chemotherapy [CT], hypofractionated RT in lymphatic drainage, hypofractionated RT after mastectomy with or without immediate reconstruction, boost during surgery, hypofractionated RT in patients under 50 years old, hypofractionated RT in large breasts, hypofractionated RT in histology of carcinoma in situ [DCIS]) was discussed during a meeting in person, and a consensus was reached when there was an agreement of at least 75% among panel members. The grade for recommendation was also suggested according to the level of scientific evidence available, qualified as weak, medium, or strong. Thus, this consensus will aid Brazilian radiotherapy experts regarding indications and particularities of this technique as a viable and safe alternative for the national reality.

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INTRODUCTION

Breast cancer represents around 29.5% of all cancer types in Brazil, and it is the most prevalent type amongst women. It is estimated there were 59,700 new cases in the country in 2018[1], around 56 cases for every 100,000 women.

Radiotherapy (RT) is an essential part of Breast cancer treatment during early stages, with proved benefits of survival after conservative surgery[2]. The conventional fractionation (1.8-2 Gy per fraction) has been used as the standard over the last decades, with a total dose of 50-50.4 Gy over 25-28 sections, distributed over 5 consecutive weeks.

Hypofractionated radiotherapy is an RT technique in which the total dose is administered over a shorter time range with fractionated doses that are higher than the conventional ones. The scientific evidence for its use is established by prospective and randomized studies, including a considerable number of patients submitted to the conventional treatment for breast cancer, with comparable safety, effectiveness, local control, and survival observed on conventional treatment. It is a technique widely used in several countries[3,4,5].

The implementation of the whole-breast hypofractionated RT in the clinical routine was larger amongst academics than in community hospitals[6]. Variations in indication, considering anatomical aspects, planning parameters, technical and prognostic factors had a significant influence in that scenario. Recent recommendations allowed for a larger scope of indications for the use of whole-breast hypofractionated radiotherapy so that the slightest variations in medical decisions could intervene in treatment individualization[6].

Brazil faces the same difficulty to include hypofractionated radiotherapy in current clinical practice, whether it is for funding reasons or technical matters; so far, it has only been implemented in reference centers. In the current Brazilian reality, the lack of RT equipment has caused difficulty of access, long waiting lines, and delays for beginning treatment, all of which can compromise the oncology effectiveness[7,8,9]. The reduction in RT time could allow for an increased in installed capacity and, consequently, expand the access:

This article aims to report the consensus for recommendation of the Brazilian Society of Radiotherapy (SBRT) for the use of whole-breast hypofractionated RT.

METHODOLOGY

A meeting was organized to take place in the city of São Paulo on March 3rd, 2018, for which were invited the leading members of SBRT with renowned expertise and dedicated to the treatment of breast cancer. Representatives of some of the main reference centers for RT from each of the country's regions were invited, both from the Public Health System (SUS) as well as from the supplementary healthcare network. The panel was attended by 18 radio-oncologists, a physician representative of the Brazilian Association of Medical Physics (ABFM) and a mastologist representing the Brazilian Society of Mastology (BSM), the last two chosen as ad hoc consultants. Only the radio-oncologists had voting rights.

The literature available on the subject was reviewed, presented and discussed during plenary. Questions were raised regarding the indications and safety of whole-breast hypofractionated RT in different clinical contexts[10], which were put to the vote of panel members according to the Delphi Method[11].

There were three possible answers to the questions: agree, disagree, abstains. The consensus was reached when there was an agreement amongst at least 75% of the panel members. The grade for recommendation was also suggested according to the level of scientific evidence available, qualified as weak, medium, or strong, as follows.

Level of scientific evidence:

Strong Level – Data obtained from multiple randomized studies of good size, concordant and/or of a robust meta-analysis of randomized controlled trials.

Medium Level – Data obtained from a less robust meta-analysis, from a single randomized trial or from non-randomized trials (observational).

Weak Level – Data obtained from experts' consensual opinions.

For organization purposes, the meeting was divided into three main discussion section:

Section I – Who is the ideal patient for whole-breast hypofractionated RT?

Section II – Controversies and contraindications

All controversial issues were discussed in section II. Since there is still no strong evidence in the current literature on certain clinical contexts, particularities and subgroup analyses were conducted for consensus on the following subjects: Hypofrac-

tionated RT in patients who underwent chemotherapy (CT), hypofractionated RT in lymphatic drainage, hypofractionated RT after mastectomy with or without immediate reconstruction, boost use during surgery, hypofractionated RT in patients under 50 years old, hypofractionated RT in large breasts, hypofractionated RT in histology of carcinoma in situ (DCIS).

Section III – Safety in the technology applied

RESULTS

Section I – Optimal scenario for the indication of whole-breast hypofractionated RT

The SBRT consensus considered hypofractionated RT to be safe and effective for women who meet all the following clinical criteria:

- Have underwent conservative treatment for breast cancer;
- Are over 50 years old.
- Have invasive carcinoma of no special type, grades I and II;
- Have clinical stages T1 and T2;
- Have negative axillary lymph nodes;
- There is no particularity regarding the laterality of the affected breast;
- There is no restriction regarding the immunohistological profile (patients with positive hormone receptors, HER2 super-expressed or triple negative).

Level of agreement	Level of evidence
100%	Strong

Dose and fractionation:

The models of moderate fractionation of 42.5 Gy in 16 fractions and of 40 Gy in 15 fractions are equally safe and effective.

Level of agreement	Level of evidence
100%	Strong

Comments: The hypofractionated models are those that use a dose above 2 Gy/fraction. The fractionation models used in the Start B[12] studies of 40 Gy in 15 fractions and in the Canadian study[4] of 42.5 Gy in 16 fractions present consistent results regarding late toxicity, survival free of locoregional recurrence, and quality of life with 10-year average follow-up[4].

Section II – Areas of controversy and contraindications

Mastectomy and reconstruction:

The panel considers the post-mastectomy hypofractionated RT of solely the thoracic wall with NO immediate breast reconstruction to be safe.

Level of agreement	Level of evidence
100%	Moderate

Comments: Despite Start studies (A[13] and B[12]) not having as the assessment of post-mastectomy hypofractionated RT as the initial objective, this group represented 8% (513 patients) of the sample[3]. There was no statistical power for a recommendation. However, locoregional recurrence happened in 6.8% of these patients. The toxicity was not different for patients who underwent mastectomy and hypofractionated RT[3]. Radiobiological ratios of similar remaining-tissue sensibility, regardless of the surgical technique, and the potential reduction of late events from breast α/β encourage the use of hypofractionated models[14].

There was NO agreement as to the safety of the indication of post-mastectomy hypofractionated RT after immediate breast reconstruction WITH prosthesis/tissue expander.

Level of agreement	Level of evidence
28%	Weak

Comments: The Start studies (A[13] and B[12]) excluded post-mastectomy patients with immediate reconstruction, and there are no other studies that can be used as a reference for the procedure.

There was NO agreement as to the safety of the indication of post-mastectomy hypofractionated RT after immediate breast reconstruction WITH autologous tissue.

Level of agreement	Level of evidence
39%	Weak

Comments: The Start studies (A[13] and B[12]) excluded post-mastectomy patients with immediate reconstruction and, to the present day, there are no other studies with results that can be used as a reference for the procedure.

The panel considers the treatment with hypofractionated RT to be safe for breasts of all sizes, as long as the recommended technical criteria presented in this document are followed.

Level of agreement	Level of evidence
100%	Strong

Comments: The Start studies (P[15], A[13], and B[12]) did not limit breast size, and classified them into small, medium, and large. There was no toxicity difference amongst different breast sizes. The restriction should be made according to dosimetric parameters[3]. The Canadian study[4] limited the inclusion of breasts with latero-lateral diameter above 25 cm². This panel strongly suggests the use of the technical parameters established in Section III - Safety in the hypofractionated RT technology applied to treat breast cancer.

CHEMOTHERAPY

The panel considers the treatment of exclusively the breast with hypofractionated RT, AFTER adjuvant CT, to be safe.

Level of agreement	Level of evidence
100%	Strong

Comments: Several randomized clinical trials allowed CT patients in their adjuvant treatment protocols. Adjuvant CT was used in 13.9%, 35.5%, 22.2%, and 11% in the Start-P[15], Start A[13], Start[12] and Canadian[4] studies, respectively. In addition, in the Cochrane meta-analysis[16], 1,728 patients (21%) received adjuvant CT.

There was no difference in local control in the Start (P[15], A[13], and B[12]) and Canadian[4] studies in the subgroup of adjuvant CT, regardless of the RT model used (hypofractionated RT or conventional RT). Similarly, upon evaluating cosmesis and regular tissue toxicity, there was no difference amongst the study groups, regardless of the the use of adjuvant CT. The use of hypofractionated RT for breast cancer has been increasing considerably over the years.

A study conducted by the US National Cancer Database showed an increase in hypofractionated RT indication for patients who received CT, with an absolute increase of 13.6% over the last decade (from 4.6% to 18.2%)[17].

The panel considers the treatment of exclusively the breast with hypofractionated RT, AFTER neoadjuvant CT, to be safe.

Level of agreement	Level of evidence
94%	Weak

Comments: None of the clinical trials that assessed hypofractionated RT included neoadjuvant CT in their respective treatment protocols[16]; however, the indication in this scenario has substantially increased over the last few years[16,17].

Randomized prospective studies are being conducted with indications and models of hypofractionated RT posterior to neoadjuvant CT. In current clinical practice, the exposure to CT, both adjuvant as neoadjuvant, prior to surgery did not alter the toxicity patterns for hypofractionated RT.

The panel does NOT consider to be safe the treatment of exclusively the breast with hypofractionated RT and concurrent CT.

Level of agreement	Level of evidence
100%	Weak

Comments: The is no data in the literature that addresses the oncologic safety of hypofractionated RT concurrent with CT since the main clinical trials available did not use that combination[17].

The panel considers the treatment of exclusively the breast with hypofractionated RT, exclusively concurrent with anti-HER2 drugs, to be safe.

Level of agreement	Level of evidence
89%	Weak

Comments: Trastuzumab, as well as other anti-HER2 drugs, were not clinically assessable during recruiting for breast hypofractionated RT. Trastuzumab can be safely used after and concurrent with conventional RT. In a mitigating scenario, trastuzumab was administered with hypofractionated RT in several clinical situations, and no increased toxicity was observed[17].

DCIS

The panel considers the treatment of exclusively the breast with hypofractionated RT to be safe in patients with pure Ductal Carcinoma IN SITU.

Level of agreement	Level of evidence
100%	Moderate

Comments: In a meta-analysis of breast hypofractionated RT conducted by Cochrane[16], only 0.15% of patients presented a diagnosis of pure DCIS, and there was no evidence of a difference in local con-

trol and toxicity. The retrospective Montreal study showed similarities in the relapse patterns for the ipsilateral breast with the hypofractionated models for the pure DCIS histology[18]

AGE

The panel considers the treatment of exclusively the breast with hypofractionated RT to be safe in patients between 40 and 50 years old.

Level of agreement	Level of evidence
100%	Strong

Comments: The Start A[13], Start B[12] and Canadian[4] studies included, respectively, 23%, 21%, and 25% of women under 50 years old. The local control was similar among different ages.

There was NO agreement regarding the safety of indication of hypofractionated RT of exclusively the breast for patients with age under 40 years.

Level of agreement	Level of evidence
61%	Strong

Comments: The Start studies (P[15], A[13], and B[12]) included only 5.8% women under 40 years old. The local control and toxicity of normal tissue presented similar results among groups; however, without the due safety of indication to this day.

DRAINAGE

There was NO agreement regarding the safety of indication of hypofractionated RT exclusively of the breast in lymphatic drainage of the supraclavicular fossa (SCF).

Level of agreement	Level of evidence
56%	Moderate

Comments: The Start studies (P[15], A[13], and B[12]) used hypofractionated RT in the SCF, respectively, in 20%, 14%, and 7% of a total of 470 patients. The Cochrane[16] meta-analysis grouped only 10% of patients who underwent hypofractionated RT in the SCF. The Canadian[4] study did not include patients for lymphatic drainage irradiation.

A Chinese[19] study randomized 811 patients with high-risk breast cancer, stage II, for conventional or hypofractionated RT in the SCF and did not observe any difference in locoregional recurrence, distant metastasis, disease free survival, and global survival. Locoregional recurrence was also similar in meta-analysis[20] [relative risk [RR]= 1.03; 95% CI (0.87; 1.23), P=0.72], and in the Start[14] studies (0.5% vs 0.3%; p=0.71). The risks of pulmonary toxicity, rib fracture, plexopathy, and upper limb lymphedema were similar between the conventional and hypofractionated RT models[14,20].

There was NO agreement regarding the safety of indication of hypofractionated RT exclusively of the breast in lymphatic drainage of the supraclavicular fossa (SCF) and axilla.

Level of agreement	Level of evidence
33%	Weak

Comments: There were no randomized clinical trials that included the axilla in RT volumes. Despite some studies suggesting the model were equivalent regarding acute and late toxicities, most panel members did not consider hypofractionated radiotherapy to be appropriate in this context due to a lack of safety for recommendation to this day.

There was NO agreement regarding the safety of indication of hypofractionated RT exclusively of the breast in lymphatic drainage of the internal mammary chain.

Level of agreement	Level of evidence
22%	Weak

Comments: The randomized studies did not include the internal mammary chain in the RT volumes. Despite some studies suggesting equivalent levels of acute and late toxicity, it is not possible to exclude the possibility of increased pulmonary, costal arch, and heart toxicity with hypofractionated radiotherapy due to lack of scientific evidence[20].

BOOST

The panel considered the administration of a boost in patients who undergo breast hypofractionated RT to be safe.

Level of agreement	Level of evidence
100%	Strong

Comments: The use of a boost during surgery, when indicated, was used in different randomized controlled trials. In the Start studies (P[15], A[13], and B[12]) and the Cochrane[16] meta-analysis compilation, a boost

was used in 75%, 60%, 43%, and 44% of patients, respectively. In MD Anderson[21] and a Chinese[22] study, all patients had a boost after the whole-breast hypofractionated RT. No increased toxicity was observed with the addition of a boost to the hypofractionated models when compared to conventional therapy[16,20,22].

The models used were: 3x3 Gy, 4x2,5 Gy, 3x2,67 Gy and 5x2 Gy.

T3 STAGE

The panel considered the use of breast hypofractionated RT to be safe in patients with T3 tumors.

Level of agreement	Level of evidence
77%	Weak

Comments: The T3 stage was included in the Start studies (P[15], A[13], and B[12]), with tumors equal or larger than T2 representing 42.5%, 48.6%, and 35.9%, respectively. There is no analysis of the results; however, the randomized controlled trials considered that the size of the resected tumor, on its own, should not be an exclusion factor for hypofractionated radiotherapy[14].

GRADE III HISTOLOGY

The panel considered the use of breast hypofractionated RT to be safe in patients with grade-III-histology tumors.

Level of agreement	Level of evidence
100%	Strong

Comments: The compilation of the Start[3] studies showed that the tumor grade was not an isolated prognostic factor. Amongst the 5,861 patients grouped in the Start studies (P[15], A[13], and B[12]), it was observed 9% of locoregional recurrence for tumors with grade III histology, and 4.5% and 3.4%, respectively, for grade II and I. In the subgroup analysis of the Canadian[4] study, grade III histology was a risk factor linked to an increase in local recurrence. However, regardless of histological grade, those patients who underwent hypofractionated RT did not present an increase in relapse when compared with conventional RT. A specific population cohort study with grade II patients who underwent hypofractionated RT also did not show evidence of increased risk of locoregional recurrence in early-stage breast cancer[23].

The summary of accepted considerations that are recommended by the panel members with over 75% of agreement is presented in Table 1.

SECTION III – SAFETY IN THE HYPOFRACTIONATED RT TECHNOLOGY APPLIED TO TREAT BREAST CANCER

This panel of specialists recommends, for the breast hypofractionated RT, the use of the three-dimensional conformal technique (3DCRT). This technique uses dedicated computer tomography, with which it is possible to assess the distribution of the radiation dose in the target volume and the adjacent organs at risk (OARs), providing increased quality and safety during the treatment.

TABLE 1. PROFILE OF PATIENT FOR WHICH THE SBRT CONSENSUS RECOMMENDS THE USE OF HYPOFRACTIONATED RT FOR BREAST CANCER TREATMENT (AGREEMENT > 75% AMONGST PANEL MEMBERS)

Variable	Level of agreement (%)	Level of evidence
Surgery Conservative	100	Strong
Mastectomy		
Without reconstruction	100	Moderate
Age		
>40 years	100	Strong
Stage of the tumor		
T1 – T2	100	Strong
T3	77	Weak
Histological grade		
G1 – G2 – G3	100	Strong
Histology		
Invasive carcinoma of no special type	100	Strong
DCIS	100	Moderate
Regardless of IHC	100	Strong
Axillary lymph nodes		
Absent	100	Strong
Breast size		
Any size	100	Strong
Systemic treatment		
After adjuvant CT	100	Strong
After neoadjuvant CT	94	Weak
Concurrent with anti-HER2 drugs	89	Weak
Boost	100	Strong

DCIS = Ductal Carcinoma IN SITU. IHC = Immunohistochemical. CT = Chemotherapy. RT = Radiotherapy

The panel members suggest complying with the following criteria:

- Image acquisition and treatment in the supine position;
- Use of proper restraining devices that allows the patient to be comfortable and the position to be reproduced;
- The delineation of target structures and OARs as recommended by breast cancer contouring atlas by the RTOG[24] (https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx) or the ESTRO[21] (https://www.ncbi.nlm.nih.gov/pubmed/25630428).
- Evaluation of the dose-volume histogram (DVH); the constraints and prescription doses according to the RTOG 1005[25] are suggested by this panel.
- PTV_Eval – Breast CTV + 5-10 mm margin for setup, editing 5 mm of skin and excluding the volume of the costal arches.
- D95%=95% in an optimal scenario, being acceptable up to D90%=90%;
- DMAX=115% in an optimal scenario, being acceptable up to 120%;
- Compliance index (CI): volume covered by 95% of the prescription isodose/ PTV_Eval volume, this being from 0.95-2 (optimal) and the acceptable value of 0.85-2.5;

OARs constraints, such as ipsilateral lung, heart, contralateral lung, thyroid, and contralateral breast, according to the RTOG 1005 – Annex IV – p. 83[25].

(https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=9366 rtog 1005 protocol) (Table 2);

- It is recommended to always use a linear accelerator;
- It is recommended to confirm the positioning with, at least, planar imaging on the first day of treatment and weekly, according to the RDC20[26].

TABLE 2. DOSE-VOLUME CONSTRAINTS FOR PLANNING WHOLE-BREAST HYPOFRACTIONATED RADIOTHERAPY, ACCORDING TO THE RTOG 1005[25] CRITERIA

Structure	Criteria
Breast CTV	D95% ≥ 38 (≥ 36)Gy D50% ≤ 43.2 (≤ 44.8)Gy
Boost CTV	D95% ≥ 9.5(9.0)Gy V11Gy ≤ 5(10)%
Heart	V16(20)Gy ≤ 5% V8Gy ≤ 30(35)% MeanD≤ 3.2(4)Gy
Lung	V16Gy ≤ 15(20)% V8Gy ≤ 35(40)% V4Gy ≤ 50(55)%
Contralateral lung – IMRT	V4Gy ≤ 10(15)%
Contralateral breast	MaxD ≤ 240(384)cGy D5% ≤ 144(240)cGy

CTV = clinical tumor volume, IMRT = Intensity-modulated radiotherapy, D_x = dose that receives the % the volume, V_{Gy} = volume that receives the dose in Gy, MeanD = mean dose, MaxD = maximum dose

FINAL CONSIDERATIONS

These recommendations presented by the SBRT for the use of whole-breast hypofractionated radiotherapy will aid Brazilian radiotherapy experts regarding indications and particularities of this technique as a viable and safe alternative for the national reality.

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RESUMO

Este consenso de recomendações para a radioterapia (RT) hipofracionada de toda a mama foi organizado pela Sociedade Brasileira de Radioterapia (SBRT) considerando o cenário ideal para indicação e segurança na tecnologia aplicada. Questões de controvérsias e contraindicações (RT hipofracionada em pacientes submetidas à quimioterapia [QT], RT hipofracionada nas drenagens linfáticas, RT hipofracionada após mastectomia com ou sem reconstrução imediata, a realização de reforço de dose em leito cirúrgico [ou boost], RT hipofracionada em pacientes com idade menor que 50 anos, RT hipofracionada em mamas volumosas, RT hipofracionada em histologia de carcinoma in situ [CDIS]) foram discutidas em encontro presencial, sendo o consenso atingido quando existisse concordância de pelo menos 75% dos panelistas. O grau de recomendação foi também sugerido de acordo com o nível de evidência científico disponível, qualificado entre fraco, médio ou forte. Assim, este consenso deverá servir para auxiliar os especialistas da radioterapia brasileira em relação às indicações e particularidades dessa técnica, como uma alternativa segura e viável para a realidade nacional.

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Lumbar herniated disc treatment with percutaneous hydrodiscectomy

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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 producers 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.

SUMMARY

Lumbar herniated disc are common manifestations of degenerative spine diseases, the main cause of radiated lower back pain. This guideline followed standard of a systematic review with recovery of evidence based on the movement of evidence-based medicine. We used the structured method for formulating the question synthesized by the acronym p.I.C.O., In which the p corresponds to the lumbar herniated disc, i to the treatment intervention with percutaneous hydrodiscectomy, c comparing with other treatment modalities, o the outcome of clinical evolution and complications. From the structured question, we identify the descriptors which constituted the evidence search base in the medline-pubmed databases (636 papers) and therefore, after the eligibility criteria (inclusion and exclusion), eight papers were selected to answer to clinical question. The details of the methodology and the results of this guideline are exposed in annex i.

INTRODUCTION

Lumbar herniated discs are common manifestations of degenerative spine diseases, being the main cause of radiated lower back pain. Conservative treatment with anti-inflammatory and physical therapy provides relief of pain in a significant proportion of patients, and surgery is indicated in nonresponsive patients after at least six weeks of conservative treatment to avoid irreversible structural changes in the nerve roots due to chronic compression[1]. Microdiscectomy is the surgical intervention of choice for hernias that cause root symptoms, not relieved by conservative treatment[2,3]. Surgery provides 85-95% of good and excellent results in the short-term postoperative period, however, the recurrence rate of LHD after microdiscectomy has been reported to be approximately 26%[4]. The surgical treatment includes a great variety of options: percutaneous, endoscopic, by minimally invasive accesses, open treatments; and segmental arthrodesis may or may not be performed.

Percutaneous hydrodiscectomy was developed as a less invasive alternative for traditional microdiscectomy. The procedure is performed under local anaesthesia with sedation, using an image guided technique and a 3.8 mm cannulated system to dilate the annular fibres in order to access the disc space. The core material of the disc is mechanically removed using a high speed (non-thermal) salt solution which sprays the tissue.

OUTCOMES

Author Type of Study	Publication Date	Publication Status	Participants	Study Length	Pre and post-op VAS MI	Pre and post-op lumbar VAS	Mac-Nab Criteria	Complications	Comments
Lo WC, et al.5(B) Case series – retrospective	2012	Preliminary Report – pending	97 participants with HDL<6 mm and radiculopathy confirmed through imaging. Extruded and sequestered discs were excluded.	6 months	8.2±1.1 2.8 ±1.0 (p<0.05)	6.5±1.7 2.9±1.2 (p<0.05)	88% excellent and good	n/r	
Han HJ, et al.6(B) Case series – retrospective	2009	Preliminary Report Source - Kor J Spine	12 participants with lower back pain (LBP) and radiculopathy, and 1 with back pain only. Extruded and sequestered discs were excluded.	6 months	8.5±1.1 2.7±1.0 (p<0.05)	6.2±1.9 3±1.4 (p<0.05)	n/a	n/r	"A long follow-up and additional cases are needed to confirm these initial results."
Hardenbrook MA, et al.7(B) Case series – retrospective	2013	Source - Internet J of Spine Surg	50 participants with lumbar HNP secondary radiculopathy confirmed through MRI in 1-2 levels. Excluded: free fragment, central stenosis or bone holding.	Mean of 4.6 months	n/a	n/a	n/a	n/r	94% of patients presented improvement of the symptoms. 6% did not experience improvement of symptoms. Seven participants with initial improvement after the procedure had recurrence of symptoms; of these, three had recurrence of LHD at the same level. Therefore, treatment failure was 20%.
Kowalkowski8(B) Case series – retrospective	2013	Abstract Accepted by ASIPP; June, 2013	15 participants with subligamentous lumbar HNP secondary radiculopathy in a single level.	4 months	60 32 (p = 0.032)	n/a	n/a	n/r	93% of the patients presented improvement of the symptoms. Five patients who reported improvement of symptoms were treated with subsequent injections of transforaminal epidural steroids.
Jasper, et al.9(B) *Case series – retrospective	2013	Pending - ePlasty	30 participants with herniated disc in levels 1-3 confirmed through imaging. Excluded: sequestrated disc, >50% loss of disc height, severe DDD or osteophytes spinal stenosis and vertebral instability.	12 months	n/a	n/a	73% excellent and good		There was a reduction in the pain score in 26 of the 30 participants (87%).
Borshchenko I, et al.10(B) Case series - retrospective	2010	Pending (Abstract - pilot study)	16 participants with confirmed disc bulging (protrusion or small extrusion) in a single level. Large disc extrusion excluded.	6 months	n/a	n/a	88% excellent and good	n/r	

Author Type of Study	Publication Date	Publication Status	Participants	Study Length	Pre and post-op VAS MI	Pre and post-op lumbar VAS	Mac-Nab Criteria	Complications	Comments
Wang W, et al.11(B) Case series – prospective	2010	Source: Chinese J Pain Med	69 participants with uncomplicated HDL imaging by MRI or CT and that met the McCulloch criteria. Exclusion: stenosis of the mixed type canal, lumbar spondylolisthesis and sequestered hernia.	9 months	n/a	n/a	98.6% excellent and good	One case of infection in the disc space	
Cristante, et al.12(B) *RCT	2013	Pending	40 pts with MRI evidence of small herniated disc or protrusion on a single level were randomized for open lumbar microdiscectomy or percutaneous hydrodiscectomy.	12 months	There was a statistically significant improvement	No statistically significant improvement	n/a	One with PO infection. One death related to underlying disease (HIV)	20% of patients had subsequent intervention.
ClinicalTrials.gov Identifier: NCT00384007 **Study 1	Closed Last Updated June 4, 2009 ClinicalTrials.gov accessed on 18/11/2015	No estimated date for publication							
ClinicalTrials.gov Identifier: NCT02414698 ***Study 2	Recruiting patients. ClinicalTrials.gov accessed on 18/11/2015								

MI = lower member; PO = postoperative; LHD = lumbar herniated disc; LBP = lower back pain, n/a = not available; n/r none reported; HNP = herniated nucleus pulposus; MRI = magnetic resonance imaging; DDD = disc degenerative disease; McCulloch Criteria = no improvement in symptoms after ≥ 3 months of conservative treatment; RCT = randomized controlled trial. * Data recovered at http://www.washawaybackpain.com/uploads/studies/Clinical%20Evaluation.docx (complete text not available).

CLINICALTRIALS.GOV PROCESSED THIS RECORD ON NOVEMBER 18, 2015

****Study 1:**
Title: A Randomized Trial Comparing SpineJet® Hydrodiscectomy to Open Lumbar Microdiscectomy for Treatment of Lumbar Radiculopathy Due to Disc Herniation
Recruitment: Completed
Study First Received: October 2, 2006
Last Updated: June 4, 2009
Study Results: No Results Available
Conditions: Disc Herniation With Radiculopathy
Interventions: Procedure: Hydrodiscectomy with Spinejet
URL: https://ClinicalTrials.gov/show/NCT00384007

*****Study 2:**
Title: Percutaneous HydroDiscectomy Compared to TESI for Radiculopathy
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Lumbar Herniated Disc
Interventions: Procedure: Percutaneous Hydrodiscectomy|Drug: TESI
URL: https://ClinicalTrials.gov/show/NCT02414

DISCUSSION

Three characteristics are essential for a good systematic review of the literature: to gather all available evidence until the most recent moment; assess the quality of the studies individually and finally, summarize the results of the studies found. In this review on the use of percutaneous hydrodiscectomy in the treatment of lumbar herniated disc, we did not find any study in the scientific information databases consulted (Medline via PubMed, Central and Lilacs via BVS, Embase and Cinahl via Ebsco). With handsearching accessing the grey literature, of the eight included studies, only three case series present full text, impairing the assessment of studies quality. Therefore, caution is advised in interpreting the results, as they may present distortions of reality. In a search in the Clinical Trials database (https://clinicaltrials.gov/ - accessed on 11/18/2015), which registers protocols of studies to be conducted, we found a randomized controlled trial completed (NCT00384007 - "Last Update June 4, 2009 "- no results available) and one in progress (NCT02414698).

RECOMMENDATION:

The available evidence related to percutaneous hydrodiscectomy in the treatment of lumbar herniated disc is very weak, and its clinical use, generalized and systemic, is not recommended at this time. Its use should be restricted to the clinical research environment, so that data on efficacy and safety are produced consistently and strongly.

(Oxford 2009[13] - Level of evidence 4 and Degree of Recommendation C; Grade[14] 1D)

RESUMO

Hérnias discais lombares são manifestações comuns das doenças degenerativas da coluna, sendo a principal causa de dor lombar irradiada. Esta diretriz seguiu padrão de uma revisão sistemática com recuperação de evidências com base no movimento da Medicina Baseada em Evidências. Utilizamos a forma estruturada de formular a pergunta sintetizada pelo acrônimo P.I.C.O., em que o P corresponde à Hérnia de disco lombar, I à intervenção Tratamento com hidrodiscectomia percutânea, C comparando com Outras modalidades de tratamento, O de desfecho de Evolução clínica e complicações. A partir da pergunta estruturada, identificamos os descritores que constituíram a base da busca da evidência nas bases de dados Medline-PubMed (636 trabalhos) e, assim, após os critérios de elegibilidade (inclusão e exclusão), oito trabalhos foram selecionados para responder à dúvida clínica. Os detalhes da metodologia e dos resultados desta diretriz estão expostos no Anexo I.

ANNEX I

Structured question

The clinical question is structured through the components of P.I.C.O.

TABLE 1 – PICO COMPONENTS

P	Lumbar herniated disc in one or more levels
I	Treatment with percutaneous hydrodiscectomy
C	Other treatment modalities
O	Clinical evolution and complications

(P (Patient); I (Intervention); C (Comparison); O (Outcome).

Evidence search strategy

The bases of scientific information consulted were Medline via PubMed, Central and Lilacs via BVS, Cochrane Library and Embase. Handsearch from references of selected papers was also performed.

PubMed-Medline

TABLE 2 – SEARCH STRATEGY USED IN THE SCIENTIFIC INFORMATION DATABASES

Without methodological filter
Search 1: (lumbar herniated nucleus pulposus OR disc herniation OR disc hernia OR intervertebral disk displacement) AND (percutaneous lumbar discectomy OR percutaneous mechanical disc decompression OR percutaneous discectomy OR diskectomy percutaneous OR hydro discectomy OR hydro surgical decompression OR spinejet OR percutaneous microdiscectomy) – 624 studies RECOVERED.
Search 2: (percutaneous hydrodiscectomy OR hydrodiscectomy OR spinejet) – One study RECOVERED.

Initially selected by the title, sequentially by the abstract, and finally by its full text, the latter being subjected to critical evaluation and extraction of the results related to the outcomes.

TABLE 3 – NUMBER OF PAPERS RECOVERED WITH THE SEARCH STRATEGY USED FOR THE SCIENTIFIC INFORMATION DATABASES

Information base	Number of papers	Number of selected papers
Primary	624	0
Grey literature	12	8

PAPERS RECOVERED (until 11/29/2015)

Inclusion criteria for the papers recovered

The selection of the studies, review of the titles and abstracts obtained with the search strategy in the consulted information bases was conducted by two researchers with skills in the preparing systematized reviews, independently and blindly, strictly following the inclusion and exclusion criteria established, thus selecting the papers with potential relevance.

According to the study designs

Narrative reviews, case reports, case series, papers presenting preliminary results were, at first, excluded from selection. Systematic reviews and meta-analyses were used with the principle of retrieving references that might have been lost at first in the initial search strategy. We included systematic reviews (SRs) of randomized controlled trials (RCTs) and randomized controlled trials not included in the SRs. The controlled clinical trials were evaluated according to the Jadad score[13] and the Grade score[14].

Papers recovery

The papers recovered were evaluated by title, abstract and full text (when available), allowing the initial selection of studies to be critically evaluated. After the critical evaluation, we obtained the final selection of the studies (8), with or without full text, that provided the data for the overall synthesis. The main reasons for exclusion were: did not respond to PICO, cadaver study and case report.

Language

Studies in Portuguese, English and Spanish languages were included.

According to the publication

Only papers for which the complete text was available were considered for critical evaluation.

Critical evaluation methods

When, after applying the inclusion and exclusion criteria, the selected evidence was defined as randomized a controlled trial (RCT), it was submitted to an appropriate critical evaluation checklist.

Results exposure

For results with available evidence, population, intervention, outcomes, presence or absence of benefit and/or damage and possible comments will be specifically defined, whenever possible.

Recommendations

The recommendations will be prepared by the authors of the review, with the initial characteristic of evidence synthesis, being submitted to validation by all the authors participating in the preparation of the guideline.

The degree of recommendation to be used comes directly from the available strength of the included studies[15] and the use of the Grade system[14].

Conflict of Interest

No conflict of interest was declares by the participants in the preparation of this guideline.

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CULPRIT-SHOCK study

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SUMMARY

The treatment of patients with ST-segment elevation myocardial infarction concomitant with the presence of multivessel disease has been studied in several recent studies with the purpose of defining the need, as well as the best moment to approach residual lesions. However, such studies included only stable patients. The best therapeutic approach to cardiogenic shock secondary to acute coronary syndrome, however, remains controversial, but there are recommendations from specialists for revascularization that include non-event related injuries. Recently published, the CULPRIT-SHOCK study showed benefit of the initial approach only of the injury blamed for the acute event, in view of the multivessel percutaneous intervention, in the context of cardiogenic shock. In this perspective, the authors discuss the work in question, regarding methodological questions, limitations and clinical applicability.

KEYWORDS: *Myocardial infarction. Cardiogenic shock. Percutaneous coronary intervention.*

In acute coronary syndromes with ST segment elevation (STEMI), primary angioplasty of the culprit artery is the therapy of choice, and should be performed as fast as possible in individuals who present themselves in a timely manner for this, according to national and international guidelines. Approximately 65% of the coronary angiography performed in this context, however, present multivessel disease, with significant lesions affecting territories not related to the acute event.[1] Until recently, the main international guidelines (American College of Cardiology Foundation/2013 American Heart Association and 2012 European Society of Cardiology)[2,3] recommended that residual lesions should not be treated concomitantly with the treatment of culprit lesions, based mainly on subgroup analyses and retrospective records.[4,5]

However, four randomized trials were designed to evaluate the possible benefit of early approach of non-infarction-related lesions, whether in the same procedure as primary angioplasty or at some point prior to hospital discharge.[6-9] Although there were methodological differences in the method for evaluation of angiographic severity (anatomical: PRAMI> 50% and CVLPRIT> 70%, or functional guided by FFR: DANAMI-3 PRIMULTI and COMPARE)

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and at the moment of approaching the residual lesions (intervention in the initial angiography: COMPARE-ACUTE and PRAMI; in a second procedure still during hospitalization: DANAMI-3 PRIMULTI; or at any time before discharge, either during the initial catheterization or after it: CVLPRIT), when evaluating data from all studies together, the option for early multivessel revascularization resulted in reduction of cardiovascular adverse events at the expense of lower incidences of additional revascularization and mortality of cardiac etiology.[10]

Thus, the latest guideline of the 2017 European Society of Cardiology recommends routine revascularization of non-culprit lesions in STEMI before hospital discharge (IIa recommendation class, level of evidence A).[11] However, in the mentioned studies, patients in cardiogenic shock were not included in the analyses, leaving a gap of evidence in this scenario.

Approximately 5%-10% of STEMI evolve with cardiogenic shock and, consequently, a high in-hospital mortality rate (around 50%)[12,13]. The majority of cases involve multivessel disease in association with the coronary lesion responsible for the acute event.[14] However, there is still doubt about the best form of therapeutic approach in this scenario.

Published in 1999, in a sample with 302 patients, the SHOCK trial evaluated the best therapeutic approach in cardiogenic shock secondary to STEMI: early revascularization (surgical or percutaneous) or initial drug therapy. Although there was no difference between groups in the primary outcome of mortality at 30 days, there was superiority of early interventionist behaviour, with a reduction in mortality at six months. In clinical practice, before a patient with cardiogenic shock, considering this study, we should prioritize myocardial revascularization.[15]

Being well-defined the option for the intervention strategy in patients who developed with cardiogenic shock in the acute context, we lacked good evidence in the comparison of the different approaches of multivessel disease in the context of cardiogenic shock: revascularization only of the culprit artery or complete multivessel revascularization.

The CULPRIT-SHOCK study was then designed to test the hypothesis that angioplasty only of the culprit lesion, with the option of staged revascularization of the residual lesions at a second moment (considering functional evaluation for FFR, symptoms and neurological status), would have better outcomes than the immediate treatment of all major stenosis (over 70% by anatomical evaluation, including chronic occlusions), in the acute phase of cardiogenic SHOCK associated with multivessel coronary disease.[16]

In a sample with 706 subjects, a primary outcome comprised of all-cause death or renal insufficiency requiring 30-day renal replacement therapy was considered. Populations of the two groups were similar, and mostly composed of tri-arterial patients (63%), with involvement of the anterior descending artery (around 40%) and presenting ST elevation on admission (about 62%). Approximately 22% of patients had at least one chronic coronary occlusion in both arms.

About 80% of the individuals in the multivessel revascularization group underwent complete immediate revascularization, while in the intervention group only in the culprit lesion, only 7.6%. In the latter group, 17.7% of the patients were submitted to angioplasty staged from non-infarct-related lesions.

Regarding the primary outcome, the group approaching only the culprit lesion presented a lower incidence of events in 30 days [45.9% x 55.4%; relative risk (RR), 0.83; 95% CI, 0.71-0.96; p = 0.01], at the cost of lower mortality (43.3% x 51.6%, RR 0.84, 95% CI, 0.72-0.98, p = 0.03). In addition, the amount of contrast used and the fluoroscopy time were also significantly lower in this group. Considering the rates of renal replacement therapy, there was no significant difference between the groups, as well as in the analysis of the secondary outcomes.

The physiopathological explanations of the results of this study, as the editorial itself warns, are still speculative.[17] It is difficult to expect an increase in mortality in a therapeutic group with higher rates of complete revascularization. The question, however, focuses on the timing of this more complete approach. The recommendation of a multivessel approach in the period of hemodynamic instability may have contributed to the increase in procedure time, greater contrast volume used and potential complications related to angioplasty, which may lead to volume overload and increased inflammatory activity, with negative repercussions myocardial recovery. The approach guided only by visual estimation of residual lesions (without documentation of FFR ischemia) and the approach of chronic occlusions may also have contributed to this outcome.

In addition, the increase in platelet reactivity associated with a prothrombotic effect due to the

cardiogenic shock state may increase the risk of ischemia and infarction during intervention in the residual arteries and, consequently, deteriorate left ventricular function.

It is worth noting that this study is not free of limitations. The management of cardiogenic shock is complex and multifactorial, allowing the appearance of biases and occasional findings in the analyses. In spite of the difference in mortality observed between the strategies, the high mortality rates similar to those observed in the Shock study 18 years ago (46.7% versus 56% for the conservative treatment and intervention groups, respectively) were observed. There was also a considerable crossover in both strategies, with 12.5% in the group only culprit injury, and 9.4% in the multivessel group. It is also observed the absence of the option of surgical revascularization, a modality indicated in 36% of the patients in the Shock study.

Although with limitations and criticism, the CULPRIT-SHOCK study is the best evidence available in the therapeutic context of cardiogenic shock. The fact is that its results should have repercussions on the recommendations of the guidelines, indicating a strategy not to be used: complete percutaneous revascularization by visual estimation of the residual lesions in the index procedure. The authors had merit in allowing the indication of staged angioplasty guided by symptoms or presence of ischemia, without considering this procedure as a cardiovascular outcome in the statistical analysis, approach that approaches the real world and the current state-of-the-art in the treatment of coronary artery disease (ischemia driven revascularization).

We can thus conclude that in the case of a patient with cardiogenic shock secondary to acute coronary syndrome, in the presence or not of ST segment elevation, the best initial therapeutic option is to approach only the artery with culprit lesion. If improvement of hemodynamic instability (excluding other shock-perpetuating factors and aetiologies, evaluating symptoms and FFR/iFR ischemia, and pondering the patient's neurological status) is not observed during the evolution, percutaneous intervention of residual lesions should be performed as soon as possible. In patients who evolve with resolution of cardiogenic shock, FFR functional evaluation of the remaining lesions is recommended after clinical stability. In the presence of functionally significant lesions or symptoms, percutaneous treatment should be considered before hospital discharge (Figure 1).

Finally, this study allows us to reflect on some pertinent questions: 1) the high mortality related to ACS complicated with shock, in spite of the evolution of the therapy in the last 20 years; 2) the need for prospective randomized studies that direct us on issues that still rest on evidence of poor quality or expert opinion.

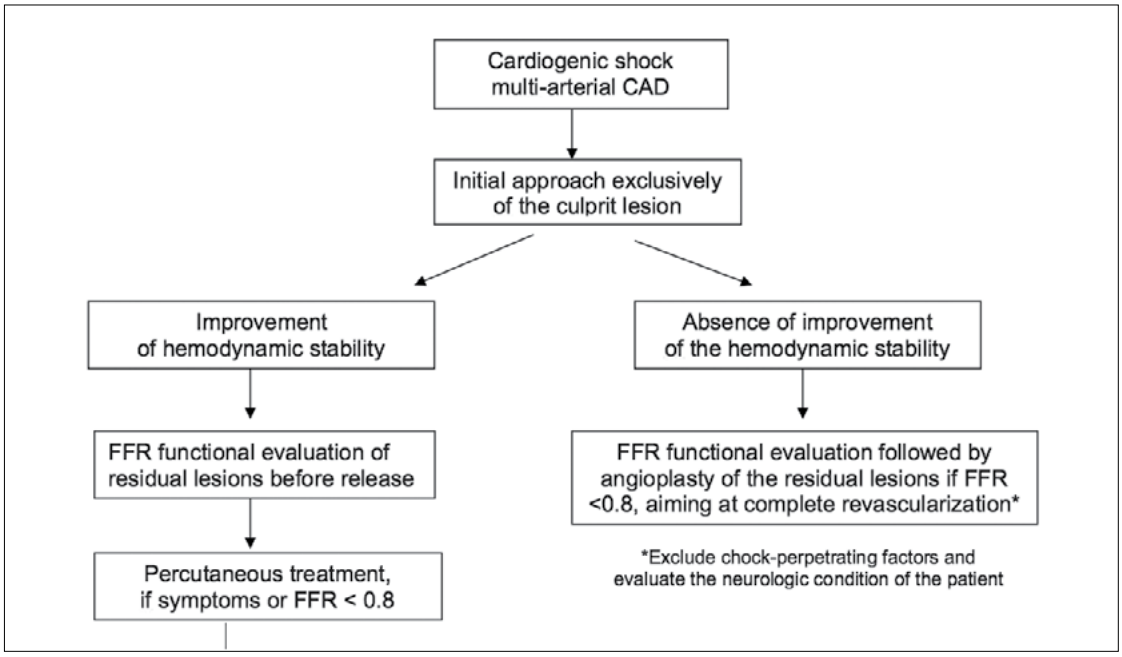

FIGURE 1: Therapeutic approach to cardiogenic shock secondary to acute coronary syndrome in a patient with multivessel coronary artery disease (CAD).

RESUMO

O tratamento de pacientes com infarto do miocárdio com elevação do segmento ST concomitante à presença de doença multiarterial tem sido estudado em vários estudos recentes com o objetivo de definir a necessidade, bem como o melhor momento, de abordagem das lesões residuais. No entanto, tais estudos incluíam apenas pacientes estáveis. A melhor abordagem terapêutica do choque cardiogênico secundário à síndrome coronariana aguda, no entanto, ainda permanece controversa, havendo porém recomendação de especialistas para uma revascularização que inclua as lesões não relacionadas ao evento. Publicado recentemente, o estudo CULPRIT-SHOCK mostrou benefício da abordagem inicial apenas da lesão culpada pelo evento agudo, perante a intervenção percutânea multiarterial, no contexto do choque cardiogênico. No presente ponto de vista, os autores discutem o trabalho em questão, no que concerne a questões metodológicas, limitações e aplicabilidade clínica.

PALAVRAS-CHAVE: *Infarto do miocárdio. Choque cardiogênico. Intervenção coronária percutânea.*

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Light chain cardiac amyloidosis - a rare cause of heart failure in a young adult

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SUMMARY

Cardiac amyloidosis is an infiltrative cardiomyopathy, resulting from amyloid deposition within the myocardium. In primary systemic (AL-type) amyloidosis, the amyloid protein is composed of light chains resulting from plasma-cell dyscrasia, and cardiac involvement occurs in up to 50% of the patients

We present a case of a 43-year-old man, with complaints of periodical swollen tongue and xerostomia, bleeding gums and haematuria for two months. His blood results showed normocytic anaemia, thrombocytopenia and a high spontaneous INR, therefore he was referred to the Internal Medicine clinic. In the first visit, he showed signs and symptoms of overt congestive heart failure and was referred to the emergency department. The electrocardiogram showed sinus tachycardia and low voltage criteria. Echocardiography showed biventricular hypertrophy with preserved ejection fraction, restrictive physiology with elevated filling pressures, thickened interatrial septum and atrioventricular valves, small pericardial effusion and relative "apical sparing" on 2D longitudinal strain. Cardiac MRI showed diffuse subendocardial late enhancement. Serum protein electrophoresis was inconclusive, however urine analysis revealed nephrotic range proteinuria, positive Bence Jones protein and an immunofixation test with a monoclonal lambda protein band. Abdominal fat biopsy was negative for Congo red stain, nevertheless a bone marrow biopsy was performed, revealing lambda protein monoclonal plasmocytosis, confirming the diagnosis of primary systemic amyloidosis.

This case represents a rare cause of heart failure in a young adult. Low-voltage QRS complexes and typical echocardiography features should raise the suspicion for cardiac amyloidosis. Prognosis is dictated by the level of cardiac involvement; therefore, early diagnosis and treatment are crucial.

INTRODUCTION

Restrictive cardiomyopathies are a heterogeneous group of myocardial diseases, whose hallmark echocardiographic finding is severe diastolic dysfunction. They are not common in daily practice, and their initial presentation is diverse. Several clinical, electrocardiographic and echocardiographic features may help in the diagnosis.

CASE

We present a case of a 43-year-old man, with history of schizophrenia, previously evaluated by different physicians because of swollen tongue and xerostomia, with an inconclusive work-up. He presented to his general practitioner with fatigue, bleeding gums and haematuria in the past two months. His blood test results showed normocytic anaemia,

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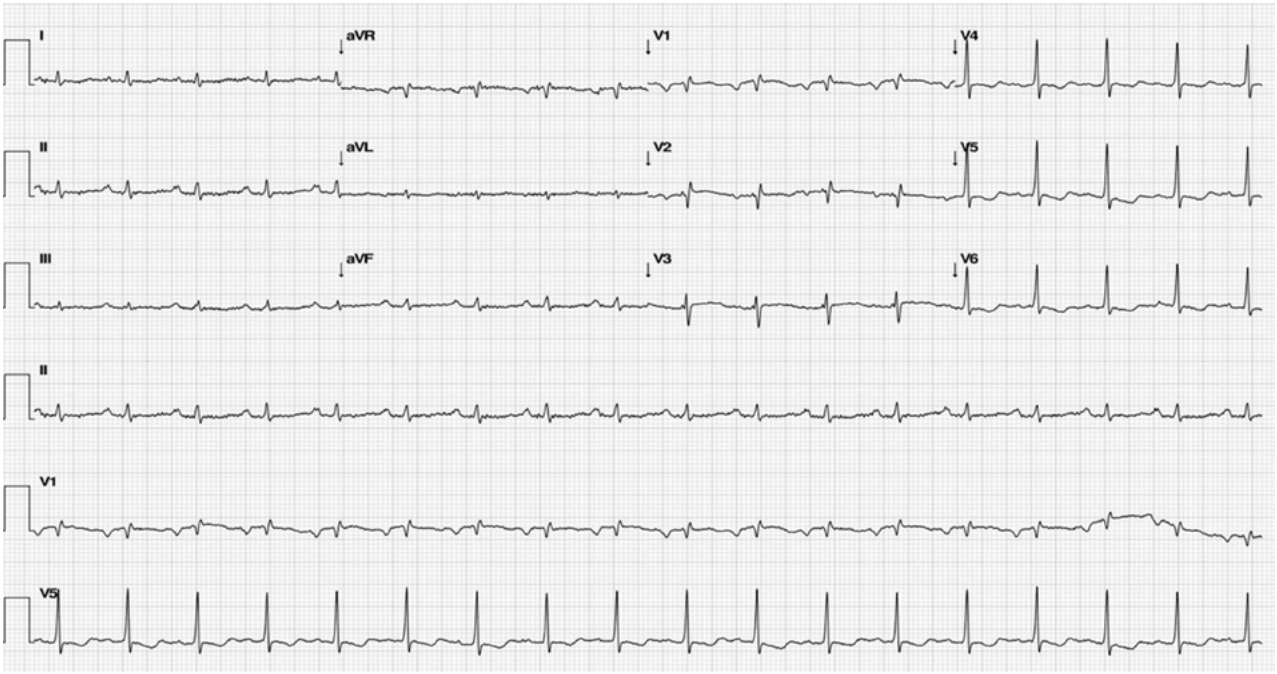

FIGURE 1 - Electrocardiogram: sinus tachycardia, low voltage criteria in the limb leads and diffuse nonspecific repolarization abnormalities.

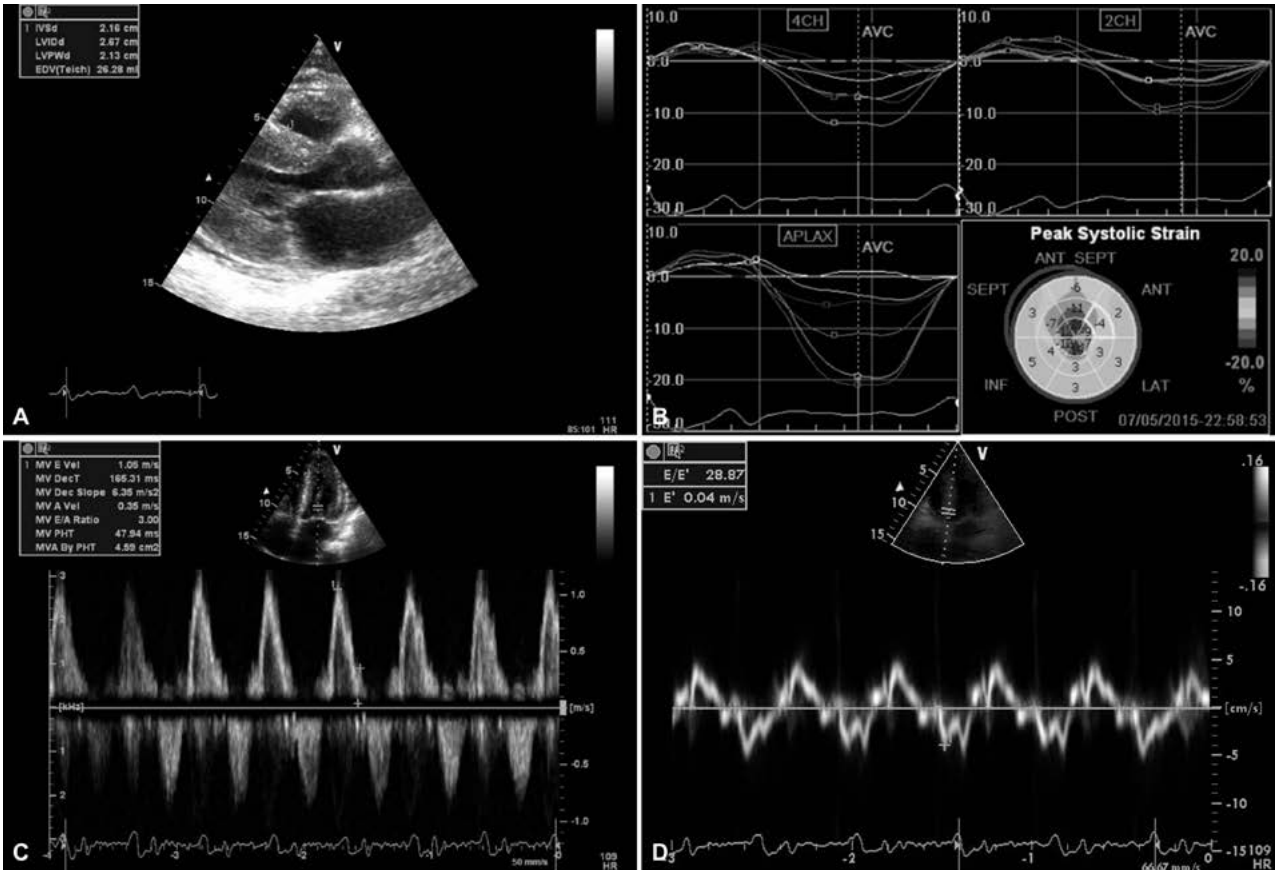

FIGURE 2 - Echocardiogram: A – Parasternal long axis view (still image): thickened left ventricular walls, dilated left atrium and small pericardial effusion. B – Speckle tracking longitudinal strain traces and bull's eye, with typical "apical sparing" pattern. C - Transmitral flow pulsed wave Doppler showing a restrictive pattern. D - Tissue Doppler with low e' and high E/e' ratio, suggestive of high left atrial pressures.

VIDEO KEY: Echocardiogram with parasternal long and short axis and apical four chamber views and 2D speckle tracking longitudinal strain bull's eye. Typical cardiac amyloidosis features are present: left ventricular hypertrophy with granular appearance, dilated atria, thickened atrioventricular valves and interatrial septum, small pericardial effusion and "apical sparing" pattern.

thrombocytopenia and a high spontaneous INR, therefore he was referred to the Internal Medicine clinic. In the first visit, he showed signs and symptoms of overt congestive heart failure and was referred to the emergency department. Chest radiography revealed interstitial oedema and bilateral pleural effusion and the electrocardiogram (ECG) showed sinus tachycardia and low voltage criteria (Figure 1). His hemogram and INR were similar to the previous, and had elevated alkaline phosphatase and gamma glutamyl transferase, high BNP and slight elevation of troponin and creatinine. Echocardiography showed biventricular hypertrophy with preserved ejection fraction, restrictive physiology with elevated filling pressures and relative "apical sparing" on 2D longitudinal strain. He also had thickened interatrial septum and atrioventricular valves and a small pericardial effusion (Figure 2; Video). He was admitted to the Cardiology Department for medical treatment, with progressive clinical improvement. Diagnostic work-up showed hypoalbuminemia, low levels of factors V and X, antithrombin III and protein C, elevated b2-microglobulin, ferritin and erythrocyte sedimentation rate, while the serum protein electrophoresis was inconclusive. Alpha-galactosidase levels were borderline low. Abdominal echography was not suggestive of chronic liver disease. Cardiac MRI showed diffuse subendocardial late enhancement. A 24-hour urine collection revealed nephrotic range proteinuria, positive Bence Jones protein and an immunofixation test with a monoclonal lambda protein band. Abdominal fat biopsy was negative for Congo red stain and the genetic study was also negative for mutations in the TTR and GLA genes. Nonetheless, a bone marrow biopsy was performed and it was notable for lambda protein monoclonal plasmocytosis, accounting for 80% of the total cellularity, confirming the diagnosis of primary systemic (AL-type) amyloidosis. He was considered a poor candidate to autologous stem-cell transplantation, due to advanced cardiac involvement, and was started on chemotherapy (CyBORD protocol). Seven cycles were administered, with excellent tolerability and response. The patient is currently on NYHA class II, two years after the initial admission, under regular haematology and cardiology follow-up.

DISCUSSION

This case represents a rare cause of heart failure in a young adult. Cardiac amyloidosis is an infiltrative cardiomyopathy, resulting from amyloid deposition within the myocardium [1,2]. In primary systemic (AL-type) amyloidosis, the amyloid protein is composed of light chains resulting from plasma-cell dyscrasia [2], and cardiac involvement occurs in up to 50% of the patients [3]. Macroglossia, nephrotic syndrome, bleeding and hepatomegaly are common clues to diagnosis[4]. Low-voltage QRS complexes and typical echocardiography features should in turn raise the suspicion for cardiac amyloidosis ([2]). The abdominal fat biopsy has a sensitivity of around 80% [2,4,5], therefore other histologic studies should be performed if the result is negative [2]. Prognosis is dictated by the level of cardiac involvement (<6 months after the onset of heart failure, without treatment), therefore early diagnosis and treatment are crucial [1,2,4].

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RESUMO

A amiloidose cardíaca corresponde a uma miocardiopatia infiltrativa, resultante do depósito da proteína amiloide no miocárdio. Na amiloidose sistêmica primária (tipo AL), a proteína amiloide é composta por cadeias leves que resultam de discrasia dos plasmócitos, havendo envolvimento cardíaco em até 50% dos doentes.

Apresentamos o caso de um homem de 43 anos, com queixas de edema periódico da língua e xerostomia, hemorragia gengival e hematúria há dois meses. Analiticamente havia a destacar anemia normocítica, trombocitopenia e um INR alto espontâneo, pelo que foi referenciado à consulta de Medicina Interna. Na primeira consulta, apresentou-se com sinais de insuficiência cardíaca congestiva franca, pelo que foi referenciado ao Serviço de Urgência. O eletrocardiograma demonstrou taquicardia sinusal e critérios de baixa voltagem. O ecocardiograma revelou hipertrofia biventricular com fração de ejeção preservada, fisiologia restritiva com elevação das pressões de enchimento, espessamento do septo interauricular e das válvulas auriculoventriculares, derrame pericárdico ligeiro e padrão de apical sparing *no* strain *longitudinal 2D. Realizou ainda ressonância magnética cardíaca, que mostrou realce tardio subendocárdico difuso. A eletroforese das proteínas foi inconclusiva, contudo a análise da urina revelou proteinúria no espectro nefrótico, presença de proteína de Bence Jones e um teste de imunofixação com uma banda monoclonal de cadeias lambda. A biópsia da gordura abdominal foi negativa. Não obstante, foi realizada uma biópsia da medula óssea, verificando-se plasmocitose monoclonal lambda, o que confirmou o diagnóstico de amiloidose primária sistêmica.*

Este caso representa uma causa rara de insuficiência cardíaca no jovem adulto. A baixa voltagem no eletrocardiograma e os achados ecocardiográficos típicos devem fazer suspeitar de amiloidose cardíaca. O prognóstico é ditado pelo nível de envolvimento cardíaco, motivo pelo qual o diagnóstico e o tratamento precoces são essenciais.

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ORIGINAL ARTICLE

Multiple factors affect the regeneration of liver

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SUMMARY

OBJECTIVE: *To study factors affecting the liver regeneration after hepatectomy*

METHODS: *With 3D reconstitution technology, liver regeneration ability of 117 patients was analysed, and relative factors were studied.*

RESULTS: *There was no statistically difference between the volume of simulated liver resection and the actual liver resection. All livers had different degrees of regeneration after surgery. Age, gender and blood indicators had no impact on liver regeneration, while surgery time, intraoperative blood loss, blood flow blocking time and different ways of liver resection had a significant impact on liver regeneration; In addition, the patients' own pathological status, including, hepatitis and liver fibrosis all had a significant impact on liver regeneration.*

CONCLUSION: *3D reconstitution model is a good model to calculate liver volume. Age, gender, blood indicators and biochemistry indicators have no impact on liver regeneration, but surgery indicators and patients' own pathological status have influence on liver regeneration.*

KEYWORDS: *Liver neoplasms. Carcinoma, hepatocellular. Hepatectomy. Liver regeneration. Imaging, three-dimensional.*

1. INTRODUCTION

As the third major pathogenic cause of cancer-related death globally[1], hepatocellular carcinoma (HCC) ranks fifth among the malignant tumour morbidity. Multiple methods have been used for HCC treatments, including surgical resection, radiotherapy and chemotherapy, biological therapy, immunotherapy, etc. Among these different types of treatments, surgical resection functions as the most mainstream method[2]. However, surgical resection would cause impaired or total loss of liver functions, therefore resulting in death of patients postoperatively [3]. HCC patients are reported to show different degrees of hepatitis and fibrosis, which significantly reduced liver functions. Given that liver regeneration

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was relatively low post-surgery, the remained liver volume cannot support the demands of metabolism and maintain homeostasis, therefore leading to impaired liver function, liver failure and the eventually death[4].

Nowadays, with development of technology, imaging technology matures and computerized simulation surgery come into play. The combination of computer-based automation image software and high-resolution imaging technology has become a new trend to conduct accurate hepatectomy for HCC patients[5,6]. Furthermore, using three-dimensional (3D) surgical simulation system, clinicians could evaluate the function of liver and simulate operations before surgery, which significantly reduced the possibility of postoperative liver failure and the potential death of patients. However, impaired liver functions would still occur post-surgery, which might result from the dis-match of the regeneration liver and the body need. Interestingly, little research has been carried out to investigate liver regeneration ability, especially regarding post-surgical liver regeneration[7]. In this study, we hypothesized that factors including age, gender, blood biomarkers, surgical methods, resected liver volume, residual liver volume, surgical margin, hepatitis, liver fibrosis etc., would affect the regeneration rate of liver. Therefore, we analysed liver regeneration rates under different experimental conditions as described below, with the aim to discover better ways to conduct liver surgery.

2. MATERIAL AND METHODS

2.1 Patients

117 HCC patients received liver resection surgery were selected (Oct 2012-Oct 2016). Standard experimental procedure was presented in Figure 1A. All patients in this study were in single lesion BCLC-A stage, confirmed of HCC by pathological analysis postoperatively; underwent liver CT scan and enhanced scan (1 week before and 1 week after the surgery); In this study, patients received regular liver resections, at right hemi-hepatic, left hemi-hepatic, left hepatic lobe or right hepatic lobe area respectively. Patients with any of the following situations were excluded: 1) had cholangiocellular carcinoma or metastatic cancer 2) received previous intervention and chemotherapy pre-surgery; 3) had previous liver resection surgery; 4) had diabetes, HIV or other malignant illnesses.

This study was carried out in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the Hospital Ethics Committee of Affiliated Cancer Hospital of Guangxi Medical University. Informed consent was obtained from every patient.

2.2 Preoperative and postoperative examination

Patients were examined using 128-slice spiral CT (GE, USA) 1 week before and 1 week after liver resection surgeries. Regular liver and kidney function examination (TBil, ALB, ferritin, ALT, AST, CRE, etc.), coagulation function examination (PT), whole-cell examination (leukocyte, erythrocyte, thrombocyte, etc.), hepatitis B screening (HBsAg, HBsAb; HBeAg, HBeAb; HBcAb), tumour markers detection (AFP) were performed as well.

2.3 3D simulated reconstruction of liver

The original thin-slice CT scan data was imported into the Myrian XP Liver 3D simulation operation system. The plain, arterial and venous images were selected respectively. Modules including liver, tumour, hepatic vein and portal vein were presented in different colour according to their range and contour (Figure 1B-C). The 3D reconstruction images were generated using the software mentioned above based on the range of the sketch. The simulated liver volume as well as the relative positions of liver, tumour and blood vessels were subsequently calculated and automatically presented.

2.4 Simulated hepatectomy

Simulated hepatectomy was performed using Myrian XP Liver software. In brief, the surgical surfaces were determined by the combination of 2D and 3D images. Simulated resection was strictly performed at surgical surface generated by 3D model in the venous regions, and adjustments were made accordingly using the 2D model. The resected liver volume and the residual liver volume were calculated automatically by Myrian XP Liver software.

2.5 Calculation of liver regeneration capacity

The surgery was carried out in accordance with the rules of preoperative liver resection, and the intraoperative and postoperative indicators were collected, including surgery time, intraoperative blood loss, intraoperative blood transfusion, intraoperative hepatic blood occlusion time, postoperative pathological liver inflammation grade and fibrosis stage. The

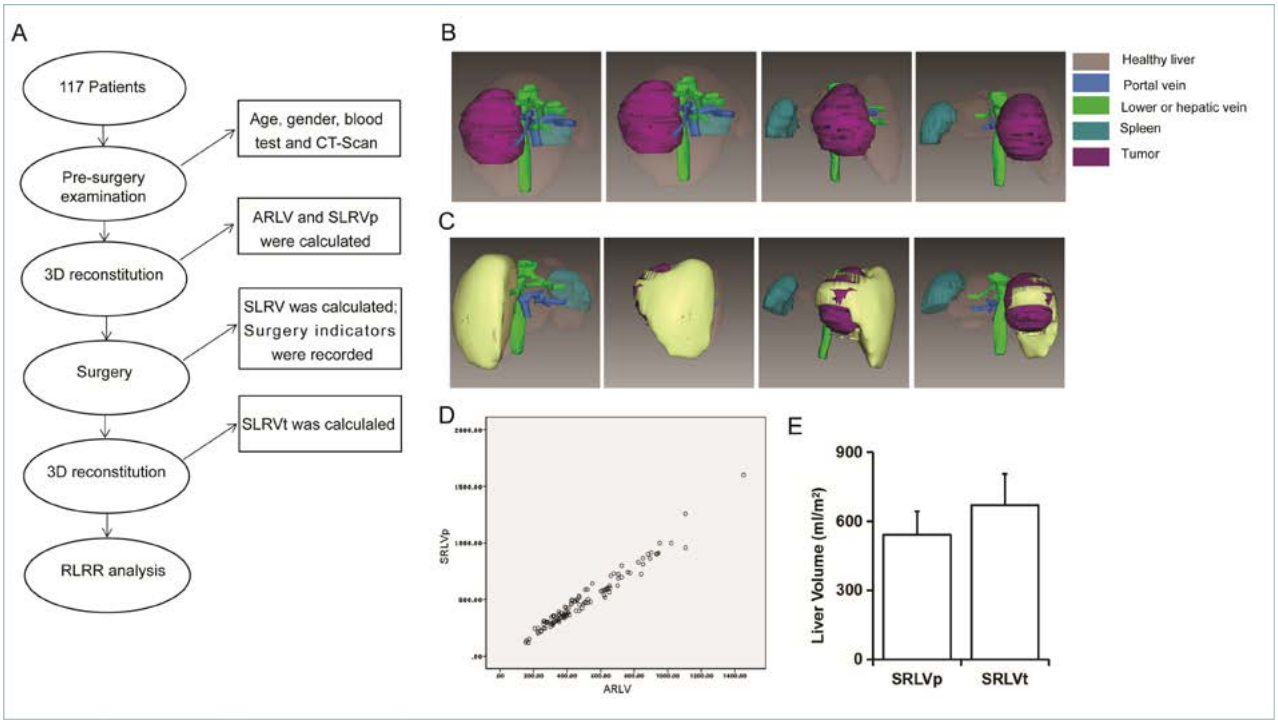

FIGURE 1. 3D reconstruction model is a good model to measure liver volume. (A) Work flow of experimental design and analysis. (B-C) 3D reconstitution of liver and simulated hepatectomy. (D) Correlation analysis of SRLVp and ARLV. (E) Comparison of SRLVp and SRLVt liver volume. Data are shown as means ± SD. and simulated hepatectomy.

volumes of specimens resected (including tumour tissue and part of normal liver tissue) were measured by drainage method (accurate to 1ml). In addition, the volumes of remnant liver before and after hepatectomy were measured using 3D simulation, actual removal liver volume (ARLV) was measured by drainage method. Body surface area (BSA), standard remnant liver volume (SRLV), preoperative expected standard remnant liver volume (SLRVp), postoperative standard remnant liver volume (SLRVt), remnant volume of liver regeneration (RVLR), and remnant liver regeneration rate (RLRR) were calculated as follows:

$$BSA(m^2) = 0.0061 \times height(cm) - 0.0128 \times weight(kg) - 0.1529$$

$$SRLV = RLV(ml) / BSA(m^2)$$

$$SLRVp = RLVp(ml) / BSA(m^2)$$

$$SLRVt = RLVt(ml) / BSA(m^2)$$

$$RVLR = SLRVt - SLRVp$$

$$RLRR = RVLR / SRLVp = (SLRVt - SLRVp) * 100\% / SLRVp$$

2.6 Statistical analysis

The statistical analysis was performed using SPSS 22.0 to calculate mean and standard error. Paired two sample t-test was used for resected liver volume, SRLVt and STLVp analysis, and unpaired two-sample t-test was used for RLRR analysis. One-way analysis of variance (ANOVA) and post-hoc analysis (LSD) were performed as indicated after confirming the homogeneity of variance. Correlation analysis between SRLVt and SRLVp was carried out using Pearson analysis. P value <0.05 was considered as statistically significant in this study (*p<0.05, **p<0.01, ***p<0.005).

3. RESULTS

3.1 Patients

Patients' information was presented in Table 1. There were 98 male patients (83.76%) and 19 female patients (16.24%) with mean age at ~50 years old (ranging from 24-83 years old). Among all the 117 patients, 96 showed HBsAg positive. According to preoperative analysis, there were 111 A-stage (94.87%) and 6 B-stage patients (5.13%). Average tumour size in this study was 5.35cm (ranging from 3.60cm-14.10cm).

19 patients received right hemi-hepatic resection (16.24%), 21 received left hemi-hepatic resection (17.95%), 21 received left hepatic lobe resection (17.95%) and 56 received right hepatic lobe resection (47.86%). Average time of surgery time was 190s (ranging from 90s-370s), average blood loss was 200ml (ranging from 50ml-2100ml), average blood

flow blockage time was 20mins (ranging from 0min-42mins).

Patients were rated into G0 (15 patients, 12.82%), G1 (34 patients, 29.06%), G2 (50 patients, 42.74%) and G3 (18 patients, 15.38%) in terms of hepatitis B stages. Based on the degree of liver fibrosis, patients were rated into S0 (14 patients, 11.97%), S1-2 (35 patients, 29.91%), S3 (42 patients, 35.90%) and S4 (26 patients, 22.22%) stages.

3.2 3D reconstruction model is a good model to measure liver volume

Measuring the volume of liver is a challenging area in liver research. Recently, people have developed 3D reconstitution method to measure liver volume; however, it is not always accurate. To measure the regeneration rate of liver, we used the Myrian XP Liver software combined with thin-slice CT scan, and 3D reconstitution was generated (Figures 1B and 1C). ASLV, SLRVp and SLRVt were measured (Figure 1A). Results showed that ASLV and SLRVp have a linear relationship (Figure 1D), and no difference was observed between ASLV and SLRVp, indicating that predicated removal liver volume is not different from the real volume of liver resection. Thus, 3D reconstitution is a good model to measure liver volume.

3.3 Comparison between preoperative and postoperative liver volumes

To investigate if residual liver regenerated after resection, we compared the liver volume preoperatively and postoperatively using experiments and 3D simulation.

SRLVt was 670.31ml/m^2, and SRLVp was 541.60ml/m^2. Statistical analysis confirmed there was significant difference between SRLVt and SRLVp (t=-26.17 – *p<0.05) (Figure 1E), suggesting that the liver regenerated significantly post-surgery. RVLR was 128.71ml/m^2, and the RLRR was 23.73% in this study.

3.4 Analysis of factors affecting liver regeneration

In this section, factors affecting liver regeneration were analysed respectively.

Our results showed that several factors exhibited none-significant impacts on liver regeneration, including age, gender, leukocyte number, erythrocyte number, ALB, ALT, TBil, AFT, PT, HBsAg, serum CRE and Child-Pugh class. These factors should not be taken into consideration for liver resection. In this section, we investigated the effects of blood loss amount, surgical methods, liver blood blocking time, surgery time, hepatitis and liver fibrosis on liver regeneration ability.

3.4.1 Effects of surgical conditions

3.4.1.1 Effects of blood loss on RLRR

To investigate if blood loss affected liver regeneration, we compared RLRR of patient group A (lost > 800ml during surgery) to that of patient group B (lost < 800ml) (Figure 2A). RLRR from patient group B (27.11%) was significantly higher than RLRR from group A (15.12%) (t = 8.459 – ***p < 0.001), suggesting blood loss inhibited postoperative live regeneration.

3.4.1.2 Effects of liver blood blocking time on RLRR

With the purpose of investigating if liver blood blocking time affected liver regeneration, we compared the RLRR of patient group C (total blocking time>30mins) to that of patient group D (total blocking time < 30mins) (Figure 2B). Statistical analysis demonstrated that RLRR from group C (17.48%) was significantly lower than that of group D (25.34%) (t = 4.191, ***p < 0.001), indicating that less liver blood blocking time would contribute to liver regeneration process.

3.4.1.3 Effects of surgery time on RLRR

To investigate if the surgery time affected liver regeneration, we compared the RLRR of patients group

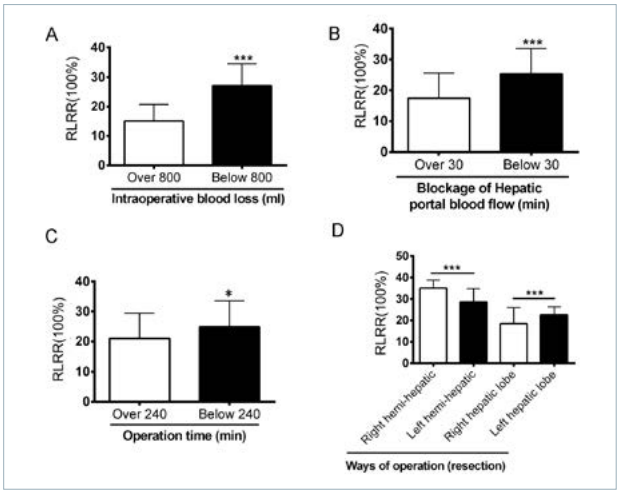

FIGURE 2. Effects of operation conditions on liver regeneration rate. Quantification of liver regeneration rate under the treatment with different blood loss amount (A), blockage time (B), operation time (C) and area of resections (D). Statistical analysis was performed as described in Material and Methods (student t-test, Error bar: ± SD; *p<0.05, ***p<0.005)

E (> 240mins) and that of patient group F (< 240mins) (Figure 2C). RLRR from group F (24.89%) was significantly higher than that of group E (21.02%) (t = 2.225, * p = 0.028), suggesting less surgery time showed a positive effect on liver regeneration.

3.4.2 Effects of surgical methods

Furthermore, we investigated the effects of resected regions on liver regeneration rate. As shown in Figure 2D, the RLRR of patients that received right hemi-hepatic resection was 35.07% (group G), that of patient who received left hemi-hepatic resection was 28.62% (group H), that of patients that received left hepatic lobe resection was 22.60% (group I), and that of patients that received right hepatic lobe resection was 18.47% (group J) respectively. One-way ANOVA and post-hoc analysis confirmed that there were significant difference between the RLRR of each group (F=38.92, ***p<0.001), indicating that patients who received right hemi-hepatic resection showed the highest liver regeneration rate.

3.4.3 Effects of hepatitis and liver fibrosis

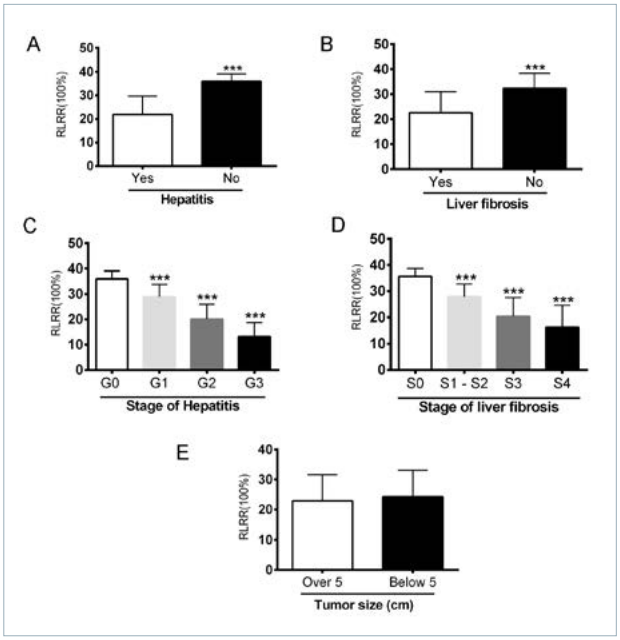

FIGURE 3. Effects of previous liver conditions on liver regeneration rate. Quantification of liver regeneration rate of patients with/without hepatitis (A) as well as that of patients with/without liver fibrosis (B). Patients at different hepatitis stages (C) or different fibrosis stages (D) were subsequently compared. Size of tumor was analyzed (E) as well. Statistical analysis was performed as stated in Material and Methods (student t-test). Multi-group comparisons of the means were carried out by one-way ANOVA with post-hoc contrasts by Levene. Statistical significance was set at p<0.05. (Error bar: ± SD; ***p<0.005).

In addition, pathology status of liver was reported to affect liver regeneration postoperatively. Here we analysed the influence of hepatitis and fibrosis on liver regeneration ability. We analysed the RLRR of patients with (group J) / without hepatitis (group K) as well as the RLRR of patients with (group L) / without liver fibrosis (group M). According to Figure 3A-B, statistical analysis showed that there were significant differences between group J (21.92%) and K (36.0%) (***p < 0.001) as well as between group L (22.56%) and M (32.37%) (***p < 0.001), suggesting that patients with previous liver pathogenetic conditions exhibited decreased liver regeneration ability.

Moreover, patients with hepatitis or liver fibrosis were further analysed according to the classification stages respectively. RLRR of patients in G0, G1, G2 and G3 stage were shown in Figure 3C. One-way ANOVA and post-hoc LSD analysis confirmed there were significant differences between each group (F = 71.39, ***p < 0.001). Similarly, RLRR of patients in S0, S1-2, S3 and S4 stage (Figure 3D) showed significant difference between each group (F=26.11, ***p<0.001), suggesting that decreased liver regeneration rate of patients with hepatitis or liver fibrosis were associated with the disease development stages.

4. DISCUSSION

With the fast development of imaging technology, multi-slice spiral CT and 3D reconstruction technology have been increasingly used in clinical practice[8]. Due to cross and integration of clinical medicine, imaging, pathophysiology and computer science, virtual liver visualization and preoperative simulated hepatectomy have become available[9].

In hepatectomy, the resection scope varied depending on the location of tumour and the severity of complicated liver cirrhosis, resulting in inconsistences between the theoretical resection line and the actual resection line. In addition, surgical margins varied due to different surgical areas. Therefore, to reduce interference by human factors, it is important to make the simulated surgical resection close to actual liver resection as possible.

In this study, we selected patients with regular liver resection for the following reasons: 1) range of regular liver resection was fixed, 2) preoperative simulation could be easily measured, intraoperative surgery could be performed according to the typical pipelines, 3) preoperative simulated resection is co-

incident with the actual resected liver volume. All of these can reflect the postoperative residual liver regeneration capacity objectively and accurately. Myrian XP Liver software was applied to perform preoperative simulated hepatectomy. There was no significant difference between ARLV-calculated and SRLVp-simulated liver volume (p=0.15), further analysis showed that there was positive correlation between ARLV simulation and SRLVp calculation (***p < 0.001) indicating that the results of the computerized simulation could be used as a relatively accurate reference for liver volume measurement in clinical applications [10, 11].

Hepatectomy has been reported as the most effective way of liver cancer treatment. To meet the requirement of metabolism, postoperative residual liver showed different degrees of proliferation under various conditions. We reported that postoperative residual livers regenerated to various degrees in this study, which is consistent with previous research[12].

Further analysis regarding liver regeneration showed that surgery time, intraoperative blood loss and hepatic blood flow blockage time were significantly correlated with residual liver regeneration (***p < 0.001). Long surgery time, severe blood loss and long blockage time would increase the difficulty of the surgery. Affecting factors including deep tumour location, heavy adhesion with surrounding tissues, and the broken blood vessels caused by the surgery, resulted in extensive intraoperative bleeding, intraoperative ischemia-reperfusion injury, thus leading to decreased production of liver regeneration factors[13], which decelerated the rate of proliferation of postoperative residual livers[14], and ultimately reduced hepatocyte regeneration. Interestingly, data obtained in this study suggested that ages and HBsAg did not affect liver regeneration significantly. Theoretically, younger patients should have the highest regeneration rate. HBsAg-positive patients should have relatively high regeneration rate due to compensatory effect. However, in this study, there were no significant differences between older patients (> 60 years old) and younger patients (≤ 60 years old), as well as between HBsAg positive and HBsAg negative patients. We speculated that the reason for this might be the limited observation time, which is not long enough to detect the effects of age and HBsAg infection on liver regeneration rate, which should be further investigated in the future.

In this study, the right hemi-hepatic resection resulted in the highest liver regeneration rate, which might be due to the highest liver volume that was removed. We observed that in patients who received right hemi-hepatic resection, there were insufficient amount of functional liver cells to maintain homeostasis, therefore the liver function did not meet requirements of normal metabolism, which urgently stimulated the fast regeneration of the liver. In addition, high amount of resection volume gave space for liver regeneration, which could also stimulate the rapid growth of liver[15]. Compared to patients discussed above, patients who received left hemi-hepatic, left hepatic lobe or right hepatic lobe resection remained with a relatively functional liver that could meet the demand of liver homeostasis, which gave rise to low rate of postoperative regeneration. Data collected in this section suggested ability of residual liver to maintain metabolic homeostasis determined liver regeneration rates.

In addition, we found that stages of liver fibrosis and liver regeneration rate were negatively correlated. We speculated that liver fibrosis might induce liver cells undergo necrosis, and this resulting in decreased regeneration rate. Furthermore, we found that compared to patients did not have hepatitis and fibrosis, patients with hepatitis and liver fibrosis exhibited decreased liver regeneration rate, which is opposite to previous reports[16, 17]. The possible reason for this was that self-repair ability of liver or that the short observation time after hepatectomy was not enough to detect significant difference, which should also be investigated in the future study.

Collectively, the liver regenerated to varying degrees post-hepatectomy. We found that rates of liver regeneration were affected by several factors, including surgery time, amount of intraoperative blood loss, blockage time of intraoperative liver blood, surgical methods, inflammation and liver fibrosis stages. In this study, patients with highest liver regeneration rate after hepatectomy showed preoperative low degrees of liver inflammation and fibrosis, they received right hemi-hepatic resection, and were treated with shorter surgery time, less intraoperative blood loss, shorter liver blood flow blocking time.

As a hot topic in research and clinical application, ALPPS surgery is known as stage II hepatectomy: Stage I is to perform transection of the liver along the falciform ligament, right portal vein

ligation and resection of gallbladder. Stage II is to perform extended right hepatectomy when residual liver volume was enough [18-20]. One week after surgery, the rate of residual liver regeneration was 74%~87%, which was much higher than that of this study. The livers of patients who received ALPPS were obviously regenerated in a shorter term. This high regeneration rate is speculated to be caused by the remaining arterial blood supply at the cancerous area, therefore supporting the metabolism as the temporary liver. Meanwhile large amount of portal vein blood flowed into the remaining liver, which promoted the rapid proliferation of the liver. But stage II hepatectomy should be carried out on the basis of the recovery of stage I hepatectomy [20], and the regeneration rate in our stage I hepatectomy was not high enough to perform stage II hepatectomy. In this study, patients showed local inflammatory response postoperatively. Under the condition of extensive resected area, liver regeneration rate of the patients who received liver resection was significantly less than that of patients that received ALPPS. Therefore, we believed the un-removed tumour tissue promoted liver regeneration, which might be due to the growth factors secreted by tumour tissue, but this hypothesis needs to be further investigated.

5. CONCLUSION

This study investigated the liver regeneration ability and the relevant affecting factors, providing scientific support and guidance for preoperative plan, intraoperative operation and postoperative prediction, therefore shedding lights on new clues aiming to improve liver regeneration ability as well as postoperative recovery rate for future clinical practice.

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Conflicts of interest

The authors declare no conflicts of interest.

RESUMO

OBJETIVO: *Estudar os fatores que afetam a regeneração hepática após hepatectomia.*

MÉTODOS: *A capacidade de regeneração hepática de 117 pacientes foi analisada com a tecnologia de reconstituição 3D e foram estudados os fatores relacionados.*

RESULTADOS: *Não houve diferença estatística significante entre o volume de ressecção hepática simulada e a ressecção atual. Todos os fígados apresentaram diferentes graus de regeneração após cirurgia. Idade, gênero e indicadores sanguíneos não tiveram impacto na regeneração hepática, enquanto que tempo de cirurgia, perda sanguínea intraoperatória, tempo de bloqueio do fluxo sanguíneo e diferentes formas de ressecção mostraram impacto significante na regeneração do órgão. Além disso, condições patológicas dos pacientes, incluindo hepatite e fibrose hepática, tiveram impacto significante na regeneração hepática.*

CONCLUSÃO: *O modelo de reconstituição 3D é um bom modelo para calcular o volume do fígado. Idade, gênero, indicadores sanguíneos e bioquímicos não tiveram impacto na regeneração hepática, mas indicadores operatórios e condição patológica dos pacientes mostraram influência na regeneração do órgão.*

PALAVRAS-CHAVE: *Neoplasias hepáticas. Carcinoma hepatocelular. Hepatectomia. Regeneração hepática. Imagem tridimensional.*

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ORIGINAL ARTICLE

Dialogue between primary and secondary health care providers in a Brazilian hypertensive population

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SUMMARY

OBJECTIVE: *To describe clinical and epidemiological profiles of patients with hypertension referred to a secondary care unit and to assess the adequacy of the referral criteria.*

METHOD: *This descriptive transversal study analysed 943 hypertensive patients referred to a secondary healthcare unit from September 2010 to August 2012. Clinical and sociodemographic data as well as data regarding the liaison between secondary and primary care services were collected.*

RESULTS: *Patients' mean age was 59±13.1 years, and 61.3% were female. Sedentary lifestyle, alcohol consumption, and smoking were observed in 80.3%, 31.1%, and 18.1% of the patients, respectively. Uncontrolled blood pressure was observed in 72.5% of the sample, and 80.1% of individuals were overweight or obese. There was a high prevalence of dyslipidaemia (73.1%), cardiovascular disease (97.5%), and reduced glomerular filtration rate (49.9%). Thirty-eight percent of patients did not meet the referral criteria, of whom approximately 25% were not hypertensive.*

CONCLUSION: *Even in a universal-access healthcare system, poor control of hypertension and high prevalence of obesity and cardiovascular diseases were observed. Inadequate referrals and the presence of clinical complications suggest low efficiency of the assistance provided in primary care and reinforce the need for sharing care with the secondary level.*

KEYWORDS: *Health services. Delivery of health care. Hypertension. Chronic disease.*

INTRODUCTION

Changes in lifestyle and population aging have led to an increasing prevalence of chronic disorders such as hypertension[1]. Therefore, health systems must adapt to the magnitude of this challenge, especially in developing countries that face scarcity of resources[2].

As in other countries, hypertension is highly prevalent in Brazil, affecting approximately 32% of the adult population[3]. Due to its asymptomatic nature, it is estimated that approximately 50% of hypertensive patients are unaware of the diagnosis, and among

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those with an established diagnosis, 65% do not receive treatment, and only 33% present adequate blood pressure control[3,4]. Despite an unfavourable socioeconomic profile, the rates of hypertension control in Brazil are close to those of other countries[5,6], which can be attributed to universal access to the public health system[2]. However, the high rates of morbidity and mortality due to cardiovascular diseases in our country point toward a need to improve the effectiveness of the health system[1,7].

To meet this challenge, the Brazilian Ministry of Health has proposed the reorganization of the Integrated Networks of Health Services, seeking a more efficient dialogue between primary healthcare (PHC) and secondary healthcare (SHC). In the state of Minas Gerais, this proposal was implemented through the Hiperdia Minas SHC centres. These centres offer an interdisciplinary approach to hypertensive patients with high cardiovascular risk, shared with the PHC[8]. Given the scarcity of data on the operation of the health system and the data needed for future planning of treatment for severe hypertension, this study aimed to describe the epidemiological profile of patients referred from PHC to the Hiperdia Minas Centre in the city of Juiz de Fora (CHDM/JF) during the implementation phase of the centre.

METHODS

Study design and population

The study was retrospective, cross-sectional, and descriptive. All patients with a diagnosis of hypertension and high cardiovascular risk, on antihypertensive drugs, of both genders, with at least 18 years old, resident in the city of Juiz de Fora, and referred by PHC to the CHDM/JF in the first 2 years of its operation (September 2010 to August 2012) were considered eligible. Juiz de Fora city has 516,247 inhabitants, of whom 99% reside in the urban area. Of 1,190 eligible patients, 247 were excluded: 241 for living in other cities, 5 due to a lack of record of the city of residence, and 1 for being under 18 years old. Thus, 943 individuals were evaluated.

Date setting and data collection

Three researchers (C.P.V., K.V.S., and M.Z.C.) who were not part of the CHDM/JF collected the data by consultation of electronic medical charts, carried out from November 2012 to May 2014. Data was analysed from February 2013 to August 2014. Demographic, clinical, and laboratory data was collected from the first consultation, and the diagnoses of cardiovascular disease and target-organ lesions (TOL) were collected at the first appointment or up to 3 months after entry into the program. Missing data was included in the category of "not informed/not available", with differentiated coding for "not applicable" cases.

Epidemiological variables

The sociodemographic data encompassed age (years), gender, ethnicity (self-declared: Caucasian vs. non-Caucasian), marital status (married/stable partner vs. other), occupation (active vs. not active), family income (in multiples of minimum wage. Brazilian minimum wage references per month were US$330.00, in 2010; US$329.27, in January and February 2011; US$328.31, from March to December 2011 and US$332.62, in 2012), education level (illiterate, up to 8 years, 8 to 11 years, >11 years), practice of physical activity (direct question: yes vs. no), currently smoking (yes vs. no) and alcohol consumption (yes, in any quantity vs. no).

Clinical data

We collected systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements, and the diagnosis of hypertension was based on blood pressure (BP) ≥ 140/90 mmHg. Blood pressure levels above these values in patients using anti-hypertensive medication were considered to indicate uncontrolled BP[9]. Obesity and/or overweight were assessed by body mass index (BMI) and abdominal obesity by waist circumference (>102 cm in men or >88 cm in women)[9]. The diagnosis of dyslipidaemia was established by one of the following criteria: triglyceride levels ≥ 150 mg/dl; LDL-c ≥ 160 mg/dl; and HDL-c < 40 mg/dl for men and < 50 mg/dl for women[10]. The TOL evaluated were hypertensive retinopathy, low estimated glomerular filtration rate (eGFR), and cardiovascular diseases[9].

Estimated glomerular filtration rate below 60 ml/min/1.73 m^2 was considered suggestive of chronic kidney disease[11]. Cardiovascular diseases included previous diagnosis of stroke or coronary disease; peripheral vascular disease, diagnosed by ankle-brachial index lower than 0.9; and presence of diastolic dysfunction of the left ventricle or left ventricular hypertrophy (LVH) on echocardiography.

System operation

Compliance with the referral criteria of the patient to the SHC centre was assessed in order to investigate the efficiency of the dialogue between PHC and the CHDM/JF. Referral criteria included refractory hypertension, hypertension associated with TOL, suspicion of secondary arterial hypertension, or high cardiovascular risk. Failures to complete medical records at the SHC service were also recorded.

Ethical considerations

The study was authorized by the City Health Office of Juiz de Fora, MG and approved by the Human Research Ethics Committee of the University Hospital of the Federal University of Juiz de Fora, under the number 133,399.

Statistical analysis

Categorical and quantitative variables were analysed descriptively, in strata. The results were presented as mean and standard deviation or median and 25–75 percentiles, according to normality, reviewed by the Kolmogorov-Smirnov test. Numerical variables were compared by Student's t test. For the analysis of the association between the variables, the Pearson's coefficient was used. The data was analysed using SPSS 19.0 software (SPSS Inc., Chicago, USA).

RESULTS

Sociodemographic data

Nine hundred forty-three patients were evaluated, with a mean age of 59±13.0 years and a predominance of individuals in the 41–60-year age range (46.8%), female (61.3%), and non-Caucasian (83.9%). Five hundred forty-five individuals (58.9%) were married or had a stable partner, 468 (49.7%) were not active professionally, and 308 (71.6%) had a family income of up to three times the Brazilian minimum wage, with a median of US$667.5 (US$54.0 - US$4,268.3). Most patients (75.8%) had up to 8 years of education, and 80 individuals (8.5%) self-declared being illiterate. The majority of the evaluated population was sedentary (80.3%), while smoking and alcohol consumption were present in 18.1% and 31.1% of the sample, respectively (Table 1).

Clinical data

Mean SBP and DBP were 151±28.3 mmHg and

TABLE 1: SOCIODEMOGRAPHIC PARAMETERS AND RISK FACTORS IN HYPERTENSIVE PATIENTS AT FIRST CONSULTATION AT THE HIPERDIA MINAS CENTER, JUIZ DE FORA, BRAZIL, FROM SEPTEMBER 2010 TO AUGUST 2012

Variable		Mean ± SD / %*
Agea		59±13.0
	> 65 years old	33.9 (320/943)
Gender	Female	61.3 (578/943)
	Male	38.7 (365/943)
Ethnicityb	Caucasian	16.1 (152/943)
	Non-Caucasian	83.9 (791/943)
Marital statusc	Married/stable partner	60.2 (555/922)
	Other	39.8 (367/922)
Occupationd	Active	27.9 (181/649)
	Not Active	72.1 (468/649)
Family incomee	Less than 1 minimum wage	3.0 (13/430)
	From 1 to less than 3 minimum wages	68.6 (295/430)
	From 3 to less than 5 minimum wages	21.4 (92/430)
	More than 5 minimum wages	7.0 (30/430)
Education	Illiterate	8.5 (80/937)
	Up to 8 years	76.3 (715/937)
	From 8 to 11 years	13.3 (125/937)
	Over 11 years	1.8 (17/937)
Sedentary lifestylef		80.3 (647/806)
Tobaccog		18.1 (125/689)
Alcoholh		31.1 (229/737)
Blood pressure	Controlled (<140/90 mmHg)	27.5 (257/936)
	Uncontrolled	72.5 (679/936)
BMI (kg/m^2)a	Women	32±7.1
	Men	29±5.8
	Total	31±6.8
Nutritional status (BMI, kg/m^2)	Underweight	0.6 (06/925)
	Eutrophic	19.2 (178/925)
	Overweight	31.8 (294/925)
	Obese	48.3 (447/925)
	Above weight (overweight + obese)	80.1 (741/925)
Waist circumference (cm)a	Women	104±14.0
	Men	101±14.1
	Total	103±14.1
Abdominal obesity	Absent	14.2 (119/837)
	Present	85.8 (718/837)
Total cholesterol ≥ 200 mg/dl		49.6 (195/395)
Triglycerides ≥150 mg/dl		45.0 (170/378)
LDL-c > 100 mg/dl		66.5 (222/336)
HDL-c below reference valuei		43.2 (161/373)
Dyslipidaemia		73.1 (274/375)

Abbreviation: BMI, body mass index. *For some variables, data were not available for all 943 patients. The number in parenthesis shows the absolute number of individuals over the total available number. **a** Data are presented as mean ± SD or frequency. **b** Ethnicity: self-declared. **c** Marital Status: Married includes married or those living with a partner; Others include divorced, widowed, and single. **d** Occupation: formal employment. **e** Brazilian minimum wage per month: 2010, US$330.00; Jan 2011, US$329.27; Mar 2011, US$328.31; 2012, US$332.62. **f** Sedentary lifestyle: no practice of physical activity outside working hours. **g** Smoking: cigarettes. **h** Alcohol: consumption of alcoholic beverages at any dose. **i** Corrected HDL-c: below 40 mg/dl for men and below 50 mg/dl for women. **j** The test results were brought by patients to begin treatment at the SHC CHDM/JF program.

91±15.9 mmHg, respectively, and 679 subjects (72.5%) presented inadequate blood pressure control. Although hypertriglyceridemia was the most frequent lipid disorder (Figure 1), the median value was 138 [35-3,255] mg/dL. The mean levels of total cholesterol and LDL cholesterol were elevated, and the level of HDL cholesterol reduced. Notably, 681 (72.2%) patients did not have complete laboratory evaluation of their lipid profile at the time of admission to SHC.

The mean body mass index (BMI) was 31±6.8 kg/m^2 and higher in women (32±7.1 *vs* 29±5.8 kg/m^2) (p<0.001). Excess weight was present in 741 individuals (79.9%), and abdominal obesity was found in 718 subjects (85.8%) (Table 1).

The correlation observed between BP control and BMI classification, education and family income were weak, with coefficient values of 0.13, -0.04, -0.07, respectively. On the other hand, the statistical significance between BP control and BMI classification, education and family income were, respectively, <0.001, 0.20, 0.04.

Target-organ lesions

We found a predominance of CVD, followed by low eGFR. The most prevalent CVD were left ventricular diastolic dysfunction, peripheral vascular disease, and LVH (Tables 2 and 3). Two hundred twenty-four individuals (23.8%) were not evaluated in relation to all possible TOL.

System functioning

With regard to meeting the criteria for referral to the CHDM/JF, 505 patients (53.6%) were using three or more antihypertensive drugs and 191 (20.3%) had hypertension associated with prior TOL (stroke and/or coronary disease). By contrast, 87 individuals (9.2%) were not taking any anti-hypertensive drug, and 247 (28.9%) were hypertensive without prior TOL and taking only 1 or 2 antihypertensive drugs, i.e. they did not meet the referral criteria for SHC. Laboratory tests of lipids and renal function were available in only 27.8% and 45.5% of the medical charts, respectively. On the other hand, 71.8% of the charts contained all the minimum standardized information.

DISCUSSION

In this study, high cardiovascular risk hypertensive patients referred to a SHC centre were predominantly elderly, obese, and sedentary women with dyslipidaemia and uncontrolled blood pressure levels. These characteristics are often found in hypertensive patients followed at the PHC and referred to specialized care. In addition, a high prevalence of TOL was observed.

The low socioeconomic level encountered in this study, a known limiting factor for the treatment of chronic conditions, must be highlighted, as it corroborates the data of Yusuf et al.[12] who evaluated 154,000 adults with CVD and observed that individuals of low-income countries face many challenges to accessing proper treatment for the disease.

Approximately 80% of the studied sample had excess weight, especially in the abdomen, consistent with studies showing an association between obesity and hypertension[13-15]. Similarly, in the study of Álvarez-Sala et al.[16], 81.4% of the hypertensive patients had excess weight, while Efstratopoulos et al.[17], who assessed 3,589 hypertensive patients, found 46.4% to be overweight and 35.0% obese. Epidemiological

TABLE 2: CARDIOVASCULAR IMPAIRMENT UPON ADMISSION TO THE HIPERDIA MINES CENTER, JUIZ DE FORA, BRAZIL, FROM SEPTEMBER 2010 TO AUGUST 2012

Variables	% *
Strokea	10.0 (82/822)
Coronary disease	15.3 (126/825)
Peripheral vascular diseaseb	58.1 (200/344)
Left ventricular diastolic dysfunctionc	76.1 (488/641)
Left ventricular hypertrophyc	45.6 (292/641)
Cardiovascular diseased	97.5 (657/674)

*For some variables, data were not available for all 943 patients. The number in parenthesis shows the absolute number of individuals over the total available number. **a** Stroke: prior history. **b** Peripheral vascular disease: assessed by the corrected ankle-arm index. **c** Diastolic left ventricular dysfunction and left ventricular hypertrophy: assessed by echocardiography. **d** Cardiovascular disease: showing some cardiovascular changes.

TABLE 3: PRESENCE OF TOL IN HYPERTENSIVE INDIVIDUALS UPON ADMISSION TO THE HIPERDIA MINAS CENTER, JUIZ DE FORA, BRAZIL, FROM SEPTEMBER 2010 TO AUGUST 2012

Variables	% *
Hypertensive retinopathya	1.5 (12/814)
Estimated glomerular filtration rate	49.9 (214/429)
Cardiovascular disease diagnosed after attendance at the SHC	85.6 (572/668)
TOL	75.7 (714/943)
Diagnosis before attendance at the SHC	27.0 (193/714)
Diagnosis after attendance at the SHC	73.0 (521/716)

Abbreviations: SHC, secondary health care; TOL, target-organ lesions. *For some variables, data were not available for all 943 patients. The number in parenthesis shows the absolute number of individuals over the total available number. aHypertensive retinopathy: diagnosed at the Hiperdia Minas Center.

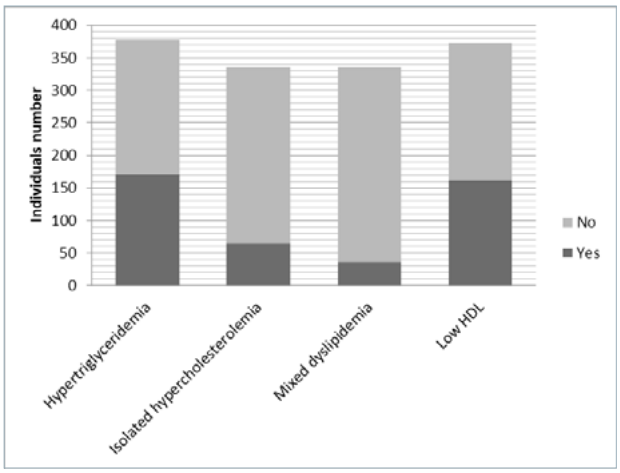

FIGURE 1: Lipid profile of studied population at the admission to SHC.

studies have reported that up to 75% of the risk for the development of hypertension may be attributed to excess weight[18]. Moreover, an alarming proportion of our study population was sedentary, contrasting with studies such as that by Gregg et al.[19], who reported a sedentary lifestyle rate of 31.5% in a population of 3,358 hypertensive American women over 65 years of age.

Even though uncontrolled BP was one criterion for entry into the program, the very high rate of uncontrolled BP we observed is worrying. Inadequate hypertension treatment not only increases cardiovascular risk but also favours evolution to more advanced stages of the disease[7]. Accordingly, in a multicentre study that included 2,649 individuals at high cardiovascular risk treated in PHC, it was found that 60% of sample had inadequate hypertension control[16]. Despite universal access to the health system, findings of inadequate blood pressure control coupled with sedentary lifestyle, overweight, and obesity at entry into SHC point to a low effectiveness of the management of chronic conditions in PHC[1,18-21].

Taking into account the characteristics of this population, risk stratification is crucial for referring individuals at high cardiovascular risk to SHC[22]. However, the high percentage of individuals referred to SHC without assessment of their lipid profile hampers the stratification of cardiovascular risk in the various levels of the healthcare network (HCN). This strategy is essential in SHC to reduce morbidity and mortality in individuals whose cardiovascular risk is often underestimated[22,23].

In addition, the finding of a high prevalence of TOL, especially left ventricular diastolic dysfunction and LVH, is compatible with inadequate control of hypertension[7,24]. In parallel, two-thirds of the patients were diagnosed with peripheral vascular disease, a condition associated with a higher risk for coronary disease[25]. Regarding chronic kidney disease, in a 13-year follow-up study of 281 patients with severe hypertension, Segura et al.[26] found that 15% of patients had reduced eGFR due to hypertensive nephrosclerosis. Other authors, in different populations, have emphasized the close relationship between hypertension and risk for chronic kidney disease[27,28], which in turn is associated with high cardiovascular risk[29]. In our sample, we found that 50% of patients

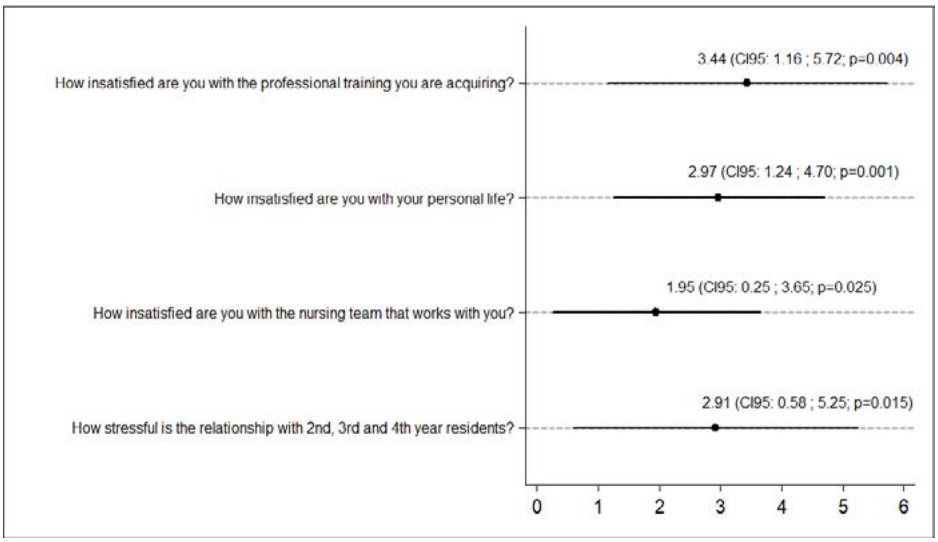

FIGURE 1: Coefficients and 95% confidence intervals of final multivariate regression model of BDI score after 8 months of medical residency

had a reduced eGFR. However, this study is not prospective and does not reflect the care at the SHC level, but rather the state of health of hypertensive patients referred from PHC. The higher prevalence of individuals with reduced eGFR observed in this study could be justified by the fact that we evaluated a population with severe hypertension, involving resistant or secondary hypertension and high cardiovascular risk.

The high blood pressure levels and lack of laboratory evaluation of dyslipidaemia in conjunction with high prevalence of obesity and sedentary lifestyle point to the low effectiveness of interventions at the PHC level, suggesting that compliance with clinical guidelines has not received adequate attention in the HCN, resulting in impaired care of patients with hypertension[30]. This weakness in patient care is consistent with a previous study conducted by our group, in which we found that 43% of PHC physicians do not follow clinical guidelines and/or do not know the criteria for forwarding to SHC services, which can result in inappropriate referral to SHC[31]. In parallel, in the SHC, we observed incompletion of a large number of medical records, suggesting that this tool, indispensable for monitoring and risk stratification of patients with hypertension, also did not receive proper attention from PHC professionals. In this context, the study of Flink et al.[32] also points to a lack of important information for the proper care of patients with chronic health conditions in the context of the HCN. Moreover, according to Paes et al[33], the assessment of health services quality is crucial for adherence to treatment, doctor-patient relationship and appropriateness in the use of services.

The present study presents limitations such as lack of basic information in the medical records, which created difficulties in the stratification of cardiovascular risk. Furthermore, the non-inclusion of patients from other cities did not allow the comparison between different PHC services. On the other hand, this study adds information in this field and may be useful for the development of policies to improve healthcare systems.

CONCLUSION

In conclusion, our study showed that in hypertensive patients referred to SHC, inadequate blood pressure control, a high prevalence of TOL and inadequate referral practices point to the ineffectiveness of treatment and to the weaknesses in the dialogue between the different levels of the HCN. These findings reinforce the importance of improving the HCN effectiveness in order to decrease morbidity and mortality secondary to inadequate treatment of hypertension.

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RESUMO

OBJETIVO: *Descrever os perfis clínicos e epidemiológicos de pacientes hipertensos encaminhados para uma unidade de atendimento secundário e avaliar a adequação dos critérios de referência.*

MÉTODO: *Estudo transversal que analisou 943 pacientes hipertensos encaminhados a uma unidade de atenção secundária à saúde de setembro de 2010 a agosto de 2012. Foram coletados dados clínicos e sociodemográficos, bem como dados de interlocução entre os serviços de atenção primária e secundária.*

RESULTADOS: *A idade média dos pacientes era de 59 ± 13,1 anos e 61,3% eram do sexo feminino. O estilo de vida sedentário, o consumo de álcool e o tabagismo foram observados em 80,3%, 31,1% e 18,1% dos pacientes, respectivamente. A pressão arterial descontrolada foi observada em 72,5% da amostra, e 80,1% dos indivíduos apresentavam excesso de peso. Houve uma alta prevalência de dislipidemia (73,1%), doença cardiovascular (97,5%) e taxa de filtração glomerular estimada reduzida (49,9%). Trinta e oito por cento dos pacientes não atendiam aos critérios de encaminhamento, dos quais aproximadamente 25% não eram hipertensos.*

CONCLUSÃO: *Mesmo em um sistema de saúde de acesso universal, observou-se um controle insuficiente da hipertensão e uma alta prevalência de obesidade e doenças cardiovasculares. Encaminhamentos inadequados e a presença de complicações clínicas sugerem uma baixa eficiência da assistência prestada na atenção primária e reforçam a necessidade de compartilhar cuidados com o nível secundário.*

PALAVRAS-CHAVE: *Serviços de saúde. Assistência à saúde. Hipertensão. Doença crônica.*

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ORIGINAL ARTICLE

Interns' depressive symptoms evolution and training aspects: a prospective cohort study

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SUMMARY

OBJECTIVE: *To study depression symptoms' incidence of medical interns (first year of medical residency) and its correlation with occupational characteristics, satisfaction and stress about their training program.*

METHODS: *Prospective Cohort Study conducted at Escola Paulista de Medicina, Universidade Federal de São Paulo. First year residents, N = 166, from a teaching hospital were invited to answer the Beck Depression Inventory (BDI) and an occupational questionnaire in a prospective longitudinal study. BDI score variation was related with socio-demographic aspects and occupational characteristics using linear regression models.*

RESULTS: *111 subjects participated (67%); the BDI-score increased in 8 months (mean = 2.75 ± 3.29 vs. 7.00 ± 5.66; p<0.0001). The depressive symptoms' incidence was 9.01% (score>15). BDI-score variation had mean = 4.25 ± 4.93, ranging from -8 to 28. Residents not satisfied with professional training acquired (β = 3.44; p = 0.004), with their personal life (β = 2.97; p = 0.001), or who felt stressed in the relationship with senior residents (β = 2.91; p = 0.015) presented 3 more points of BDI-score after 8 months comparing to those without these perceptions; and being unsatisfied with the nursing team increased BDI-score after 8 months in 2 more points (β = 1.95; p = 0.025).*

CONCLUSION: *Among the factors that interfere with depression in interns is the occupational characteristics, which might be enhanced by the training facility. Addressing these dissatisfaction and stressful issues should help the university provide better care of interns' mental health.*

KEYWORDS: *Depression. Internship and Residency. Stress, psychological. Mental health. Educational, medical.*

INTRODUCTION

It is known that to become a physician many stressful challenges have to be faced. However, it must be acknowledged that at a certain level, this situation is no longer bearable and starts to harm the medical intern (first year of postgraduate medical residency) and resident. Studies on mental health of doctors, residents, interns and medical students have been substantially published over the years.[1-10] Depressive symptoms in medical residents related to individual characteristics, educational and occupational environment, have been an aspect of particular importance.[1, 8-11]

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It has been described[1] that the typical intern goes through distinct phases during the first postgraduate year. It begins with an initial stage of excitement as the year begins. This period is followed by one of self-doubt when the intern begins to recognize his/her limitations. Depressive symptoms may follow and then it starts a quiet, often tedious period, and by mid-year, another period of more intense depression may ensue. After the 9th month the intern begins to recognize the tangible accomplishments and enters the stage of success.

Another study described "the house officer stress syndrome". It was stated that residents present episodic cognitive impairment, chronic anger, pervasive cynicism, family discord, depression, suicidal ideation and suicide, and substance abuse. Some factors were associated as the aetiology of this syndrome: sleep deprivation, excessive work load, patient care responsibility, perpetually changing work conditions, and peer competition.[12]

In a three year prospective study,[3] internal medicine residents indicated their level of agreement answering questions about their emotional state. Depression reached its highest level during the first year, mainly between the 6th and 8th month, and lessened significantly and rapidly after the 13th month.

Depressive symptoms prevalence for medical residents has been studied in several researches. One of these found depressive symptoms in 28.7% of postgraduate year 1 (PGY-1), 21.5% of PGY-2 and 10.3% of PGY-3.[2] Other study conducted during a 3-year period showed the evolution of depressive symptoms in internal medicine residents: they started low, peaked between the 7th and 9th month of the first year and improved by the end of internship; on the 2nd and 3rd years, residents improved to the point where they were not different from baseline.[5] The prevalence of moderate depression increased from 4.3% at the beginning of residency to 29.8% after one year, however no one had scores indicating severe depression.[6] In another study conducted during one year, a lower percentage of interns presented medium and high levels of symptoms of depression at the beginning of the year; this percentage peaked in the fourth month, and showed a second elevation at the end of the year.[4]

In a systematic review and meta-analysis, a pooled prevalence of depression or depressive symptoms among resident physicians was 28.8% (from 20.9% to 43.2%) and this study presented heterogeneity as included interns, residents, cross-sectional and longitudinal studies. In secondary analysis restricted to longitudinal studies, it was found a significant increase in depressive symptoms among interns after the start of residency, the median absolute increase in depressive symptoms among interns was 15.8% within a year of beginning training (range from 0.3% to 26.3%). No statistically significant differences were observed between cross-sectional vs longitudinal studies, studies with interns only vs upper-level residents only, or studies of nonsurgical vs both nonsurgical and surgical residents.[11]

The association between depressive symptoms and medical residency has been presented as a popular topic, but its popularity is a double-edged sword. Much has been published in this domain, and it is unclear how new studies could advance the field beyond what is already known. Some factors related are a two-way causal relationship, i.e., a reverse causation, such as depressive symptoms and dissatisfaction with the training.

In a prospective longitudinal cohort study we aimed at identifying the incidence of depressive symptoms in interns; identifying depressive symptoms' association with some occupational characteristics (considering dissatisfaction, stressful situations and difficulties with the training program); and assessing whether the depressive symptoms are related to the quality of the training received (considering their opinion about the education received); and to peer and teamwork relationship and to stressful patients.

METHODS

In 2006, 166 new interns entered the medical residency programs in a teaching hospital. All of them were invited to participate in the study, and were told that their participation would be voluntary and only aggregated group data would be reported. This study was approved by the university's institutional review board. Written informed consent was obtained from each study participant.

One hundred forty-six interns answered the instruments at the baseline survey (T1). There was no statistically significant difference ($P < 0.05$) between them and the 20 interns who did not answer the instruments according to gender, age and residency program. Data about gender, age, and residency program for these 20 interns was obtained from the administrative record of interns in the university.

On the 8th month, all those 146 interns were invited to answer the second survey (T2), which was completed by 112 interns. Thirty-four interns did not participate due to refusal, vacation or work in a medical facility outside the university hospital. The data of the 34 interns, who did not answer the second survey (at T2), did not differ significantly from those 112 who answered them considering gender, age, BDI score at T1 and residency program ($P < 0.05$).

In order to calculate the incidence at the eighth month, the one intern who scored for depressive symptoms at T1 was excluded. Thus, the set of data analysed was composed of 111 interns, 67% of 166 interns (answered both phases).

At the orientation session (T1) – a meeting in which general guideline for the training is provided to all new residents – during the first week of the medical residency program, each intern received personally the consent form, the socio-demographic questionnaire and the Brazilian version[13, 14] of the Beck Depression Inventory (BDI)[15] and they were asked to return them in the session. The interns who did not return them or did not appear during orientation session were contacted by one of the researchers during the following days until 20 days after this session. During the first month, 18 new interns were admitted in substitution of dropouts and received the questionnaire and instrument to be answered in their first day at admission office. Eight months later (T2) all interns who answered T1 received personally the BDI and a questionnaire about occupational characteristics during the training.

For the purpose of the analysis, the residency programs were grouped in two major sections: clinical area, including dermatology, family medicine, infectious diseases, internal medicine, medical genetic, neurology, paediatrics, physical medicine and rehabilitation, and psychiatry; and surgical area, including anaesthesiology, neurosurgery, otorhinolaryngology, obstetrics and gynaecology, ophthalmology, orthopaedics, and general surgery.

The socio-demographic questionnaire comprises data about gender, age, marital status, place of birth, medical school, number of years living in that city, place where the intern was living during training, whether the resident was on mental health treatment, and personal/family psychiatric history. The BDI[15] assesses the existence and severity of depression symptoms, considering a cut-off score higher than 15 as depressive symptoms according to the Brazilian validation.[14] The questionnaire on occupational characteristics during training is a self-report structured questionnaire developed for this study that explores the intern's difficulties during the first 8 months of training. The questionnaire covers training dissatisfaction, difficulty with patients, and stressful relationships.

BDI scores at T1 and T2 were analysed, and the incidence of depressive symptoms was calculated. Both scores were compared using the Wilcoxon Signed-Rank Test, and they were distributed by social-demographic characteristics using the Mann-Whitney Test.

Thus, the difference of BDI scores at T2 and T1 was calculated to each subject. This new variable, the "BDI scores variation" was the main outcome studied in a series of linear regressions. First, univariate linear regression models were developed to evaluate the relationship between the BDI score variation and each of the following items: training dissatisfaction, stressful relationships, difficulty in dealing with patients, work load, gender, specialty area and age.

Second, these linear regression models were adjusted using gender, specialty and age as controlling variables of the others, simultaneously, using the entry method. Third, variables with no statistically significant associations ($p>0.05$) were excluded, one by one, in order of significance (backward method).

The regression linear models presented, as one of the assumption, a normal distribution of the outcome variable which were verified using Kolmogorov-Smirnov test ($p=0.071$). There were not any multicollinearity problems (according to VIF) and the residual analysis did not indicate existence of influence points. It was used 5% significance level to all statistical tests.

The statistical analysis was carried out using SPSS 20.0 software.

This study was approved by the university's institutional review board and written informed consent was obtained from each study participant.

RESULTS

The group of 111 interns, who did not score for depressive symptoms at T1, and answered both phases (67% of 166 interns) was considered for the analysis.

The 111 interns were 50.5% female, with median age of 25 years old (ranged from 23 to 30) and all Brazilian. More than 60% (61.3%) of interns obtained

their undergraduate degree as medical doctors in the same medical school where this study was developed. The socio-demographic characteristics are showed in Table 1.

Ten of the 111 interns scored for depression symptoms at T2 in the BDI inventory. Both BDI scores showed an asymmetric distribution, with median of 2 (mean of 2.75, standard deviation of 3.29, ranged from 0 to 14) at T1 and median of 5 (mean of 7.00, standard deviation of 5.66, ranged from 0 to 30) at T2. There was an increase in BDI score from T1 to T2 (z= -7.43 P < 0.0001), and the incidence of depressive symptoms after 8 months of training was 9.01% (cut-off score higher than 15).

Of all 10 interns who scored for depressive symptoms, only one was under mental health treatment. Additionally, another 11 interns who did not score for depressive symptoms reported to be under mental health treatment (medication and/or psychotherapy).

BDI scores showed differences across different sub-populations of the study related to socio-demographic characteristics (Table 2). At T1, it was found a statistically significant difference between interns who lived with relatives and those who did not (BDI mean score of 1.96±2.92 versus 3.44±3.46; z= -2.84, P = 0.005), which showed lower BDI score for those with larger social network. At T2, it was found a statistically significant difference between interns at clinical and surgical programs (BDI mean score of 6.25±5.63 vs. 8.19±5.57; z= -2.23, P = 0.026); it was found a higher BDI score in surgery than in other group (Table 2).

The mean of the BDI score variation was 4.25 (standard deviation of 4.93). It was observed a range of symptoms from -8 (decreasing symptomatology) to 28 (increasing symptomatology). The median of the BDI-variation was 3.00.

Table 3 shows three linear regression models to evaluate the BDI score variation in eight months: univariate, multivariate with all independent variables and the final multivariate model. Considering the controlling variables – gender, age and specialty – only specialty area showed an association between BDI score variation and the surgical intern. This means that surgical interns had 2 more points of BDI score after 8 months than clinical interns. In multivariate regression models, as gender and age, specialty had no statistically significance, due to other variables in the models. Other factor, dissatisfaction with own performance, also presented a significant value when analysed by univariate model; (P<0.001),

TABLE 1. SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE 111 MEDICAL RESIDENTS IN THE STUDY COLLECTED AT BASELINE SURVEY (T1)

		N	%
Residency Programs	Surgical	43	38.7
	Clinical	68	61.3
Medical School	The same that the subject is intern	68	61.3
	Other	43	38.7
Marital status	Single	106	95.5
Years living in São Paulo (city where the university is)	< 6 years	40	36.7
	≥ 6 years	69	63.3
Place where the resident lives during the training	Parent/ relative house	52	46.8
	Dormitory/ own or rental apartment	59	53.2
Current Medical Treatment	No treatment	91	82.0
	Under psychiatric medication	4	3.6
Mental health treatment (present or previous)	Never	88	79.3
	Psychotherapy	14	12.6
	Medication and psychotherapy	9	8.1
Family Psychiatric History	Presence in any relative	34	30.6
	Presence in father or mother	17	15.3

TABLE 2. BDI MEAN DISTRIBUTION AT T1 AND T2 RELATED TO SOCIO-DEMOGRAPHIC CHARACTERISTICS

		T1		T2	
		Mean ± SD	P	Mean ± SD	P
Gender	Male	2.85 ± 3.38	.663	6.91 ± 5.79	.841
	Female	2.64 ± 3.22		7.09 ± 5.88	
Residency Programs	Clinical	2.78 ± 3.35	.887	6.25 ± 5.63	.026
	Surgical	2.70 ± 3.23		8.19 ± 5.57	
Medical School	The same that the subject is intern	2.59 ± 3.09	.382	7.29 ± 5.99	.618
	Other	3.09 ± 3.58		6.53 ± 5.14	
Years living in São Paulo	≥ 6 years	2.39 ± 3.05	.063	6.99 ± 5.12	.568
	< 6 years	3.48 ± 3.64		7.10 ± 6.10	
Place where the resident lives during the training	Parent/Relative house	1.96 ± 2.92	.005	7.48 ± 5.26	.466
	Dormitory/ own or rental apart	3.44 ± 3.46		6.58 ± 5.78	
Marital status	Single/Divorced	2.65 ± 3.24	.135	6.91 ± 1.00	.129
	Married	4.80 ± 4.15		9.00 ± 1.00	

NS = non-significant, SD = standard deviation

TABLE 3. SIMPLE AND MULTIVARIATE LINEAR REGRESSION STUDIES OF BDI SCORE VARIATION IN EIGHT MONTHS OF MEDICAL RESIDENCY ACCORDING TO DISSATISFACTION, DIFFICULTIES AND STRESSFUL RELATIONSHIPS WITH THE TRAINING

	Univariate Model	Multivariate Model				
		Initial Model (Method "Enter")		Final Model (Method "Backward")		
	Coefficient (CI95%)	P	Coefficient (CI95%)	P	Coefficient (CI95%)	P
Gender male (ref. = female)	-0.39 (-2.26 ; 1.47)	0.678	-0.90 (-2.62 ; 0.81)	0.299	-	NS
Medical Specialty surgical (ref. = clinical)	2.02 (0.14 ; 3.89)	0.035	1.48 (-0.42 ; 3.39)	0.126	-	NS
Age (years)	0.09 (-0.64 ; 0.82)	0.803	0.07 (-0.55 ; 0.70)	0.812	-	NS
How unsatisfied are you with the professional training you are acquiring?	3.88 (1.46 ; 6.30)	0.002	3.21 (0.2 ; 6.22)	0.037	3.44 (1.16 ; 5.72)	0.004
How unsatisfied are you with the amount of leisure time you have?	3.37 (1.47 ; 5.27)	0.001	1.99 (-0.13 ; 4.1)	0.065	-	NS
How unsatisfied are you with your personal life (time spent with family, romantic relationship and friends)?	3.55 (1.75 ; 5.35)	<0.001	1.87 (-0.11 ; 3.85)	0.064	2.97 (1.24 ; 4.70)	0.001
How unsatisfied are you with your personal health habits (time for sports, healthy	2.34 (-0.1 ; 4.77)	0.060	-0.56 (-2.97 ; 1.86)	0.648	-	NS
How unsatisfied are you with the school faculty?	0.27 (-1.75 ; 2.29)	0.790	-2.97 (-5.25 ; -0.70)	0.011	-	NS
How unsatisfied are you with the nursing team that works with you?	1.89 (-0.03 ; 3.80)	0.053	1.62 (-0.23 ; 3.46)	0.085	1.95 (0.25 ; 3.65)	0.025
How unsatisfied are you with residency colleagues from all programs that you work with?	-1.15 (-5.26 ; 2.97)	0.582	-1.88 (-6.27 ; 2.51)	0.396	-	NS
During these 8 months of residency, how unsatisfied are you with your own performance?	5.99 (2.94 ; 9.04)	<0.001	0.88 (-2.9 ; 4.65)	0.645	-	NS
How difficult for you is to deal with patients?	-0.58 (-3.36 ; 2.20)	0.680	-2.37 (-5.41 ; 0.66)	0.124	-	NS
How difficult for you is to deal with patient' family?	-0.33 (-2.80 ; 2.14)	0.792	0.86 (-2.48 ; 4.20)	0.609	-	NS
How stressful is giving bad news for patients and their families?	1.13 (-0.72 ; 2.98)	0.230	1.04 (-0.76 ; 2.84)	0.253	-	NS
How well oriented are you by the school faculty?	0.62 (-1.57 ; 2.82)	0.574	0.00 (-2.25 ; 2.25)	0.999	-	NS
How well respected are you by the school faculty?	-0.73 (-2.93 ; 1.47)	0.511	-1.10 (-3.33 ; 1.13)	0.330	-	NS
How stressful is the relationship with the nurse team and other health professionals in the hospital?	1.75 (-0.54 ; 4.04)	0.132	1.21 (-1.01 ; 3.42)	0.281	-	NS
How stressful is the relationship with 1st year residents?	0.18 (-2.97 ; 3.32)	0.910	1.11 (-2.20 ; 4.42)	0.507	-	NS
How stressful is the relationship with 2nd, 3rd and 4th year residents?	3.24 (0.71 ; 5.76)	0.013	3.43 (0.78 ; 6.08)	0.012	2.91 (0.58 ; 5.25)	0.015
How stressful is the relationship with undergraduate medical students?	1.04 (-3.96 ; 6.03)	0.682	-1.95 (-6.32 ; 2.42)	0.376	-	NS
How many hours per week are you working at this rotation (including nightshifts)?	0.05 (0.00 ; 0.10)	0.041	-0.01 (-0.06 ; 0.04)	0.732	-	NS
How many hours per week are you working outside the university this month (including nightshifts)?	0.10 (-0.02 ; 0.22)	0.118	0.04 (-0.07 ; 0.15)	0.475	-	NS

CI 95% – Confidence Interval 95%; NS – non significant (the variable was not included in the model)

but no longer maintained this effect in multivariate models.

Final multivariate model showed that only four occupational characteristics were related to BDI score variation: dissatisfaction with professional training acquired (p=0.004); dissatisfaction with personal life (p=0.001); dissatisfaction with the nursing team they work with (p=0.025); and feeling stressed in the relationship with 2nd, 3rd and 4th year residents (p=0.015). In this way, it was noted that residents who were not satisfied with professional training acquired, or with their personal life, or who said they

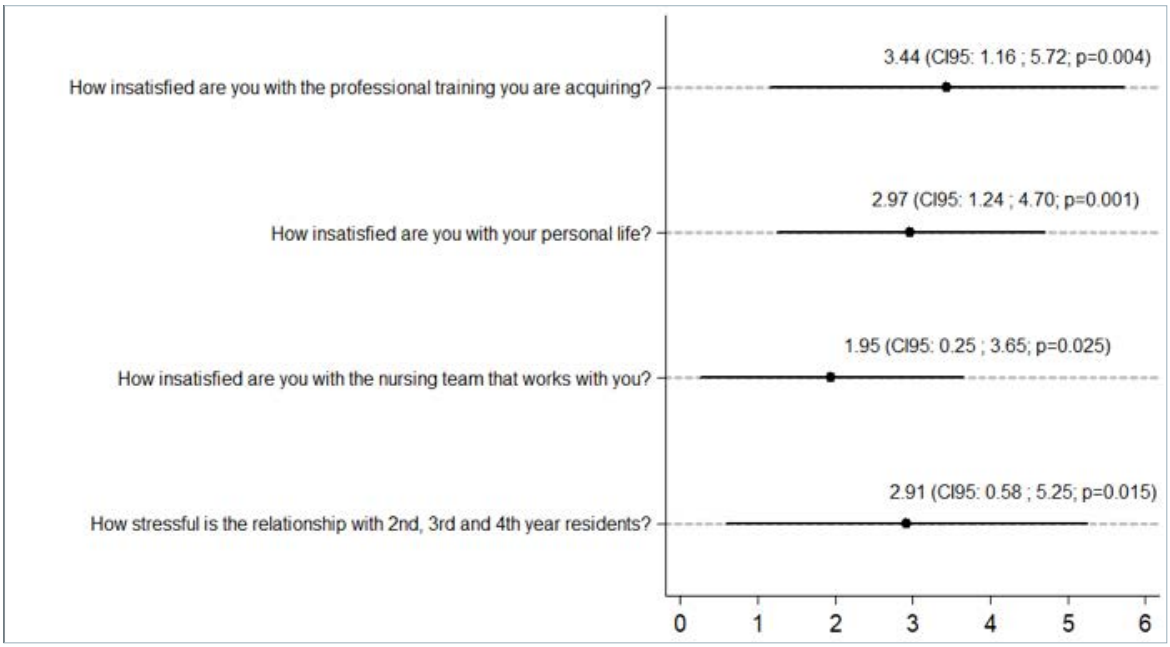

FIGURE 1 – COEFFICIENTS AND 95% CONFIDENCE INTERVALS OF FINAL MULTIVARIATE REGRESSION MODEL OF BDI SCORE AFTER 8 MONTHS OF MEDICAL RESIDENCY

were feeling stressed in the relationship with 2nd, 3rd and 4th year residents presented 3 more points of BDI score after 8 months comparing to those without these perceptions. Being unsatisfied with the nursing team increased BDI score after 8 months in 2 more points. Figure 1 shows the impact of each one of these characteristics over the BDI score variation.

DISCUSSION

Increase in BDI score after 8 months of training and consequently the incidence of depressive symptoms of 9% (score > 15 for depressive symptoms) reaffirm findings of increase in depressive symptoms during first year of medical residency.[3-6, 9,11] It was found that the increase of depressive symptoms was related to some occupational characteristics such as dissatisfaction with personal life, dissatisfaction with the nursing team they work with, and feeling stressed in the relationship with seniors residents. Depressive symptoms were also related to dissatisfaction with professional training acquired.

Reflecting about the dissatisfaction with the nursing team, it has been described that enhancing nurse–intern partnerships are associated with improved provider satisfaction, patient satisfaction and the provision of individualized care.[16] One assumption is that having an unsatisfactory relationship with the nursing team could affect directly or indirectly the resident-patient relationship. It would be relevant to investigate this assumption in further studies.

Although few studies were found discussing the relationship among medical residents from different years, some comments were identified in the literature revealing some reasons for interns to feel stressed in these relationships.[12, 17] Lack of compassion, competitiveness and even cruelty abounds among them, problems not openly discussed but frequent in their clinical experience.[17] One study specifically about surgery residents indicated that those individuals are more likely to prefer competition to cooperation.[18] In a study that examined job stress, satisfaction, and the psychological and social functioning of orthopaedic residents, it was found that residents had more psychiatric morbidity when the stress in relationships with senior residents is higher, whereas satisfaction from speaking with a mentor was associated with decreased morbidity.[19] Competition is a reality of medical training and motivates the resident to do a better job; when excessive, however, it may lead to social isolation.[12] Another aspect is an association between both lack of social skills and personal variables and depression in medical residents.[10]

There is a recommendation for the need for a strong working relationship, suggesting leaders of educational programs to address the relationship between interns – considering their conflicts, defining clear delineation of roles and a fair distribution of work, avoiding competition for clinical experiences.[20] Also relevant is a recommendation to provide teamwork and leadership training to clinicians in a way to affect stress levels.[21] A protective factor against resident stress is camaraderie with peers.[19]

The association between depressive symptoms and dissatisfaction with professional training and personal life reaffirms findings from prior works described in the literature,[1,6, 8, 9] in which some aspects of the training were observed such as long hours, sleep deprivation, limited time for personal pursuits, mood disturbances, among other factors. Still, it should not be neglected that these results related to these two variables – dissatisfaction with professional training and personal life – may reflect inherent characteristics of physicians such as being demanding and perfectionist professionals,[4] and self-criticism, a significant predictor of depression for interns.[8, 22]

Considering occupational characteristics, medical specialty was a factor related to depressive symptoms at T2. This characteristic was relevant when it was studied without considering other occupational characteristics; however, when different aspects of the training were analysed, medical specialty lacked significance. One possible explanation is that the impact of being a surgical or clinical specialty on depressive symptoms is assembled in one of the four variables that resulted as statistically relevant in the multivariate model. As a possibility, it may be that the variable "Satisfaction with nursing team" is already covering the specialty impact as the impact of the nursing team might be expected to be greater for surgical specialties.

About gender, it is an important influence to depression, being the prevalence in women usually twice higher than that of men.[23] Studies about this issue for medical residents are unclear, suggesting that gender is not important.[4, 8, 9, 11] This is in concordance with our findings since there was no significant difference on gender in this study.

One aspect in the socio-demographic characteristics is that residents who lived in a parent' or relative' house presented a lower BDI score (T1) when compared with those who lived in dormitory or their own or rented house (P=0.005); this pattern could be attributed to receiving a good social support in the beginning of the medical training. After 8 months this aspect is no longer significant, which may be due to an adaptation process.

The findings from this study are limited to this group of entrants for residency at this university. For this particular sample, there are also some possible bias. Residents who chose not to participate may have done so because they wanted to avoid revealing themselves in testing, what might have changed the results. The rate of depressive symptoms might also be inaccurate doe to residents who answered what they thought it would to be more appropriated, instead of their actual feeling.

The relationship between depressive symptoms and dissatisfaction with the program is really a two-way causal relationship; always taking into account that depression is influenced by other characteristics such as personality traits, previous experiences, genetic aspects, etc.

This study raises some questions. Being the professional training unsatisfactory, is there something that could be done by interns to improve their experience? In addition, how do they cope with a stressful situation, and how do they use their spare time? Which actions can the intern develop by themselves? Could the program develop wellbeing strategies or tutorial programs for this population? Studying stressful and satisfactory aspects for residents may improve the discussion on critical actions for developing a better mental health during training. This study may motivate a new research about resilient residents, the impact of competitive behaviour on the quality of medical training.

CONCLUSION

The increase in BDI score after 8 months of training and consequently the incidence of depressive symptoms were related to some occupational characteristics as dissatisfaction with personal life, dissatisfaction with the nursing team they work with, feeling stressed in the relationship with senior residents, and dissatisfaction with professional training obtained. It is important to help these interns to improve their training experience and take care of their needs.

Among the many factors that interfere with depression incidence in interns (including personal as-

pects), the occupational characteristics might be the only one that can be enhanced by the university that offers the training. Thus, addressing these dissatisfaction and stressful issues should provide the university better care of interns' mental health.

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RESUMO

OBJETIVO: *Estudar a incidência de sintomas depressivos em residentes de medicina de 1º ano e sua correlação com características ocupacionais, satisfação e estresse no programa.*

MÉTODOS: *Coorte prospectivo realizado na Escola Paulista de Medicina, Universidade Federal de São Paulo. Foram convidados 166 médicos residentes do hospital universitário para responder ao Inventário de Depressão Beck (BDI) e a um questionário ocupacional num estudo prospectivo longitudinal. O escore da variação do BDI foi relacionado com aspectos sociodemográficos e características ocupacionais usando um modelo de regressão linear.*

RESULTADOS: *Cento e onze sujeitos participaram (67%); o escore do BDI aumentou em oito meses (média = 2,75 ± 3,29* vs. *7,00 ± 5,66; p<0,0001). A incidência dos sintomas depressivos foi de 9,01% (escore>15).*

A variação do escore do BDI teve média = 4,25 ± 4,93 (de −8 a 28). Residentes não satisfeitos com o treinamento profissional (β = 3,44; p = 0,004), com a vida pessoal (β = 2,97; p = 0,001) ou que se sentem estressados na relação com residentes seniores (β = 2,91; p = 0,015) apresentaram 3 pontos a mais do escore do BDI depois de oito meses em comparação com aqueles sem tais percepções; estar insatisfeito com a equipe de enfermagem aumentou o escore do BDI em 2 pontos (β = 1,95; p = 0,025).

CONCLUSÃO: *Entre os fatores que interferem na depressão em residentes estão as características ocupacionais que podem ser melhoradas no treinamento. Esclarecer tais pontos pode ajudar a instituição a prover um melhor cuidado em saúde mental.*

PALAVRAS-CHAVE: *Depressão. Internato e residência. Estresse psicológico. Saúde mental. Educação médica.*

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ORIGINAL ARTICLE

Epidemiological profile of Brazilian oncological patients seen by a reference oncology center of the public health system and who migrate in search of adequate health care

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SUMMARY

INTRODUCTION: *Structural disparities between different Brazilian regions in public health system cause patients to migrate in search of better conditions to treat their diseases. Besides patient's discomfort, there is a concentration of care in large centres, causing overload to current capacity.*

OBJECTIVE: *To evaluate migratory flow and associated factors in a reference service in oncology.*

METHODS: *Cross-sectional study conducted at a referral oncology service in Great ABC region of São Paulo. Patients were interviewed, and clinical and demographic data collected.*

RESULTS: *Between March-July 2016, 217 patients were included. Analysis showed a divergence between the postal code registered in the medical record and that recorded during the interview in approximately 10% of cases. Of these, 42.9% were residents of other states. Search for treatment motivated most patients to seek service outside their city.*

CONCLUSION: *Results reflect the informal search for medical care outside the home area. Besides the direct impact on patients' quality of life, migratory flow has an economic-social impact because these patients place a burden and impose costs on services of cities where they do not perform their responsibilities as citizens. Confirmation of the existence of a significant migratory flow demonstrates the need to discuss restructuring public health policies.*

KEYWORDS: *Human migration. Neoplasms. Health services accessibility. Health policy.*

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INTRODUCTION

Brazil displays large socioeconomic differences between states and cities.[1] However, the Federal Constitution guarantees, through the principle of Universality of the Unified Health System (Sistema Único de Saúde - SUS), that all Brazilian citizens have the right to access health services and actions.[2-4] Furthermore, the principles of hierarchization and regionalization demonstrate that those services offered must be organized at levels of increasing technological complexity, arranged in a defined geographical area and defined by the population to be served.[3]

In practice, the socioeconomic disparities between the different regions of the country[1] lead some users of the system to seek more complex and quality care away from their homes, particularly regarding diseases that require complex, costly, and prolonged treatments, such as cancer. However, there is no data in the Brazilian literature that express this occurrence.

Thus, the present study aimed to measure the actual migratory rate of patients, who informally sought medical care outside their residential area, present at a reference centre for cancer treatment.

OBJECTIVES

To evaluate the migratory flow of patients to a reference centre in oncology.

METHODS

This cross-sectional study was performed at the oncology department of the Padre Anchieta Teaching Hospital (Hospital de Ensino Padre Anchieta) in São Bernardo do Campo. This study was approved by the Institution's Research Ethics Committee prior to beginning the research - Certificate of Presentation for Ethical Appreciation (*CAAE*), number: 54167116.8.0000.0082. The participants signed an informed consent form (*termo de consentimento livre esclarecido - TCLE*), and the confidentiality of the data collected was assured.

Oncology patients who had over 18 years old and received treatment or follow-up participated in the study. Patients who did not understand the nature and procedures of the research were excluded.

For data collection, patients were interviewed using Form 1 (attached). Next, their respective charts were analysed, and their postal code (Código de Endereçamento Postal - CEP) reported in the interview was compared to that reported in the system/medical records.

STATISTICAL ANALYSIS

The sociodemographic data collected from the studied population was described in terms of their relative and absolute frequencies. The association between categorical variables was verified by chi-square test. For associations with values less than 5, Fisher's exact test was used. The statistical program used was Stata®, version 12.1.

RESULTS

From March to July 2016, a total of 217 patients were included, of which 134 (61.7%) were female. The median age was 59.7 years old, ranging from 20 to 89 years. Regarding marital status, the two most frequent categories were married and single, with 119 (54.8%) and 41 (18.9%) individuals, respectively. Most patients (63.6%) were individuals with little education, up to only elementary school. The family income of 86.6% of individuals was limited to three minimum wages (approximately USD 1,000), and the majority (93.6%) did not have health insurance. Among the patients who had health insurance (corresponding to only 14 patients in this sample), 78.6% used it to complete part of the treatment. Table 1 shows the sociodemographic data of the studied population.

The CEP analysis showed that there was a divergence between the CEP recorded in the medical record and that declared by the patient during the interview in approximately 10% (21) of the cases. Of these, 17 (81%) lived with a relative, and the search for treatment was the main reason for the change in postal code (66.7%). Of the patients who migrated, 42.8% were from non-ABC cities in the state of São Paulo, 42.8% were from other states, and the remainder (14.3%) were from the Great ABC. There was no relationship between the educational level or the primary tumour location and the migration rate. Table 2 summarizes the characteristics found among the patients who migrated.

In the exploratory analysis of possible factors contributing to or associated with migration in search of treatments, no statistically significant relationships

TABLE 1: SOCIODEMOGRAPHIC DATA

		N = 217	100%
Gender	Female	134	61.7%
	Male	83	38.3%
Age	Median	59.7 years	
	Interval	20 to 89 years	
Marital Status	Single	41	18.9%
	Married	119	54.8%
	Other	57	26.3%
Education	Illiterate	14	6.4%
	Elementary school	138	63.6%
	High school	52	24%
	Higher education	13	6%
Income	Up to 3 minimum wages	188	86.6%
	4 minimum wages or more	29	13.4%
Has insurance	Yes	14	6.4%
	No	203	93.6%
Uses insurance as part of the treatment	Yes	11	78.6%
	No	3	21.4%
Religion	Catholic	135	62.2%
	Evangelical	62	28.6%
	Other	14	6.4%
	No religion	6	2.8%
Primary tumor location	Breast Gastrointestinal tract Gynecological Genitourinary tract Other	61 59 25 22 49	28.2% 27.3% 11.6% 10.2% 22.7%
City of origin	São Bernardo do Campo	160	73.7%
	Great ABC	36	16.6%
	Other cities (SP)	12	5.5%
	Other states	9	4.2%

TABLE 2: SOCIODEMOGRAPHIC DATA OF PATIENTS WHO MIGRATE

Lives with family	Yes	N = 21 17	100% 81%
	No	4	19%
Reason for change	Search for treatment	14	66.7%
	Family company	4	19%
	Other	3	14.3%
City of origin	Great ABC	3	14.3%
	Other cities in the state of São Paulo	9	42.8%
	Other states	9	42.8%
Got treatment in the city of origin	Yes No	8 13	38.1% 61.9%

TABLE 3 - ASSOCIATIONS BETWEEN SOCIOECONOMIC CHARACTERISTICS AND MIGRATION

		Migration No	Migration Yes	Chi² Test / Fisher's * p
Education	Up to elementary school	139	13	0.391
	High school or higher education	57	8	
Income	Up to 3 minimum wages	168	20	0.322*
	4 or more minimum wages	28	1	
Date of diagnosis	Up until 2012	44	4	1.000*
	After 2012	151	17	
	Breast	59	2	
	Gastrointestinal	52	7	
Location of primary neoplasm	Gynecological tract	25	0	0.036*
	Genitourinary tract	18	4	
	Other	41	8	

were observed regarding the divergence between CEPs and schooling or family income level. However, the primary location of the disease was related to the migratory process (Table 3).

DISCUSSION

This study was performed in a reference centre for oncology in the Great ABC, which is a region composed of seven cities that together total over 2.5 million inhabitants.[5] Regarding the included subjects, it is important to mention that, although the exact amount of patients that have been attended by the Hospital has not been recorded, the inclusion of 217 subjects is in accordance to what has been previously stipulated to be a suitable sample for this article.

Of the patients seen in the service, 73.7% live in São Bernardo do Campo (the city where the service is established), whereas 16.6% live in other cities of the Great ABC, which is not defined by migration because the hospital in question is a regional reference centre.

However, approximately 10% of the patients seen do not live effectively at the addresses provided in the hospital registry, and 42.8% of those patients do not even live in the state of São Paulo. We also noted a significant difference regarding the location of the primary tumour presented in patients who migrated as compared with those who did not. For example,

regarding those who did not migrate, 59 out of 195 patients (approximately 30%) had Breast Cancer, while it corresponds to roughly 10% (2 out of 21 patients) of those who did migrate. On the other hand, the proportion of those who did not migrate *versus* those who did goes up to approximately 26% (52 patients) and 33% (7 patients), respectively, for those patients who had Gastrointestinal tumours. We believe that these differences may be due to the higher complexity of the care of some types of tumours such as those of GI origin as compared with breast primaries. Interestingly, Athanasakis et al.[6] mentions that more severe cases tend to migrate hoping for better healthcare services, whereas benign cases tend to stay where they reside. Whether to get treatment or to be close to their relatives, these patients left their homes, characterizing the process of informal migration.

This problem is not restricted to Brazil. In Greece, where there is a health system similar to SUS, a study showed a migratory flow equivalent to 13.4% of all cancer patients in the country in search for better treatment.[6] In addition, a Canadian study has shown that moving to receive oncological treatment has significant economic impacts, in addition to presenting biopsychosocial sequelae for both the patient and his/her caregivers.[7]

Although frequent, there are few studies in the literature addressing this issue. Some papers on the subject worldwide have shown the inequality of cancer treatment access in different countries resulting in a migration process, but do not seem to have reached consensus on the motivations for this migration nor do they agree on the consequences for citizens, although it appears to be harmful.[8-12] The present study showed that about 10% of patients treated in a cancer centre in Brazil were from different regions of the country, demonstrating a social health problem.

The description of the phenomenon of migration in different countries, with different levels of development and distinct cultures, points to the universal problem of inequality between regions of the same country. The origin of the problem may lie in the concentration of wealth in some regions to the detriment of others, which is reflected in the health area.[1] As in previous studies, our results show non-compliance with SUS principles.[13]

The fact that someone who does not live in a certain city intends to live in that municipality so he/she can use its health system is alarming. This causes a cost to that city that was not foreseen in its budget and is a burden to the system, which was not designed to receive an extra number of patients.

Thus, a potential proposal is the creation of a single register for the citizen. The single register would allow the exercise of citizenship, such as the vote in the municipal elections and taxes payment, to be linked to the municipality where the individual lives. The single register could avoid forging documentation and/or providing false home address data, thus avoiding the services burden, both economically and physically.

LIMITATIONS OF THE STUDY

Although other studies relate the socioeconomic condition to the migration process, this relationship was not statistically relevant in our study.[14] However, the study in question was performed in a single centre of reference, reflecting the migratory flow existing only in this region and for a specific specialty (oncology). Overall, more comprehensive national data involving multiple reference centres in oncology could provide more accurate information. The same methodology could be used for other specialties.

CONCLUSION

In the present study we found a migration rate of approximately 10% of patients interviewed, which demonstrates the inequalities in the supply of health services in SUS. Because this situation can have a strong economic and social impact on both the individual need for migration among cancer patients and the municipality, the study in question highlights the need for extending more complex oncological therapies to larger parts of the Country to further decrease human migration.

Summary Box
What is already known on this subject?
It is already known that socioeconomic disparities between regions of the same country lead to people searching for more complex treatments away from their homes
What does this study add?
The study adds data regarding the Brazilian reality on this topic, showcasing its occurrence on a reference centre for cancer treatment
It also highlights the need for restructuring public health policies in Brazil

Data Sharing Statement

There is no additional data to be shared.

Funding and Conflicts of interest

There was no funding for this research. The authors declare not having any conflicts of interest regarding this paper.

Author contribution

Regarding the author's participation in the present study, we declare that:

1) All authors have equally contributed to this paper and data gathering;

2) Authors Daniel Cubero, Claudia Sette and Auro del Giglio were responsible for the supervision of the research and the statistical analysis review;

3) Authors Beatriz Piscopo, Camila Monteiro, Jean Schoueri and Igor Argani were assigned the methodology, review and final writing of the Manuscript;

4) Authors Heloísa Tavares, Marília Garcia and Karoline Passarela were responsible for the initial writing of the paper.

Therefore, all authors have intellectually contributed to the present research.

RESUMO

INTRODUÇÃO: *As disparidades estruturais entre diferentes regiões brasileiras no sistema de saúde pública fazem com que os pacientes migrem em busca de melhores condições para tratar suas doenças. Além do desconforto do paciente, há uma concentração de cuidados em grandes centros, causando sobrecarga da capacidade atual.*

OBJETIVO: *Avaliar o fluxo migratório e fatores associados em um serviço de referência em oncologia.*

MÉTODOS: *Estudo transversal realizado em um serviço de oncologia de referência na região do Grande ABC, em São Paulo. Os pacientes foram entrevistados e dados clínicos e demográficos coletados.*

RESULTADOS: *Entre março e julho de 2016 foram incluídos 217 pacientes. A análise mostrou uma divergência entre o código de endereçamento postal registrado no prontuário médico e o registrado durante a entrevista em aproximadamente 10% dos casos. Desses, 42,9% eram residentes de outros estados. A busca de tratamento motivou a maioria dos pacientes a buscar serviços fora de sua cidade.*

CONCLUSÃO: *Os resultados refletem a busca informal de cuidados médicos fora da área de residência. Além do impacto direto na qualidade de vida dos pacientes, o fluxo migratório tem um impacto econômico-social porque esses pacientes colocam um fardo e impõem custos aos serviços das cidades onde não executam suas responsabilidades como cidadãos. A confirmação da existência de um fluxo migratório significativo demonstra a necessidade de discutir a reestruturação das políticas de saúde pública.*

PALAVRAS-CHAVE: *Migração humana. Neoplasias. Acesso aos serviços de saúde. Política de saúde.*

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ORIGINAL ARTICLE

Effect of generalized ligamentous hyperlaxity related of quality of life in the foot: a case controlled study

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SUMMARY

Generalized ligamentous hyperlaxity (GLH) has been shown to predispose an individual to a number of orthopaedic conditions. Little is known about how GLH affects people' foot health-related quality of life. This study analyses a sample of people with GLH and people without GLH with normalised reference values of the scores collected with regard to using the Foot Health Status Questionnaire (FSHQ). A total of 100 respondents with mean age of 22.69 ± 3.78 years old, who attended a health centre were classified as GLH (n = 50) or non-GLH (n = 50). The GLH was determined of the patients with and without GLH using assessment with Beighton tool and the scores on the FHSQ were compared. The control group recorded higher scores in the First Section for foot pain, foot function and general foot health, and lower scores in footwear. In the Second Section, they obtained higher scores in social capacity and lower scores in physical activity, vigour and general health. Differences between the two groups were evaluated through a t-test for independent samples, showing statistical significance (P<0.001). This study has detected measurable differences of association between GLH (Beighton score ≥4) with impaired quality of life related to foot health.

KEYWORDS: *Foot diseases. Musculoskeletal system. Quality of life.*

INTRODUCTION

Generalized ligamentous hyperlaxity (GLH) is more common in individuals who present a musculoskeletal conditions[1], affecting approximately 5 to 64% of the population[2-4] and its prevalence is higher in African ethnic group and females[1,3,5]. Bin Abd Razak et al.[1] evaluated musculoskeletal problems of patients with GLH compared with subjects without GLH and these patients showed to be 3.35 times more likely to present GLH.

Also, the GLH is characterized by an excessive joint mobility and increased distractibility, beyond the range of motion regarded as normal[6]. In the foot, may be associated with foot pain[7], ankle sprains[8], metatarsalgia[9], pes planus[10], overpronation[11], plan-

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tar fasciitis[12], hallux valgus[13], tarsal tunnel[14] and ingrown nails[15].

Thus, this foot disorders may be associated to high cost, and increase economic burden and are one of the leading motivations for physicians care visits regarding the diagnosis and treatment of their foot problems[16]. Also, the multifactorial aetiology is an important factor that might performance restrict, well-being, mobility and autonomy[17].

Despite this, no studies have been carried out so far to analyse the quality of life related to foot health in population with GLH.

Therefore, this study analyses a sample of people with GLH and people without GLH with normalised reference values of the scores collected with regard to using the Foot Health Status Questionnaire (FSHQ).

MATERIALS AND METHODS

Design and Sample

This is a case-controlled study and a convenience sample method was used to select the participants who gave consent and were enrolled into the research. Records of 17 men and 33 women with GLH (mean ± standard deviation [SD] age, 23.18 ± 3.02 years) and compared with 25 male, and 25 female controls (matched for age and gender) without GLH with normalised reference values, who was carried out in a Clinic of Podiatric Medicine and Surgery that provides treatment of diseases and disorders of the foot at University of Extremadura, in the city of Plasencia (Spain) between October 2015 and September 2016.

The main inclusion criteria included subjects under 40 years old, with availability to work full-time during the research, good patience, communication skills, responsibility, no other lower limb injury or surgery over the last six months preceding and no pregnancy. The exclusion criteria included patients with a history of Marfan's syndrome or Ehlers-Danlos, immunocompromised, neurological condition, rheumatoid or systemic conditions, pharmacotherapy, non- or semi-autonomous in daily activities, and unable to understand instructions relating to the study and/or carry them out.

Procedure:

All examinations, measurements and controls from enrolment using an identical protocol were carried out by the same independent trained clinician. In the first phase, each subject was interviewed and details of medical records were collected including age, gender, previous sporting history, medical history and family history of laxity and musculoskeletal problems were obtained.

In the second phase, anthropometric features, height, weight with the participant barefoot and wearing light clothing was measured, and body mass index (BMI) was calculated from the height (m) and weight (kg^2), applying Quetelet's equation follow BMI=weight / height^2 [18]calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

In the third phase, it determined GLH using the modified Beighton 9-point scoring system [19]. This test is validity for diagnosis of GLH showed high Cohen's kappa values (intraobserver: 0.75; interobserver: 0.78) [2]an overall agreement and a test phase. The subjects were examined following of the five body areas: fifth metacarpophalangeal joint, elbows, knees and trunk. A positive result was recorded if the participant present a cutoff of ≥ 4 hypermobile joints [20,21].

Finally, patients were asked to complete the FHSQ [22]. This validated instrument on health-related quality of life is intended specifically for the foot [23]. FHSQ, scores provide three separate section scores, with four domains or subscales for each section and two composite scores from 0 being the poorest score to 100 being the best score conditions. First section assesses foot pain, foot function, footwear, general foot health and has demonstrated a high degree of content, criterion, construct validity (Cronbach α= 0.89–0.95) and high retest reliability (intraclass correlation coefficient = 0.74–0.92)[22]. Second section looks at general health, physical activity, social capacity and vigour, largely adapted from the Medical Outcomes Study 36-Item Short-Form Health [23], which has demonstrated validated [24]foot function, footwear and general foot health. RESULTS The MID for the VAS using the anchor-based approach was -8 mm (95% CI: -12 to -4. Third section focuses on socio-demographic data such as age, gender and medical record.

Ethical considerations

This research was approved by the Bioethics and Biosafety Committee of the University of Extremadura (Spain), record number: 85/2016. All participants provided informed written consent before being included, and the ethical standards in human experimentation contained in the WMA Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, the UNESCO Universal Dec-

laration on the Human Genome and Human Rights and those of the relevant national agencies and institutions were observed at all times.

Sample size

Having established a minimal difference score of at least 21 (as clinically relevant) among the groups under study in the FHSQ, and considering that the standard deviation on that scale for people is around 29 [25,26], for a bilateral hypothesis, an alpha risk of 5% and a statistical power of 80%, at least 47 cases must be studied in each group with a total population of 94 people. Controls were matched to cases according to age and gender.

Statistical analysis

Population demographic data including age, height, weight, BMI, marital status, level of education and professional activity, and independent variables were summarized as mean and standard deviation (SD), maximum and minimum values and compared between people with and without GLH.

All variables were examined for normality of distribution using the Kolmogorov-Smirnov test, and data were considered normally distributed if $p > 0.05$. Independent Student t-tests were performed to find if differences are statistically significant when showing a normal distribution. Measurements which were not normally distributed were tested using non-parametric Mann-Whitney U test to examine differences between the two groups.

The Foot Health Status Questionnaire Version 1.03 was used to obtain quality of life scores related to foot health. In all of the analyses, statistical significance was established with a p-value < 0.01 with a confidence interval of 99%. All the analyses were performed with commercially available software (SPSS 19.0, Chicago, IL, USA).

RESULTS

All the variables showed a normal distribution (P<0.05) except for BMI and Vigour (P>0.05). Mann-Whitney U tests were used to examine differences between two groups, except for BMI and vigour where independent t student test were applied.

A total of one hundred individuals between 18 and 35 years of age, the mean age being 22.69 ± 3.78 years old, completed the research course. Table 1 shows the sociodemographic characteristics of the participants showing according to GLH. Only a significant difference at Beighton 9-point scoring were found (P<0.01).

Furthermore, as part of their clinical evaluation, fifty subjects met the criteria for GLH and had a Beighton mean score recorded of 6.98 ± 1.635, and the results of a comparison between FHSQ scores of the cases and control groups are shown in table 2. These scores were higher for the control group, in the First section for the foot pain, foot function and general foot health and lower scores in footwear. In the Second section, they obtained higher scores in social capacity and lower scores in physical activity, vigour and general health.

The differences between groups were statistically significant (p=0.001) only for footwear (Figure 1): There were no significant differences for dimensions in the questionnaire that assessed foot pain, foot function, general foot health, general health, physical activity, social capacity and vigour (P>0.01).

DISCUSSION

Persons with or without GLH require a complete musculoskeletal examination that should include a specific assessment of feet because of factors present in the foot that allow the detection of this problem [27].

Thus, in this study, we analyse a sample of people with GLH and people without GLH with normalised

TABLE 1 – SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE POPULATION.

	Total Group Mean ± SD Range N= 100	GLH Mean (SD) Range N= 50	Non-GLH Mean (SD) Range N= 50	P Value
Age, years	22.87 ± 3.16 (18-35)	23.18 ± 3.01 (18-35)	22.56 ± 3.31 (18-35)	0.191
Weight (kg)	68.71 ± 12.32 (47-105)	64.86 ± 11.69 (48-95)	68.56 ± 12.77 (47-105)	0.129
Height (cm)	160.00 ± 0.16 (150-193)	168.26 ± 8.32 (156-186)	170.04 ± 1.03 (150-193)	0.394
BMI (kg/m2)	23.19 ± 3.03 (17.68 – 31.86)	22.79 ± 2.99 (18.50 - 31.86)	23.58 ± 3.05 (17.69 - 30.79)	0.135
Beighton 9-point scoring	3.91 ± 3.36 (0.00 – 9.00)	6.98 ± 1.63 (4.00 – 9.00)	0.84 ± 0,95 (0.00 – 3.00)	<0.001
Marital status	1.39 ± 1.11 (1-5)	1.58 ± 1.31 (1-5)	1.20 ± 0.81 (1-5)	0.066
Level of education	3.35 ± 0.63 (2-5)	3.40 ± 0.67 (2-5)	3.30 ± 0.58 (2-5)	0.386
Professional activity	1.14 ± 0.493 (1-3)	1.66 ± 0.479 (1-3)	1.04 ± 0.28 (1-3)	0.029

Abbreviations: BMI, body mass index; SD, standard deviation; GLH, generalized ligamentous hyperlaxity. In all the analyses, P < .01 (with a 99% confidence interval) was considered statistically significant.

reference values of the scores collected with regard to using the FSHQ. We found, for the first time in the control group that recorded higher scores in the First Section for foot pain, foot function and general foot health and lower scores in footwear that in the group of GLH.

These results suggest that GLH is related with more foot pain, greater restrictions in terms of footwear and they consider that their feet are in a worse state of foot health and may favour the presence of a number of foot pathologies [28]however, its association with musculoskeletal pain remains controversial. There is lack of data from developing countries like India. This study aimed to look at the prevalence of musculoskeletal complaints and hypermobility in Indian school children. METHODS This was a cross-sectional, school-based study. Initially, a questionnaire regarding musculoskeletal pain was filled in by the schoolchildren (or their parents.

Also, in the Second Section in the control group, they obtained higher scores in social capacity and lower scores in physical activity, vigour and general health and this findings are different from other studies linking GLH to poor health-related quality of life [29,30]to compare these with other chronic paediatric conditions and to determine whether symptoms experienced by children with JHS can predict their HRQOL. METHODS Eighty-nine children with JHS and one of their parents completed

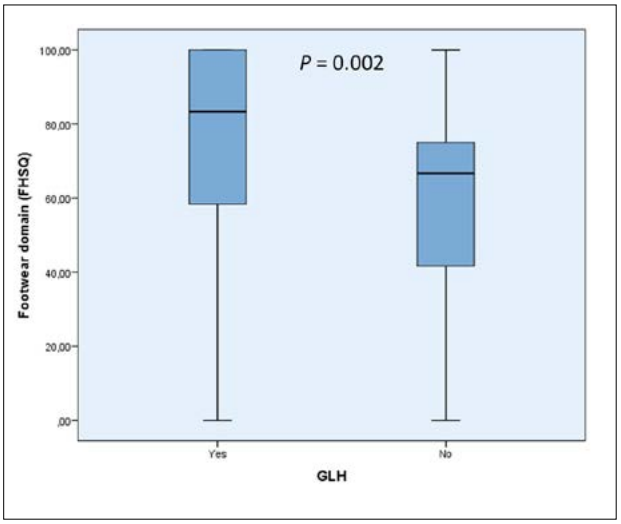

FIGURE 1. Box-plot to illustrate the footwear domain differences of the FHSQ between subjects with and without GLH. Abbreviations; FHSQ, Foot Health Status Questionnaire (FHSQ); GLH, Generalized ligamentous hyperlaxity.

the Pediatric Quality of Life Inventory 4.0 Generic Core Scale, the Multidimensional Fatigue Scale and the Pediatric Pain Questionnaire. Anthropometric measures and reported symptoms were recorded. Child-reported HRQOL scores were compared with parent report, and both child- and parent-reported HRQOL scores of children with JHS were compared with those of children with other chronic conditions. Stepwise multiple regression was undertaken to determine whether any combination of measures could predict HRQOL. RESULTS Parent- and child-reported HRQOL scores were strongly correlated (r = 0.6-0.84, all P < 0.001.

We acknowledge that the present research has limitations. Notably, this study included a larger number of participants from various countries; random sample size would be beneficial to improve the strength of the study. In addition, even though sample size calculation was carried out, the consecutive sampling bias should be considered and a simple randomization sampling process could be more adequate for future studies. Finally, it should be determined other variables such as shoe wearing or socioeconomic status on impact of GLH related of quality of life. This highlights the need for regular foot care and monitoring in people with GLH.

TABLE 2 – COMPARISONS OF FHSQ SCORES FOR THE CASE AND CONTROL GROUPS.

	Total Group Mean ± SD Range N= 100	GLH Mean (SD) Range N= 50	Non-GLH Mean (SD) Range N= 50	P Value
Foot Pain	81.86 ± 15.51 (40.62-100)	81.67 ± 17.48 (40.62-100)	82.05 ± 13.43 (41.25-100)	0.539
Foot Function	89.63 ± 15.03 (43,75-100)	89.25 ± 15.42 (43.75-100)	90.00 ± 14.78 (25-100)	0.729
Footwear	67.42 ± 29.61 (0-100)	74.67 ± 30.54 (0-100)	60.17 ± 27.06 (0-100)	0.002
General Foot Health	65.87 ± 21.43 (0-100)	65.10 ± 25.00 (0-100)	66.65 ± 17.38 (10-100)	0.912
General Health	75.50 ± 23.19 (0-100)	77.00 ± 22.24 (0-100)	74.00 ± 24.24 (0-100)	0.443
Physical Activity	93.28 ± 9.58 (61.11-100)	94.44 ± 8.02 (61.11-100)	92.11 ± 10.89 (61.11-100)	0.379
Social Capacity	86.63 ± 20.2 (0-100)	86.25 ± 23.72 (0-100)	87.00 ± 16.16 (50-100)	0.432
Vigour	63.81 ± 16.93 (12.5-100)	64.00 ± 17.66 (12.50-100)	63.62 ± 16.35 (25-100)	0.922

Abbreviations: FHSQ, Foot Health Status Questionnaire; SD, standard deviation; GLH, generalized ligamentous hyperlaxity. In all the analyses, P < .01 (with a 99% confidence interval) was considered statistically significant.

CONCLUSIONS

This research identified measurable differences of association between GLH (Beighton score ≥4) with

impaired quality of life related to foot health. Our findings suggest a negative impact on the quality of life related to foot health which appears to be associated with the GLH.

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RESUMO

*A hiperlaxia ligamentosa generalizada (HLG) demonstrou predispor um indivíduo a várias condições ortopédicas. Pouco se sabe sobre como a HLG afeta a qualidade de vida relacionada à saúde do pé das pessoas. Este estudo analisa uma amostra de pessoas com HLG e pessoas sem HLG com valores de referência normalizados das pontuações coletadas no que diz respeito ao Foot Health Status Questionnaire (FSHQ). Um total de 100 informantes com média de idade de 22,69 ± 3,78 anos que eram atendidos em um centro de saúde foi classificado como HLG (n = 50) ou não HLG (n = 50). A HLG foi determinada com os pacientes com e sem HLG usando a ferramenta Beighton e os escores na FHSQ foram comparados. O grupo de controle registrou pontuações mais altas na primeira seção para a dor no pé, função do pé e saúde geral do pé, e menores pontuações no calçado. Na segunda seção obtiveram maiores escores em capacidade social e menores escores em atividade física, vigor e saúde geral. As diferenças entre os dois grupos foram avaliadas por meio de um teste **t** para amostras independentes, mostrando significância estatística (P<0,001). Este estudo detectou diferenças mensuráveis de associação entre HLG (pontuação de Beighton≥4) com deterioração da qualidade de vida relacionada à saúde dos pés.*

PALAVRAS-CHAVE: *Doenças dos pés. Sistema musculoesquelético. Qualidade de vida.*

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ORIGINAL ARTICLE

Home-based exercise therapy for treating non-specific chronic low back pain

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SUMMARY

OBJECTIVE: *To evaluate pain, functional capacity, and quality of life of patients with non-specific chronic low back pain, after home-based exercise therapy with different kinds of supervision.*

METHOD: *Thirty individuals of both gender, between 18 and 65 years old, performed the proposed exercises three times a week, for eight weeks. Group A (N = 17) performed the exercises after a single supervised session. Group B (N = 13) was supervised once a week at the rehabilitation center. Both groups received a booklet with instructions, and questionnaires to evaluate pain, functional capacity and quality of life; during the initial evaluation, after four and eight weeks.*

RESULTS: *There was an improvement in pain and functional capacity between the initial evaluation and week 4, and the initial evaluation and week 8 in both groups ($p < 0.05$). In the quality of life evaluation, the criteria for pain, functional capacity, and physical aspects had significant improvement after 8 weeks ($p < 0.05$). There was no difference when comparing groups A and B ($p > 0,05$).*

CONCLUSION: *Home-based exercise therapy, when performed in a period of eight weeks, using the booklet, was effective for improving level of pain, functional capacity, and quality of life in patients with non-specific chronic low back pain. The weekly supervision did not significantly influence the final outcome between the groups.*

KEYWORDS: *Low back pain. Exercise therapy. Paraspinal muscles. Abdominal muscles.*

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INTRODUCTION

Non-specific chronic low back pain (NSCLP) is defined by a symptom of pain or discomfort from the lower costal arches to the gluteal sulcus that lasts for at least 12 weeks and may be accompanied by irradiation to the lower limbs. The unspecific nature of the symptom may be related to a muscle-ligament source, associated with quality of life, psychological, or physical factors. However, it is not possible to state with full certainty the anatomical structure responsible for the symptom.[1,2]

The dysfunction of back muscles responsible for stabilization and coordination is considered to be the primary cause for NSCLP.[3,4] Poor muscle resistance and changes in the neuromuscular control affect the stability of the trunk, the efficiency of movement, and the balance of the entire local musculature, which can lead to a mechanical overload in other structures, such as discs, facet joints, vertebral body, an adjacent muscle groups.

Prescription of supervised exercises is recommended as first-line treatment for NSCLP. However, the availability of secondary rehabilitation centers in the public health system is insufficient to meet the demand of these patients.[6,7]

Since NSCLP cases do not present neurological deficit or clinical signs indicative of fracture, tumor, or infection, they are considered less severe and qualify for treatment in Basic Health Units, with a multi-professional approach by means of ergonomics guidance, posture training, workplace, and home exercises. The major challenge with that type of intervention is the adherence and discipline of the patients to the proposed treatment, with no supervision.[7,9]

The objective of this study was to assess the pain, functional capacity, and quality of life of patients with non-specific chronic low back pain after a home exercise program.

METHODOLOGY

Study design

A non-randomized clinical trial with unblinded assessment, conducted from April 2016 to April 2017 at the Spine Clinic of the Sports Injury Center of the São Paulo Federal University, Brazil (Cete-Unifesp).

The study was approved by the research ethics committee, N° CEP: 1527/2015, registered under *Universal Trial Number* (UTN): U1111-1185-1871.

Sample size calculation

The sample size calculation was based on a pilot study conducted with 14 individuals, eight of them part of Group A (home) and six part of Group B (weekly supervision).

A significant improvement in the Roland Morris scale, between the initial assessment and after eight weeks, was chosen as the primary parameter for the sample size calculation.

Using the sample size calculation formula for paired means, with bilateral significance threshold set at 5% and a power of 99%, we found significant variation only in Group A, and it was necessary to have at least 12 individuals in Group B to show significant variation.[10]

Population

Thirty patients with NSCLP from the Spine Clinic were selected, after a medical assessment, to participate in the study.

The inclusion criteria were: age between 18 and 65 years; both gender; having lumbar pain with no specific cause for over 12 weeks; having front and lateral lumbosacral x-rays; agree to participate in the study by reading and signing the informed consent form (ICF).

The exclusion criteria were: pregnancy; radiographic changes (fractures, deformities, spondylolisthesis, and tumors); prior surgical procedure in the spine; clinical symptoms of neural compression; any other disease that can cause back pain.

Intervention

After the initial medical assessment and inclusion into the study, the participants were arranged in two unblinded groups, according to their availability to get to the Rehabilitation Center: Group A (N=17), exercise therapy with no weekly supervision; and Group B (N=13) with weekly supervision.

Patients in both groups carried out exercise therapy for eight weeks. Each session included 10 minutes of aerobic activity (walking or stationary bicycle), followed by five types of muscle stretches and eight types of ground exercises aimed at strengthening the lumbar muscles responsible for stabilization (Figure 1).

After initial guidance, individuals in Group A carried out three home training sessions, unsupervised, for each week. Individuals in Group B also carried out three sessions per week – two at home and one

supervised by the physical therapist at the rehabilitation center. Both groups received a booklet with instructions.

Data collection instruments

The participants of the study filled out the Pain Numerical Rating Scale – PNRS, Roland Morris (RM)[11] and Short Form-36 (SF-36)[12] questionnaires, translated and validated into Portuguese, at the initial assessment and after four and eight weeks.

In order to control adhesion, the participants were instructed to take note on the booklet of the dates when the sessions were carried out.

Statistical analysis

The scores from the questionnaires were analyzed using models of generalized estimating equation (GEE)[13], considering the relationship between the different assessments of the same patient. We included in these models the effects of the exercises in the group (A or B), the time of assessment (initial, week 4, and week 8), and the interaction between group/time.

The results were presented through estimated means with confidence intervals of 95% (CI95%). The comparison between groups and times of assessment were presented through estimated mean differences and its respective CI95%, and p values were corrected using Bonferroni.

The models were adjusted with Normal, Gamma, or Poisson distribution, seeking to find the one that provided lower residuals. The analyses were conducted using the SPSS® software, version 18, with the significance level set at 5%.

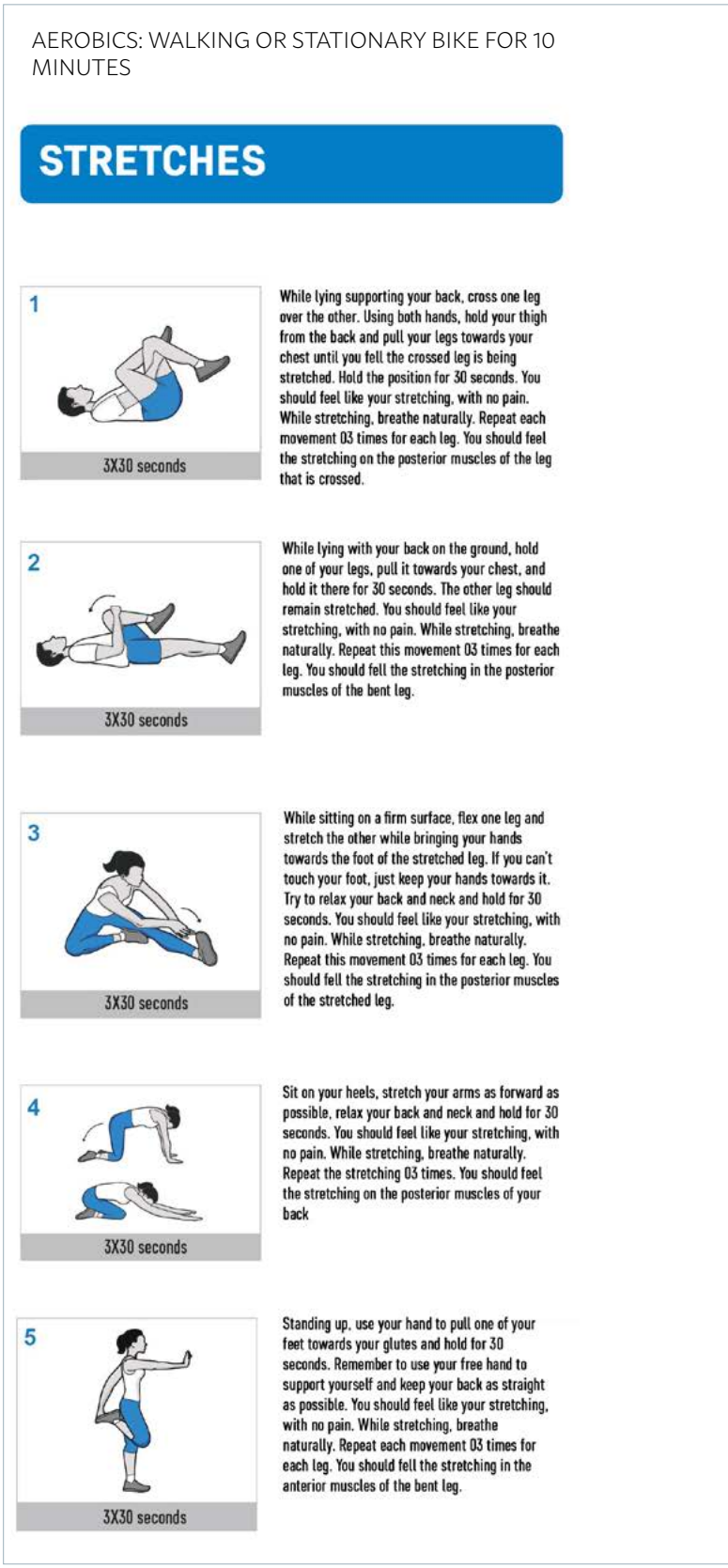
RESULTS

Individuals in Group B were more assiduous to the home exercise sessions prescribed – they carried out an average of 13.6 of the 16 sessions; participants in Group B carried out an average of 13.9 out of 24. There was a higher proportion of male individuals in Group A (12M:5F), in relation to Group B (6M:7F).

After analyzing the scores from the Pain Numerical Rating Scale (PNRS), we found evidence of reduction in scores between the initial assessment and week 4 in groups A (p=0.036) and B (p=0.025), and between the initial assessment and week 8 in groups A (p=0.036) and B (p<0.001) (Table 1).

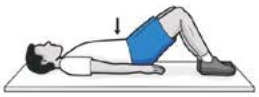
As for the score from the Roland Morris Scale

FIGURE 1: HOME EXERCISE PROGRAM BOOKLET (FRONT), DESCRIPTION OF THE STRETCHES AND MUSCLE-RECRUITMENT EXERCISES.



MUSCLE-RECRUITMENT

1



10X10 seconds

Lying down with your back well-supported, bend your knees and keep your shoulders relaxed. Using your abdomen muscles (without putting to much strength in them), pull in your navel as if trying to make it touch the ground. Once it is pulled in, hold the position for 10 seconds. Repeat the movement 10 times a day.

2

3x30 seconds (15 seconds min.)

Lie on your stomach with your forearms resting on the ground and your elbows well below your shoulders. Carry out exercise 01 (pull navel in) and lift your knees off the floor until they are straight. Keep your back straight and hold that position for 15-30 seconds (as long as you can). If it is too difficult, keep your knees on the ground and just raise your hips, keeping your back straight. It is important that you maintain your abdomen contracted and your navel pulled in for the entire duration of the exercise. Repeat the movement 03 times.

3

3x30 seconds (15 seconds min.)

On a surface that is comfortable for your knees, position yourself on your hands and knees, keeping your back straight. Carry out exercise 01 (pull navel in) and then straighten the left knee up to your hips and the right arm up to your shoulders. Hold the position for 15-30 seconds (as long as you can). Return to the initial position. Straighten the right knee and the left arm and hold for another 15-30 seconds. It is important that you maintain your abdomen contracted and your navel pulled in for the entire duration of the exercise. Repeat the exercise 03 times.

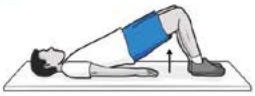
4

3x15 repetitions

While lying with your back well-supported, bend your knees. Place a soft ball or pillow between your legs and press it while, at the same time, tightening the pelvic muscles, as if trying to "hold in pee."

It is important to "hold in pee" every time you press the ball between your knees. Carry out 03 series of 15 repetitions.

5



3x30 seconds (15 seconds min.)

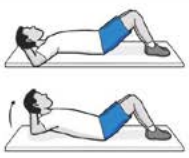
Lie on your back with your knees bent. Carry out exercise 01 (pull navel in) and raise your hips until your back is straight, forming a line between your knees and shoulders. Hold the position for 15-30 seconds (as long as you can). It is important that you maintain your abdomen contracted and your navel pulled in for the entire duration of the exercise. Repeat the movement 03 times.

6

3x30 seconds (15 seconds min.)

Lying on your side with your elbow aligned with your shoulder and your forearm resting on the ground, carry out exercise 01 (pull navel in) and raise your hips until your body is well stretched, forming a line from your feet to your shoulder. Hold that position for 15-30 seconds (as long as you can). It is important that you maintain your abdomen contracted and your navel pulled in for the entire duration of the exercise. Repeat this movement 03 times for each side.

7

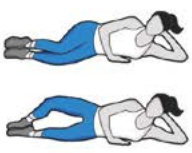


3x10-15 repetitions

Lying on your back, bend your knees and put your hands behind your head, raising your trunk until your shoulders are off the ground. Try to keep your back on the ground while doing this exercise.

Carry out 03 series of 10 or 15 repetitions.

8



3x10-15 repetitions

Lying on your side with your knees bent, move your knees away from each other by rotating or opening and closing or legs.

It is important that you keep your feet together during the exercise. Repeat the exercise on both sides, with 03 series of 5 repetitions.

TABLE 1. ANALYSIS BETWEEN GROUPS: ESTIMATED MEANS AND CONFIDENCE INTERVALS OF 95% FOR OUTCOMES IN THE INITIAL, WEEK 4, AND WEEK 8 ASSESSMENTS

Variables	Group A N= 17	p	Group B N= 13	p
PNRS				
Baseline and 4 weeks	0.9 (0.3;1.5)	p=0.036	1.7 (0.5;2.8)	p=0.025
Baseline and 8 weeks	1.5 (0.5;2.4)	p=0.011	2.0 (1.2;2.8)	p<0.001
4 weeks and 8 weeks	0.6 (-0.1;1.3)	p=0.521	0.3 (-0.4;1.0)	p>0.999
Roland Morris				
Baseline and 4 weeks	2.5 (1.4;3.5)	p<0.001	1.6 (0.8;2.4)	p=0.001
Baseline and 8 weeks	3.6 (1.9; 5.4)	p<0.001	2.8 (1.5;4.0)	p<0.001
4 weeks and 8 weeks	1.2 (0.1; 2.3)	p=0.225	1.2 (0.5; 1.9)	p=0.008
SF-36				
Functional capacity				
Baseline and 4 weeks	-5.6 (-10.0; -1.1)	p=0.084	-6.2 (-9.6; -2.8)	p=0.002
Baseline and 8 weeks	-9.7 (-15.6; -3.9)	p=0.007	-9.2 (-12.4; -6.1)	p<0.001
4 weeks and 8 weeks	-4.1 (-7.0; -1.3)	p=0.028	-3.1 (-6.4; 0.2)	p=0.402
Physical aspects				
Baseline and 4 weeks	-7.4 (-18.7; 4.0)	p>0.999	-38.5 (-57.4 -19.5)	p<0.001
Baseline and 8 weeks	-25.0 (-40.8; -9.2)	p=0.011	-42.3 (-61.8; -22.8)	p<0.001
4 weeks and 8 weeks	-17.6 (-29.0; -6.3)	p=0.014	-3.8 (-16.7; 9.0)	p>0.999
Pain				
Baseline and 4 weeks	-12.9 (-20.2; -5.6)	p=0.003	-15.2 (-23.1; -7.4)	p=0.001
Baseline and 8 weeks	-20.5 (-28.9; -12.0)	p<0.001	-20.0 (-30.7; -9.3)	p=0.001
4 weeks and 8 weeks	-7.6 (-12.2; -2.9)	p=0.009	-4.8 (-12.7; 3.2)	p>0.999
Overall health condition				
Baseline and 4 weeks	-2.5 (-6.3; 1.3)	p>0.999	6.5 (-11.9; -1.2)	p=0.101
Baseline and 8 weeks	-4.2 (-8.8; 0.5)	p=0.479	-5.0 (-12.5; 2.5)	p>0.999
4 weeks and 8 weeks	-1.7 (-4.4; 0.9)	p>0.999	1.5 (-13.8; 10.8)	p>0.999
Vitality				
Baseline and 4 weeks	-6.8 (-15.4; 1.9)	p=0.746	-3.8 (-10.2; 2.5)	p>0.999
Baseline and 8 weeks	-8.5 (-18.0; 0.9)	p=0.457	-6.9 (-13.6; -0.2)	p=0.258
4 weeks and 8 weeks	-1.8 (-5.0; 1.5)	p>0.999	-3.1 (-6.9; 0.7)	p=0.661
Social aspects				
Baseline and 4 weeks	-2.3 (-7.3; 2.8)	p>0.999	3.0 (-7.1; 13.0)	p>0.999
Baseline and 8 weeks	-7.4 (-15.5; 0.7)	p=0.441	0.1 (-10.9; 11.1)	p>0.999
4 weeks and 8 weeks	-5.1 (-9.7; -0.6)	p=0.159	-2.9 (-12.9; 7.2)	p>0.999
Emotional aspects				
Baseline and 4 weeks	-7.8 (-23.7; 8.1)	p>0.999	-5.2 (-23.8; 13.3)	p>0.999
Baseline and 8 weeks	-19.5 (-35.9; -3.2)	p=0.117	-18.0 (-38.9; 2.8)	p=0.540
4 weeks and 8 weeks	-11.7 (-19.3; -4.2)	p=0.014	-12.8 (-26.2; 0.5)	p=0.359
Mental health				
Baseline and 4 weeks	-2.8 (-7.9; 2.2)	p>0.999	-1.9 (-6.9; 3.1)	p>0.999
Baseline and 8 weeks	-5.9 (-9.5; -2.2)	p=0.009	-3.8 (-9.1; 1.6)	p>0.999
4 weeks and 8 weeks	-3.1 (-7.4; 1.3)	p>0.999	-1.8 (-3.9; 0.2)	p=0.440

Estimated mean differences and confidence intervals of 95%. PNRS: Pain Numerical Rating Scale

(RM) for functional capacity, we found evidence of reduction in scores between the initial assessments and week 4 in groups A (p<0.001) and B (p=0.001), between the initial assessments and week 8 in groups A (p<0.001) and B (p<0.001), and between the week 4 and 8 assessments in Group B (p=0.008) (Table 1).

The analysis of the score progression for SF-36 was described separately for eight domains. Functional capacity: We found evidence of an increase in scores between the initial and week 4 assessments in Group B (p=0.002), between the initial and week 8 assessments in groups A (p=0.007) and B (p<0.001), and between the week 4 and 8 assessments in Group A (p=0.028). Physical aspects: We found evidence of an increase in scores between the initial assessments and week 4 in Group B (p<0.001), between the initial assessments and week 8 in groups A (p=0.011) and B (p<0.001), and between week 4 and 8 assessments in Group A (p=0.014). Pain: We found evidence of an increase in scores between the initial assessments and week 4 in groups A (p=0.003) and B (p=0.001), between the initial assessments and week 8 in groups A (p<0.001) and B (p=0.001), and between the week 4 and 8 assessments in Group A (p=0.009). Overall health condition: We found no evidence of variation in the scores between the assessments in Groups A (p>0.05 in all comparisons) and B (p>0.05 in all comparisons). Vitality: We found no evidence of variation in scores between assessments in Groups A (p>0.05 in all comparisons) and B (p>0.05 in all comparisons). Social aspects: We found no evidence of variation in the scores between the assessments in Groups A (p>0.05 in all comparisons) and B (p>0.05 in all comparisons). Emotional aspects: We found evidence of an increase in scores between the week 4 and 8 assessments in Group A (p=0.014). Mental health: We found evidence of an increase in scores between the initial and week 8 assessments in Group A (p=0.009) (Table 1).

We found no evidence of differences when comparing the groups in all three assessments (p>0.05) (Table 2).

TABLE 2. ANALYSIS INSIDE GROUPS: ESTIMATED MEANS AND CONFIDENCE INTERVALS OF 95% FOR OUTCOMES IN THE INITIAL, WEEK 4, AND WEEK 8 ASSESSMENTS, WITH A COMPARISON BETWEEN GROUPS

Variables	Group A vs. Group B	p
PNRS		
Baseline	0.4 (-1.9; 1.2)	p>0.999
4 weeks	-1.2 (-2.7; 0.4)	p=0.408
8 weeks	-0.9 (-2.3; 0.5)	p=0.655
Roland Morris		
Baseline	-1.1 (-5.0; 2.8)	p>0.999
4 weeks	-0.3 (-3.9; 3.4)	p>0.999
8 weeks	-0.2 (-3.8; 3.3)	p>0.999
SF-36		
Functional capacity		
Baseline	3.3 (-10.5; 17.1)	p>0.999
4 weeks	3.9 (-8.5; 16.3)	p>0.999
8 weeks	2.9 (-9.4; 15.1)	p>0.999
Physical aspects		
Baseline	-18.2 (-45.1; 8.7)	p=0.554
4 weeks	12.9 (-13.6; 39.4)	p>0.999
8 weeks	-0.9 (-24.6; 22.8)	p>0.999
Pain		
Baseline	9.8 (-6.5; 26.0)	p=0.714
4 weeks	12.1 (-3.1; 27.3)	p=0.355
8 weeks	9.3 (-5.8; 24.4)	p=0.682
Overall health condition		
Baseline	-2.3 (-13.0; 8.4)	p>0.999
4 weeks	1.8 (-9.0; 12.5)	p>0.999
8 weeks	-1.5 (-13.8; 10.8)	p>0.999
Vitality		
Baseline	0.5 (-14.3; 13.4)	p>0.999
4 weeks	-3.4 (-15.6; 8.8)	p>0.999
8 weeks	-2.1 (-14.3; 10.2)	p>0.999
Social aspects		
Baseline	3.2 (-11.2; 17.7)	p>0.999
4 weeks	-2.0 (-17.6; 13.6)	p>0.999
8 weeks	-4.3 (-18.2; 9.7)	p>0.999
Emotional aspects		
Baseline	0.6 (-23.7; 24.9)	p>0.999
4 weeks	-2.0 (-25.8; 21.8)	p>0.999
8 weeks	-0.9 (-20.9; 19.1)	p>0.999
Mental health		
Baseline	0.4 (-9.3; 10.1	p>0.999
4 weeks	-0.5 (-12.2; 11.2)	p>0.999
8 weeks	-1.7 (-12.6; 9.2)	p>0.999

Estimated mean differences and confidence intervals of 95%. PNRS: Pain Numerical Rating Scale

DISCUSSION

It is well established in the Literature that exercise-based treatment for NSCLP is effective. However, there is no consensus on the best models.[6,14]

The study by Chang et al.[15] showed that exercises focused in strengthening and activation of deep trunk muscles were superior in comparison with other exercises.

The selection of exercises for this study also took into account their applicability in a home environment, simplicity, and focus on activating the deep trunk muscles, as shown in the electromyography-based study by Okubo et al.[16]

Of the targeted muscles, the rotatores, which are directly connected to each vertebral segment, the transverse abdominal muscle, and the internal oblique, which provide segmental stabilization to the spine during contraction, are considered primary stabilizers. These muscles act in synergy, forming a co-contraction mechanism; thus, allowing the individual to be prepared to handle impact during functional activities without overloading the adjacent structures.[17,18]

The choice of the age range for participants (18-65 years old), as well as the indifference regarding gender, was based in similar previous studies and had no influence on the treatment prescribed.[19-21] Some participants, especially the older ones, found it difficult to carry out some exercises. In those cases, they were instructed to follow an adapted version of the exercise.

Confirming the finding previously described on home exercise programs, the booklet and low complexity of exercises seemed to contribute to a zero abandonment throughout the eight weeks.[8,9,22]

Individuals in Group A were less disciplined regarding the number of sessions carried out, showing that the weekly assistance and guidance of the physical therapist were important to improve adhesion to the program. However, there was no significant difference in the comparison between groups, indicating the effectiveness of unsupervised exercise therapy.

There is no recommendation concerning the ideal duration of an exercise program for NSCLP treatment.[6,14] Our study found significant improvement when comparing most of the initial parameters with those from week 4 and 8; however, that was not what happened in the comparison between week 4 and 8, indicating a stabilization of the parameters. Medium and long-term follow up of these patients will help determine the duration of improvement, in addition to verifying if participants will continue to carry out the exercises on their own.

The study assessed the effect of home exercise programs in NSCLP comparing initial parameters with those from week 4 and 8. Other studies have shown the advantages of home exercise programs in comparison to other types of therapy, such as the use of anti-inflammatory drugs.[14,23]

The method used to analyze the improvement of symptoms was based on self-administered questionnaires. Studies that used ultrasound and electromyography to assess hypertrophy and activation of trunk muscles after exercises also found positive results.[24]

Low back pain is an extremely common problem that affects around 70% of the adult population and represents the second most frequent reason for seeking medical assistance. It needs to be seen as a public health issue, and it is of the utmost importance for general physicians or specialists, to know how to treat and guide these patients adequately.[25]

The improvement in levels of pain, functional capacity, and quality of life obtained from home exercise programs confirm the theory that cases of NSCLP with lower complexity can be treated and prevented in Basic Health Units. They do not require complex facilities or continuous supervision by a physical therapist, so other health professionals, with adequate training, can apply exercise therapy, lowering costs and preventing an overload of secondary rehabilitation centers, which then would be able to focus in more severe cases, such as of patients with neurological deficit and post-operative.[7]

Individuals with time restrictions or difficulty in traveling to physical therapy centers can also benefit from partially-supervised rehabilitation programs, provided they have some instrument to guide them during treatment.

Study limitations

It was not possible to blind the physical therapist that supervised the Group B sessions, nor to randomize the grouping of individuals, due to the nature of the intervention and availability of participants. Furthermore, the participants were responsible for controlling the frequency of sessions, which generates a risk of bias.

CONCLUSION

Therapy through home exercise programs, when conducted for 8 weeks, with the assistance of a booklet, was effective for improving levels of pain, functional capacity, and quality of life, in patients with NSCLP. The weekly supervision by the physical therapist had no significant impact on the final results when comparing both groups.

RESUMO:

OBJETIVO: *Avaliar dor, capacidade funcional e qualidade de vida de pacientes com dor lombar crônica inespecífica após terapia por exercícios domiciliares, com diferentes maneiras de supervisão.*

MÉTODO: *Trinta indivíduos de ambos os sexos, com idade entre 18 e 65 anos, apresentando dor lombar crônica inespecífica, realizaram os exercícios propostos três vezes por semana, durante oito semanas. Indivíduos do Grupo A (N=17) realizaram os exercícios após única sessão supervisionada. Já os indivíduos do Grupo B (N=13) foram supervisionados uma vez por semana no centro de reabilitação. Ambos receberam cartilha com orientações e questionários para avaliar dor, capacidade funcional e qualidade de vida; durante avaliação inicial, após quatro e oito semanas.*

RESULTADOS: *Houve melhora da dor e capacidade funcional entre as avaliações inicial e semana 4, e inicial e semana 8 nos dois grupos (p<0,05). Na avaliação de qualidade de vida (SF-36), os critérios de dor, capacidade funcional e aspectos físicos obtiveram melhora significativa após oito semanas (p<0,05). Não houve diferença significativa ao comparar os grupos (p>0,05).*

CONCLUSÃO: *A terapia por exercícios domiciliares, quando realizada num período de oito semanas, com auxílio da cartilha, foi eficaz para melhora da dor, capacidade funcional e qualidade de vida, em pacientes com dor lombar crônica inespecífica. A supervisão semanal não influenciou de forma significativa o resultado final quando comparados os grupos.*

PALAVRAS-CHAVE: *Dor lombar. Terapia por exercício. Músculos paraespinais. Músculos abdominais.*

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ORIGINAL ARTICLE

Palliative approach in acute neurological events: a five-year study

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SUMMARY

INTRODUCTION: *Acute neurological illness often results in severe disability. Five-year life expectancy is around 40%; half the survivors become completely dependent on outside help.*

OBJECTIVE: *Evaluate the symptoms of patients admitted to a Hospital ward with a diagnosis of stroke, subarachnoid hemorrhage or subdural hematoma, and analyze the role of an In-Hospital Palliative Care Support Team.*

MATERIAL AND METHODS: *Retrospective, observational study with a sample consisting of all patients admitted with acute neurological illness and with a guidance request made to the In-Hospital Palliative Care Support Team of a tertiary Hospital, over 5 years (2012-2016).*

RESULTS: *A total of 66 patients were evaluated, with an age median of 83 years old. Amongst them, there were 41 ischaemic strokes, 12 intracranial bleedings, 12 subdural hematomas, and 5 subarachnoid hemorrhages. The median of delay between admission and guidance request was 14 days. On the first evaluation by the team, the GCS score median was 6/15 and the Palliative Performance Scale (PPS) median 10%. Dysphagia (96.8%) and bronchorrhea (48.4%) were the most prevalent symptoms. A total of 56 patients had a feeding tube (84.8%), 33 had vital sign monitoring (50.0%), 24 were hypocoagulated (36.3%), 25 lacked opioid or anti-muscarinic therapy for symptom control (37,9%); 6 patients retained orotracheal intubation, which was removed. In-hospital mortality was 72.7% (n=48).*

DISCUSSION AND CONCLUSION: *Patients were severely debilitated, in many cases futile interventions persisted, yet several were under-medicated for symptom control. The delay between admission and collaboration request was high. Due to the high morbidity associated with acute neurological illness, palliative care should always be timely provided.*

KEYWORDS: *Palliative care. Stroke. Cerebrovascular disorders.*

INTRODUCTION

Acute neurological pathologies usually affect several dimensions of the human being: their identity, cognition, and communication. Due to their natural severity, they often result in death, and the vast disability that derives from them often prevents the patient from making decisions regarding their own treatment[1].

The majority of in-hospital deaths of hospitalized patients with cerebrovascular accidents (CVA) or traumatic brain injury happens after a clinical decision of limiting or suspending life support therapies[2-4]. These decisions are, frequently, the result of complex and multidisciplinary discussions that involve setting a prognosis, a medical opinion, pref-

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erences of the patient and/or family, institutional regulations, and social values.

Therapeutic restrictions for patients of cute neurological events are different from those adopted for chronic diseases since the continued maintenance of the treatment can often increase survival by months or years; however, it can also perpetuate a level of disability that might not be desired[5,6]. The uncertainty that surrounds the circumstances of death, the difficulty in establishing a prognosis, and the concern in "prematurely" discontinuing active interventions with healing intent are the main factors responsible for the late introduction of palliative care for patients with acute neurological events[7]. In fact, 1-year mortality is around 11% after lacunar stroke, 16% after partial anterior circulation infarct, 19% after posterior infarct, 60% after total anterior circulation infarct, and 62% after intracerebral hemorrhage. SFive-year survival rates following an acute neurological event are around 40%, with half of the survivors facing disability and becoming entirely reliant on others[8].

Most patients who survive an acute neurological event and are discharged from hospital, develop persistent symptoms that require specialized care; the most frequent are pain (in up to 50% of patients within six months after the event), more specifically, central post-stroke pain and hemiplegic omalgia; fatigue (in over 50% of patients); fecal incontinence (50% during the acute stage; only 10% to 20% at the end of six months); vascular epilepsy with seizures (5% to 12%); psychological symptoms, such as depression (at least 33%), anxiety (20%) and delirium (10%-48%, particularly in older patients and with more prolonged hospitalizations)[9,10].

The purpose of this study is to assess the intervention of an In-hospital Team for Palliative Care Support (IHTPCS) in the approach of patients with a CVA, SAH, or SDH, interaction with medical assistant teams and evaluating the IHTPCS's impact on symptom control.

MATERIAL AND METHODS

A retrospective observational study of all patients with a primary diagnosis of acute neurological event (CVA, ICH, SAH, or SDH) with a request for collaboration to the IHTPCS of a tertiary hospital over a period of five years (2012-2016) We collected information concerning patients symptoms upon the IHTPCS's assessment by means of a specific questionnaire designed and filled out by the this data was then digitally stored. In order to quantify pain, for patients aware an able to communicate, a numerical scale was applied; for those unable to communicate, the Pain Assessment in Advanced Dementia (Painad) scale was used. We extracted data relating to therapy in progress by means of computerized clinical records. Data was analyzed using IBM Statistics SPSS 20®.

RESULTS

A total of 66 patients were included in the study, with a mean age of 83 years, 51.5% of whom were male (n=34). Most requests of collaboration to the EIHSCP came from the Neurology Service (65.2%, n=43), followed by the Traumatic Brain Injury Unit (TCE) (27.3%, n=18), and Internal Medicine (3.0%, n=2). Most events recorded were of ischemic etiology (cerebral infarction), corresponding to 62.1% of cases (n=41), in comparison with hemorrhagic events (ICH, SAH, SDH), which correspond to the remainder 37.9% (n=25) (Table 1). Within hemorrhagic events, the most frequently admitted etiologies were traumatic in 72.0% (n=18) of cases, uncontrolled hypertension in 12.0% (n=3), bleeding disorders in 8.0% (n=2), arteriovenous malformation in 1.5% (n=1), and severe thrombocytopenia in 1.5% (n=1).

The mean time between diagnosis and the request for collaboration with the EIHSCP was of 14 days. The EIHSCP intervened within 48 hours after receiving each request.

TABLE 1: CHARACTERIZATION OF THE POPULATION

Total number of patients, n	66
Age, years	
Mean (IQR 13.5)	83
Gender, n (%)	
Female	32 (49.5)
Men	34 (51.5)
Referencing service, n (%)	
Neurology	43 (65.2)
TCE Unit	18 (27.3)
Internal Medicine	2 (3.0)
Others	3 (4.5)
Type of event, n (%)	
Ischemic	41 (62.1)
Hemorrhagic, traumatic	18 (27.3)
Hemorrhagic, non-traumatic	7 (10.6)
In-hospital mortality, n (%)	
Ischemic	29 (70.7)
Hemorrhagic	19 (76.0)

IQR: Interquartile range; TCE: Traumatic Brain Injury

In the first observation by the IHTPCS, the mean value for the Glasgow Coma Scale (GCS) was 6/15, and the mean value of the Palliative Performance Scale (PPS) was 10%.

Symptoms and signals most frequently identified during the first assessment by the IHTPCS were dysphagia (96.8%), aphasia or acute dysarthria (91.9%), bronchorrhea (48.4%), dyspnea (48.4%), constipation (46.8%), dry mouth (30.6%), and pain (30.3%) (Table 2).

At the moment of the first assessment, medical treatments in progress considered potentially futile included, nasogastric intubation (84.8%), urinary catheterization (66.7%), continuous cardiorespiratory monitoring (50.0%), and hypocoagulation in therapeutic or prophylactic dose (36.3%) (Table 3). Six patients had tracheal intubation (5 orotracheal and 1 tracheotomy): the orotracheal tube was later removed from all five patients. The mean number of antibiotic cycles per patient prior to the request for collaboration with the IHTPCS was two, with one case of nine complete antibiotic cycles prior to the initial assessment.

We found that 25 patients (37.9%) needed opioid therapy for pain or dyspnea control, and 25 patients needed antimuscarinic therapy to reduce bronchial secretions, which were not prescribed prior to the IHTPCS assessment and were initiated afterwards. In 25 cases pain control and antimuscarinic therapy were already correctly prescribed by the assisting medical team upon the arrival of the EIHSCP.

In-hospital mortality was of 72.7% (n=48); for the group of patients with ischemic events, it was 70.7% (n=29); and for hemorrhagic events was 76.0% (n=19), with no significant changes in survival according to the etiology or location of the hemorrhage (Table 1). The average time between diagnosis death was of 24 days.

None of the patients studied had advanced care directives.

TABLE 2: FUNCTIONAL STATUS AND SYMPTOMS

GCS, mean (between 3-5 values)	6
PPS, mean (between 0%-100%)	10
Signals/Symptoms, n (%)	
Changes in swallowing	64 (96.8)
Serious dysarthria or aphasia	60 (91.9)
Bronchorrhea	32 (48.4)
Dyspnea	32 (48.4)
Constipation	31 (46.8)
Dry mouth	21 (30.6)
Pain	20 (30.3)
Vascular epilepsy	19 (29.0)
Delirium	13 (19.4)
Anxiety/depression	9 (12.9)

GCS: Glasgow Coma Scale; PPS: Palliative Performance Scale

TABLE 3: POTENTIALLY FUTILE MEASURES IDENTIFIED

Potentially futile measures, n (%)	
Nasogastric intubation	56 (84.8)
Urinary catheterization	44 (66.7)
Cardiac monitoring	33 (50.0)
Hypocoagulation	24 (36.3)
Intravenous fluid therapy	22 (33.3)
Orotracheal tube (UTCE)	22 (33.3)

UTCE: Traumatic Brain Injury Unit

DISCUSSION

The sample studied is, regarding age and gender distribution, similar to those documented in other studies on acute neurological events (especially in publications on ischemic stroke), as reported by Burton et al.[11]. The exceptions are studies regarding palliative care that used patients admitted into Intensive Care Units (ICU), for which the mean age is considerably lower, as is the case in the study conducted by Creutzfeldt et al[4] on the palliative needs in a Neuro-ICU.

Up until 2014, there were no recommendations in the European or American guidelines concerning end of life care in patients with ischemic stroke, SAH, or traumatic brain injury[1,12,13]; it was only in 2014 that a document was published by the American Heart Association (AHA) and American Stroke Association (ASA)[9] which contained guidelines for the palliative approach of patients with cerebral infarction, and in 2015 they were also included in the American guidelines on spontaneous ICH[14]. In addition, most studies published on the palliative care needs of neurological patients rarely include different types of acute event; studies that most often include in the same sample cases of cerebral infarction, ICH, SAH, and SDH are those conducted in neurocritical care context[4].

Authors who study palliative care needs in hemorrhagic neurological events report mortality rates above 50%, in situations of significant intracranial hemorrhage – similar to those found in middle cerebral artery (MCA) territory extensive infarction – and the need for palliative care, especially when decompression surgery is not indicated or is ineffective[15]. In situations of subarachnoid hemorrhage, it is estimated

that, similarly to intracranial hemorrhages, 50% of cases result in death, and one third in severe disability[15]. In this present study, we found higher mortality rates in all groups (Ischemic and hemorrhagic stroke, SAH, and SDH), which might be explained by the increased age and, consequently, decreased functional status of the patients included, in comparison with other publication, as previously mentioned.

We highlight the mean time between diagnosis and the request for collaboration to the IHTPCS, of over 20 days, associated with the high degree of frailty of these patients at the moment of the first assessment by the team – particularly evident when compared to other studies with a similar scope, like the one by Mazzocato et al.[16], in which only 26% of patients were in stupor or coma. Even though it is possible for the neurological status to deteriorate during hospital stay – it is impossible to evaluate this progression without a PPS score at the moment of admission, and in some cases even the initial GCS was omitted from the records –, it would be beneficial to signal these cases in a more timely fashion, regardless of any healing goals established by the assistant team, so that symptomatic control can be optimized in the early stages of treatment. This model of early signaling is already followed by several units and wards, as described in the studies published by Creutzfeldt et al.[4] e Burton et al.[11], among others.

There are many possible symptomatic manifestations with patients of acute neurological events, with considerably variable intensity. In the AHA/ASA guidelines on this topic[12], the management of several symptoms is described – pain, fatigue, fecal incontinence, vascular epilepsy, sexual dysfunction, sleep apnea, and psychological symptoms –, whose incidence in this sample, as in the populations described in other studies[16], is less evident in comparison to other complaints. We highlight, for example, the presence of dyspnea, dysphagia, constipation, and dry mouth, all of which whose frequency is considerable and which cause significant discomfort for the patients.

In this context, the evident cognitive deterioration of most patients becomes even more relevant, as does the high incidence of aphasia in conscious patients –restrictions which limit the expression of most symptoms, making it harder to identify and manage them in due time by the clinician. In these situations, a correct evaluation of suggestive signs of discomfort is of great importance, among which are bronchorrhea, polypnea, or muscle contractions indicatives of underlying pain.

Identification and suspension of futile therapeutic measures is as important as proper symptomatic control. In comparison with other published studies, we found that there is still a high prevalence of interventions whose benefits in terminal neurological patients are questionable. One example of that is the number of patients with NG tubes at the time of the first assessment – present in 84.8% of patients – in comparison with data from the study by Blacquiere et al.17, according to which 56.4% (n=53) of their sample was never subjected to NG tubes, and 40.4% had it removed. The monitoring of vital signs, continuous or regular, still remains one of the futile measures most often found by IHTPCS, as well as the use of non-palliative medication in terminal patients[17].

Similarly to what is found in other publications[16], the intervention by IHTPCS was necessary for optimization of symptomatic medical therapy in one-third of cases of uncontrolled pain/dyspnea and bronchorrhea.

The primary limitation of this study is the retrospective nature of data analysis. The scarcity of details in medical and nursing records, especially regarding patients' evolution during treatment, limits the possibilities for interpretation of some data. In the same way, the advanced disability of most patients often compromised the process of correctly assessing their palliative needs, as was the case with the absence of advanced care directives or records stating the opinions of close care providers.

CONCLUSIONS

Patients with major acute neurological events are often dependent on others, have multiple symptoms, are incapable of expressing their symptoms and desires and are frequently referred to Palliative Care teams too late in the course of their illness. It is the responsibility of health professionals to look after the best interests of these patient, providing timely symptomatic control and avoiding therapeutic obstinacy which might worsen the discomfort or anguish, with no expectation of clinical benefit. The development of new tools aimed for this type of situation, which allow for easier identification of these patients' needs, will likely bring significant benefits, as will increased awareness of clinicians about implementation of palliative measures and when to refer these cases to specialized teams.

RESUMO:

INTRODUÇÃO: *Eventos neurológicos agudos resultam frequentemente em incapacidade grave que impede o doente de participar ativamente nas decisões do seu próprio tratamento. A sobrevida a cinco anos ronda os 40%; metade dos sobreviventes fica dependente de terceiros. Objetivo: Avaliar a sintomatologia de doentes internados com acidente vascular cerebral (AVC), hemorragia subarcnoideia (HSA) ou subdural (HSD) e analisar a intervenção de uma Equipe Intra-Hospitalar de Suporte em Cuidados Paliativos (EIHSCP).*

MATERIAL E MÉTODOS: *Estudo retrospetivo observacional dos doentes com diagnóstico principal de evento neurológico agudo com pedido de colaboração à EIHSCP, num hospital terciário, durante cinco anos (2012-2016).*

RESULTADOS: *Avaliados 66 doentes, com média de idade de 83 anos. Destacam-se 41 AVC isquêmicos, 12 hemorrágicos, 12 HSD e 5 HSA. A média da demora entre internamento e pedido de colaboração à EIHSCP foi de 14 dias. Na primeira observação, a média na escala de coma de Glasgow foi de 6/15 e na Palliative Performance Scale (PPS) foi de 10%. Disfagia (96,8%) e broncorreia (48,4%) foram os sintomas mais frequentes. A maioria dos doentes (56/66) mantinha sonda nasogástrica (84,8%); 33 encontravam-se em monitorização cardiorrespiratória (50,0%); 24 estavam sob hipocoagulação (36,3%); 25 necessitavam de opioide e antimuscarínico que não estavam prescritos (37,9%); seis tinham tubo orotraqueal, que foi retirado. A mortalidade intra-hospitalar foi de 72,7% (n=48).*

DISCUSSÃO E CONCLUSÃO: *Destaca-se o estado debilitado dos doentes; em muitos casos, intervenções fúteis persistiam, mas várias foram submedicadas para o controle dos sintomas. Verificou-se um tempo de espera elevado até o pedido de colaboração. Pela elevada morbilidade associada a esses eventos, cuidados paliativos diferenciados deveriam ser oferecidos no tempo adequado.*

PALAVRAS-CHAVE: *Cuidados paliativos. Acidente vascular cerebral. Transtornos cerebrovasculares.*

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ORIGINAL ARTICLE

Malnutrition associated with inflammation in the chronic renal patient on hemodialysis

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SUMMARY

INTRODUCTION: *Malnutrition-Inflammation-Atherosclerosis Syndrome is very frequent in patients with chronic kidney disease on haemodialysis. In these patients, the inflammation associated with malnutrition is observed by the Malnutrition-Inflammation Score.*

OBJECTIVE: *To analyse the relationship between malnutrition-inflammation-atherosclerosis syndrome and anthropometric and biochemical parameters of patients on haemodialysis.*

METHODS: *A cross - sectional study was performed at the Haemodialysis Clinic of the Barão de Lucena Hospital, Recife, Brazil, between July and August 2016, with patients cared at the clinic for at least six months. Patients with amputees, hospitalized, visually impaired, HIV positive, with catheters in the neck, ascites and/or oedema, and those who were unable to provide information at the time of the interview were excluded. The patients were submitted to anthropometric evaluation for the classification of the nutritional status by waist circumference, neck circumference, body mass index, waist-to-hip ratio and waist-to-height ratio. Nutritional status related to inflammation was measured by the Malnutrition-Inflammation Score and nutritional status assessment using biochemical indicators that used urea, creatinine and albumin.*

RESULTS: *Twenty-seven individuals of both genders, adults and elderly, aged 51.3 ± 13.3 years old participated in the study. The anthropometric evaluation showed that most of the population presented cardiovascular risk. The biochemical evaluation reported low frequencies of malnutrition. Malnutrition-Inflammation-Atherosclerosis syndrome was evidenced in 3.7% of the patients. The Malnutrition-Inflammation Score had a moderate negative correlation with body mass index, waist circumference, neck circumference, waist-to-height ratio and creatinine.*

CONCLUSION: *The correlation seen among the parameters suggests that most of the parameters evaluated can be used as an indirect indicator of malnutrition-inflammation-atherosclerosis syndrome.*

KEYWORDS: *Renal insufficiency, chronic. Renal dialysis. Malnutrition. Inflammation.*

INTRODUCTION

The change in the diet pattern of the Brazilian population contributes greatly to the high prevalence of chronic noncommunicable diseases (NCDs), such as systemic arterial hypertension (SAH), dyslipidaemias, obesity and diabetes mellitus (DM)[1]. These pathologies, in turn, tend to injure several organs, such as the kidneys. The nephropathies group encompasses several diseases that affect the kidneys and that can subsequently lead to chronic kidney disease (CKD), characterized by irreversible, slow

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and progressive loss of renal function, being a major public health problem[2], mainly due to its social and economic implications[3].

Among the types of treatments available for CKD, haemodialysis (HD) is one of the most used. This method filters and purifies undesirable substances from the blood, such as urea and creatinine[4], and is considered a good tool for the treatment of CKD and for the clinical improvement of the patient. Despite its benefits, HD can cause some undesirable changes to the dialytic patient, such as hypotension, cramps, protein loss and inflammatory process[5].

Malnutrition-Inflammation-Atherosclerosis (MIA) occurs in chronic kidney patients on HD due to several factors. Anorexia, presence of obesity, metabolic disorders and the dialysis itself are among the main causes of this syndrome, leading to the loss of body proteins and to the production and action of pro-inflammatory cytokines[6].

In patients with CKD on HD, it is possible to observe the presence of inflammation associated with malnutrition by means of the Malnutrition-Inflammation score (MIS)[7]. This method can replace parameter values that quantify the inflammatory process, such as interleukin-6 (IL-6) and ultra-sensitive C-reactive protein[8].

Thus, this study aimed to evaluate the possible correlation between MIS and nutritional parameters of chronic renal patients on HD, and it was also intended to identify, among the indicators studied, those that could be used as a marker of MIA syndrome with low cost, easy application and reduced time.

METHODS

A cross-sectional study that was carried out at the Haemodialysis Clinic of the Barão de Lucena Hospital (HBL), Recife, Brazil, between July and August 2016. The study participants were patients with CKD of both genders, adults and elderly, attended at the clinic for at least six months. Patients with amputees, hospitalized, HIV positive, with catheters in the neck, ascites and/or oedema, and those who, for some reason, were unable to provide information at the time of the interview and anthropometric evaluation were excluded.

The characterization of the sample was made based on socio-demographic (gender, age, socioeconomic conditions), clinical (comorbidities) and lifestyle (smoking, alcoholism and physical activity practice) parameters. Socioeconomic conditions were assessed based on the criteria of the Brazilian Association of Population Studies (Abep)[9], while the demographic and clinical data were collected from the patient's chart. The practice and type of physical activity were analysed according to parameters of the Brazilian Society of Cardiology; Brazilian Society of Hypertension; Brazilian Society of Nephrology[10]. Alcohol consumption was classified as "consumes" and "does not consume", and the smoking aspect according to Silva et al.[11], which rates the individual as a smoker, former smoker and never smoked.

The patients were submitted to anthropometric evaluation to rate their nutritional status. The measures were carried out by the head of the research, previously trained, in order to minimize errors in measurements. The following measures were taken: weight, height, waist circumference (WC), hip circumference (HC), neck circumference (NC), body mass index (BMI), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR).

Dry weight was obtained on a Welmy scale, with a capacity of 200 kg (440 pounds). Height was measured by an aluminium stadiometer coupled to the scale. Wheelchair and elderly patients had their height estimated by the formula proposed by Chumlea et al.[12]. Both weight and height were determined according to the technique standardized by Lohman et al.[13].

WC and HC measurements were performed using an inelastic tape, according to a technique described by Lohman et al.[13]. The cut-off points for WC and WHR rating were based on Cook et al.[14] and Pereira[15], respectively. For the WHtR indicator, the calculation proposed by Haun et al.[16] was considered and the cut-off points used were those of Pitanga and Lessa17. The NC measurement was made and rated according to Bem-Noun et al.[18]. All anthropometric measurements were performed twice, after the dialysis session, considering the mean values.

The nutritional status of the patients related to inflammation was measured by the MIS, comprised of ten components, seven of them being from the Global Subjective Assessment and three items (BMI, serum albumin and total iron-binding capacity - TIBC)[7]. Each component of the MIS has four levels of severity, being scaled from 0 (normal) to 3 (very severe). The final score ranges from 0 to 30.

The assessment of nutritional status according to the biochemical indicators used urea, creatinine and albumin. The cut-off for normality of these parame-

ters was according to Riella and Martins[19], with urea equal to 130-200 mg/dL, creatinine at 7-12 mg/dL and albumin at 3.5-5 g/dL. All values were collected from the patient's chart.

Statistical analysis was performed with the help of the Statistical Package for Social Sciences - SPSS version 13.0 (SPSS Inc., Chicago, IL). Continuous variables were tested for normality of distribution by the Kolmogorov Smirnov test (to evaluate the symmetry of the variables distribution curve). Data from the normal distribution variables were expressed as mean and standard deviation. Categorical data were expressed in frequency. To verify the correlation between MIS and the anthropometric and biochemical variables, the Pearson correlation test was used, values between 0.3 and 0.5, whether positive or negative, were considered as weak correlation, whereas values between 0.5 and 0.7, as a moderate correlation. Factors for which the p-value was less than 0.05 were considered to be significantly associated.

The study was approved by the Human Research Ethics Committee of the Hospital Otávio de Freitas, on May 3, 2016 (CAAE: 54883816.8.0000.5200), based on ethical standards for research involving human beings, contained in resolution 466/2012 of the National Health Council. Participants were previously informed of the objectives of the research, as well as the methods to be adopted. All patients who agreed to participate and were within the eligibility criteria of the research signed the Informed Consent Term.

RESULTS

Twenty-seven individuals of both genders, aged 51.3 ± 13.3 years old and haemodialysis time of 2.59 ± 1.78 years, participated in the study. Table 1 shows the sociodemographic, clinical and lifestyle characteristics presented by the participants of the study, in which the similarity in the frequency between the genders, prevalence of sedentary life and SAH, followed by DM, is observed in the sample studied.

Table 2 shows the frequency of nutritional indicators. Regarding the anthropometric parameters, the majority of the evaluated population was at cardiovascular risk, according to the measures of circumferences used. According to the biochemical parameters, low frequencies of risk of malnutrition stand out; the MIS score assessment identified 3.7% of patients with MIA, with a mean score of 4.89 ± 2.32.

The correlation between MIS and anthropometric and biochemical parameters can be seen in Table 3, which highlights the moderate negative correlation between MIS and serum creatinine (r = -0.644, p = 0.000). It is noted that MIS presented a moderate negative correlation with BMI, NC, WC and serum creatinine.

DISCUSSION

The majority of the study population were adults and males. Other studies have shown a higher prevalence of males compared to females in haemodialysis clinics[20], while age has been described predominantly higher (59.4 ± 9.9 years old), according to data from the Brazilian Society of Nephrology[21].

Regarding the cause of CKD, studies report that SAH, followed by DM, are the main etiological factors of CKD[22], and this is quite concerning, since these pathologies are related to higher mortality[23]. Databases

TABLE 1 – SOCIO-DEMOGRAPHIC, CLINICAL, AND LIFESTYLE CHARACTERISTICS OF CHRONIC RENAL PATIENTS FROM HAEMODIALYSIS CLINICS OF HOSPITAL BARÃO DE LUCENA, RECIFE – PE / 2016.

Variables	Quantity (%)
Men	15 (55.6)
Women	12 (44.4)
Level of Education	
Illiterate / Uncomplete Primary School	7 (25.9)
Complete Primary School	6 (22.2)
Complete Secondary School	2 (7.4)
Further Education	12 (44.4)
Economic Classification	
B1	2 (7.4)
B2	3 (11.1)
C1	7 (25.9)
C2	10 (37)
D	5 (18.5)
Physical Activity	
Yes	3 (11.1)
No	24 (88.9)
Ingestion of Alcoholic Beverages	
Yes	2 (7.4)
No	25 (92.6)
Smoker	
Never Smoker	20 (74.1)
Former Smoker	7 (25.9)
Comorbidities	
Hypertension	24 (88.8)
Diabetes	8 (29.6)
Dyslipidaemia	1 (3.75)
Others	2 (7.4)

TABLE 2. FREQUENCY OF NUTRITIONAL INDICATORS IN CHRONIC RENAL PATIENTS FROM HAEMODIALYSIS CLINICS OF HOSPITAL BARÃO DE LUCENA, RECIFE – PE / 2016.

Variables	Quantity (%)
Waist Circumference	
With Cardiovascular Risk	18 (66.7)
Without Cardiovascular Risk	9 (33.3)
Neck Perimeter	
With Cardiovascular Risk	21 (77.8)
Without Cardiovascular Risk	6 (22.2)
Waist-to-Hip Relation	
With Cardiovascular Risk	16 (64)
Without Cardiovascular Risk	9 (36)
Waist-to-Height Relation	
With Cardiovascular Risk	18 (66.7)
Without Cardiovascular Risk	9 (33.3)
Albumin	
Normal	25 (92.6)
Decreased	2 (7.4)
Creatinine	
Normal	21 (80.8)
Decreased	5 (19.2)
Urea	
Normal	21 (77.8)
Decreased	6 (22.2)
MIS	
Eutrophics / Light Undernourished	26 (96.3)
Moderate Undernutrition	1 (3.7)

MIS: Undernutrition – Inflammation Score

TABLE 3 – CORRELATION OF UNDERNUTRITION – INFLAMMATION SCORE (MIS) WITH ANTHROPOMETRIC AND BIOCHEMICAL PARAMETERS OF CHRONIC RENAL PATIENTS FROM HAEMODIALYSIS CLINICS OF HOSPITAL BARÃO DE LUCENA, RECIFE / 2016.

Parameters	Correlation Ratioa	p-value
IMC	-0.599	0.001**
Waist Circumference	-0.509	0.007**
Neck Perimeter	-0.541	0.004**
Waist-to-Hip Relation	-0.315	0.125
Waist-to-Height Relation	-0.466	0.014*
Serial Creatinine	-0.644	0.000*
Serial Urea	0.284	0.152
Serial Albumin	-0.189	0.345

IMC: Body Mass Index; aPearson Correlation; *p<0.05; **p<0.01

from the USRDS in 2009 showed that, generally, of diabetic patients initiating the haemodialysis process, only 30% survive after five years of treatment[24].

Most of the patients who participated in the study did not perform any kind of physical activity, and this reality is quite common among patients who are on HD. In other studies with CKD on HD performed in Brazil, there is also a high prevalence of sedentary patients, with a predominance of up to 73.1% of sedentary lifestyle[23]. Dyspnoea, anaemia, fatigue, generalized muscle weakness, SAH and other factors that constitute uremic syndrome are the main causes of low adherence of CKD patients on HD to physical exercise[25].

In the present study, WC showed a higher cardiovascular risk than a survey carried out in 2013 in the Northeast region of Brazil, in which the WC reported was increased in 51.4% of the sample, and this prevalence was higher in females[26]. WC is considered a good predictor of abdominal fat and cardiovascular risk[27]. In addition, abdominal obesity, evaluated by WC, seems to be closely related to age and genetic factors, eating behaviour and reduction in the level of physical activity[28].

The highest percentage of inadequacy was observed by the NC, which also assesses the risk for cardiovascular diseases. The neck region is responsible for a high release of systemic fatty acids. For this reason, the cardiovascular risk of NC is compared to the cardiovascular risk evidenced by WC[29]. In addition, NC is shown to be connected to insulin resistance indicators, such as fasting glycaemia and glycated haemoglobin, in addition to the PCR and BMI[30].

The WHtR measure also assesses the presence of cardiovascular risk. Increased WHtR is slightly related to increased risks of cardiovascular events over a period of up to ten years[27].

The high risk of cardiovascular disease seen in this study by the anthropometric parameters can be justified by several factors. Chronic kidney disease is considered to be an independent factor for cardiovascular events alone and the drop in glomerular filtration rate (GFR) is directly proportional to the risk of CVD[31]. Some research has shown that elevation of pro-inflammatory cytokines and the haemodialysis process itself, due to characteristics such as duration and time interval between dialysis sessions, are also major cardiovascular risk factors, since they cause cardiac stress[32]. In addition to these possible causes, other factors such as hyperphosphatemia, dyslipidaemia, sedentary lifestyle, high calcium-phosphorus product, SAH and DM are related to cardiovascular risk in dialysis patients[33].

Among the anthropometric parameters studied, the WHR was the only one that did not present a correlation with MIS, suggesting that this indicator

would not be adequate to evaluate the risk of MIA syndrome. In fact, in the literature there are several limitations to the use of WHR to assess nutritional diagnosis, such as failure to detect the proportional increase of the waist and hip, the influence of hormonal modification and imprecision of internal fat disposition.[34]

The biochemical parameters showed a lower percentage of patients with albumin, creatinine and serum urea levels below the reference values for HD patients when compared to other studies.

In a study conducted by Cavalcante et al.[35], the prevalence of 85.3% serum albumin <4.0 mg/dL was observed. This high prevalence of hypoalbuminemia, compared to the current study, can be justified by the higher cut-off point used in the Cavalcante et al.[35] study. The prevalence of hypoalbuminemia in Brazil varies from 15% to 85.3%, and there are several factors that trigger this difference in prevalence, as characteristics of the studied population and cut-off points of the hypoalbuminemia used by the HD centres[36]. Appropriate rates of serum albumin are quite important for the chronic renal patient, since reduced levels of albumin are related to a worse prognosis and a greater risk of hospitalization in these patients[36].

A survey conducted between 2009 and 2010 in the state of Goiás showed that 56% of the patients studied had serum creatinine levels below that recommended for renal patients,[37] a very disturbing result different from the current study, where about 19.2% had serum creatinine reduced. In this study, the lower frequency of inadequacy of serum creatinine rates may demonstrate a certain adequacy of protein intake by patients.

Urea, in turn, also showed within its range for HD in most of the patients studied. Oliveira et al.[38] found a very similar result in their research. Urea levels may be influenced by factors such as protein ingestion or breakdown, and in dialysis patients, decreased rates of serum urea depend on the patient's residual renal function, and this is directly proportional to the mortality of these patients[39].

As for MIS, similar results were observed by Barros et al.[40] in 2014, who found an average MIS score of 4.0. A multicentre European study obtained a different result in their research, describing a mean MIS of 9.85[41]. Several factors, such as different dialysis protocols, population differences and different clinical conditions among the evaluated patients are one of the causes that may justify this difference between the studies[40].

As it was observed with the biochemical indicators, the percentage of MIS inadequacy was considered low, indicating few patients at risk of presenting MIA syndrome. However, when MIS was associated with anthropometric and biochemical parameters, a moderate negative correlation was observed with BMI, WC, NC and creatinine, and a weak negative correlation with WHtR, suggesting that the making these anthropometric measurements may be a good alternative to identify and monitor the risk of nutrition associated with inflammation in these patients.

BMI correlated negatively with MIS, suggesting that the lower the BMI of a dialysis patient, the greater the risk of malnutrition and inflammation. However, in MIS, a BMI greater than 20 kg/m² does not score for nutritional risk, which may be an instrument bias, since it does not take into account the BMI range for the elderly population[20]. BMI is a parameter widely used in clinical practice to classify the nutritional status of individuals and, despite its limitations, such as not differentiating between lean mass and fat mass, it is one of the most commonly performed in HD patients, since it is low cost, non-invasive and practical[42].

Some authors report the relationship between a higher BMI and a good prognosis in CKD, since low weight is associated with higher mortality[43]. Studies suggest that patients who perform HD should maintain their BMI> 23.0 kg/m² to ensure a positive impact on morbidity and mortality[38]. Low weight and malnutrition are widely found among patients who perform HD. Factors such as dietary restriction, metabolic acidosis, protein catabolism and reduction of antioxidant capacity are involved in the presence of malnutrition and inflammatory process in patients with CKD on HD[44].

Regarding WC, NC and WHtR, it is known that these are indicators of visceral fat and their levels, when elevated, are associated with increased mortality due to the risk of cardiovascular diseases[27]. However, levels that are much lower than the values recommended for WC and NC, since these measures are generally directly proportional to BMI, may be associated with malnutrition and, consequently, with the presence of inflammation.

The parameter that presented a better correlation with the MIS was serum creatinine. Several studies indicate the association of creatinine with the prog-

nosis of patients with CKD on HD[45]. According to the literature, serum creatinine values below 10 mg/dL increase mortality of dialysis patients and may be related to malnutrition[46]. Thus, it is important to routinely monitor serum creatinine levels in patients with CKD on HD, aiming at the rapid identification of patients with impaired nutritional status, to make a nutritional intervention adequately and precociously.

Demir et al.[47], in 2010, found a negative correlation between MIS and serum albumin (r = -0.42 and p = 0.0001). Some research suggests that the association between low serum albumin levels and elevated MIS increases mortality in patients with terminal CKD[8]. Thus, the presence of malnutrition, inflammation and reduction of serum albumin would lead to poor prognosis of the dialytic patient, causing an increase in oxidative stress and inflammatory markers, reinforcing the applicability of MIS as a clinical tool in the identification of inflammatory process in the dialysis stage of CKD[48].

The absence of a relationship between serum albumin and MIS suggests that the presence of malnutrition in these patients is type 1, in which the cause is related to low food intake (total energy), since the aetiology of malnutrition in patients with CKD on haemodialysis can be caused either by factors associated with food intake or by inflammatory factors[49].

The waist-to-hip ratio also did not prove to be a good parameter for the evaluation of the nutritional status and the presence of malnutrition and inflammation of the patients on HD in this sample, since it did not present a correlation with the MIS.

The present study presented some limitations, such as the small sample number and the impossibility of evaluating PCR. However, in spite of the limitations, it was possible to obtain a significant result that should be further investigated, aiming at the adequate choice of the parameters used to evaluate the nutritional status of patients with CKD on HD. In addition, research with a design that allows studying the cause and effect of the events addressed should be carried out.

CONCLUSION

MIS presented a moderate negative correlation with BMI, WC, NC and creatinine, suggesting that these anthropometric and biochemical parameters can be used as indirect indicators of Malnutrition-Inflammation-Atherosclerosis syndrome in this series, particularly the serum creatinine that, among the studied parameters, was the indicator that presented the highest level of correlation and significance.

The applicability of MIS to clinical practice is quite important. This score had a moderate negative correlation with BMI, WC, NC and creatinine, suggesting that these anthropometric and biochemical parameters, particularly serum creatinine, can also be considered as an alternative to be used as an indirect indicator of MIA syndrome in this case, in a quick, simple and low cost manner.

RESUMO:

INTRODUÇÃO: *A síndrome Desnutrição-Inflamação-Aterosclerose é frequente nos pacientes com doença renal crônica em hemodiálise, acarretando perda de proteínas corporais e produção de citocinas pró-inflamatórias.*

OBJETIVO: *Verificar, entre os indicadores nutricionais estudados, aqueles que melhor se correlacionam com a síndrome Desnutrição-Inflamação-Aterosclerose em pacientes submetidos à hemodiálise.*

MÉTODOS: *O estudo foi transversal, realizado na Clínica de Hemodiálise do Hospital Barão de Lucena, no Recife (PE), entre julho e agosto de 2016, com pacientes atendidos há pelo menos seis meses. Foram excluídos pacientes amputados, internados, com deficiência visual, cateter no pescoço, HIV positivo, ascite e/ou edema e aqueles incapazes de prestar informações no momento da entrevista. Os pacientes foram submetidos à avaliação antropométrica para a classificação do estado nutricional pela circunferência da cintura, perímetro do pescoço, índice de massa corporal, relação cintura-quadril e relação cintura-estatura. O estado nutricional relacionado à inflamação foi mensurado pelo escore Desnutrição-Inflamação e a avaliação do estado nutricional pelos indicadores bioquímicos: ureia, creatinina e albumina.*

RESULTADOS: *Participaram do estudo 27 indivíduos de ambos os sexos, adultos e idosos, com idade de 51,3 ± 13,3 anos. A avaliação antropométrica mostrou que a maior parte da população apresentava risco cardiovascular. A avaliação bioquímica relatou baixas frequências de desnutrição. Foi evidenciada síndrome Desnutrição-Inflamação-Aterosclerose em 3,7% dos pacientes. O escore Desnutrição-Inflamação apresentou correlação moderada negativa com o índice de massa corporal, circunferência da cintura, perímetro do pescoço, relação cintura-estatura e creatinina.*

CONCLUSÃO: *A correlação observada entre os parâmetros sugere que a maioria dos parâmetros avaliados pode ser utilizada como indicador indireto da síndrome Desnutrição-Inflamação-Aterosclerose.*

PALAVRAS-CHAVE: *Insuficiência renal crônica. Diálise renal. Desnutrição. Inflamação.*

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ORIGINAL ARTICLE

The relationship between malnutrition and quality of life in haemodialysis and peritoneal dialysis patients

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SUMMARY

BACKGROUND: *One of the most important factors affecting the quality of life of chronic kidney disease (CKD) patients is nutrition. Prevention of malnutrition increases patients' quality and length of life. In this study, we aimed to determine the frequency of malnutrition, quality of life, and the relationship between them in patients with end-stage renal disease (ESRD).*

METHOD: *The study was conducted with a total of 60 CKD patients including 50 haemodialysis patients and 10 peritoneal dialysis patients. Patients' data associated with socio-demographics, body mass index (BMI), waist circumference, triceps skin-fold thickness (TSFT), pre-dialysis systolic and diastolic blood pressure, Kt/V and urea reduction ratio (URR) values, laboratory parameters, Mini-Nutritional Assessment-Short Form (MNA-SF) and European Quality of Life 5-Dimensions (EQ5D) scale were recorded.*

FINDINGS: *Of the total 60 patients; 27 were male (45%), 33 were female (55%), 83.3% were receiving haemodialysis treatment (HD), and 16.7% were receiving peritoneal dialysis treatment (PD). The mean MNA-SF score was 10.4 ± 2.8 in the HD group and 10.5 ± 2.9 in the PD group; there was no difference between the scores of the HD and PD groups. The mean EQ5D score was 0.60 ± 0.29 in the HD group and 0.68 ± 0.33 in the PD group, no significant difference was found between the HD group and the PD group. The quality of life was found lower in malnourished group (p=0.001).*

CONCLUSION: *The quality of life needs to be increased by early diagnosis and treatment of malnutrition in patients at risk.*

KEYWORDS: *Renal insufficiency, chronic. Malnutrition. Quality of life. Nutrition assessment. Nutrition surveys. Surveys and questionnaires.*

INTRODUCTION

Malnutrition is a frequent finding in patients with chronic kidney disease (CKD). The incidence of malnutrition is between 18-75% in haemodialysis patients and 10-50% in peritoneal dialysis patients, depending on the criterion that the patient is assessed by[1,2]. Malnutrition is associated with delayed recovery and an increase in hospitalization, susceptibility to infection, mortality, and morbidity[3-5]. Chronic diseases are often associated with chronic functional impairment and adversely affect the quality of life[6]. Malnutrition is one of the factors affecting the quality of life[7,8]. Early intervention in patients with malnutrition increases the quality of life and reduces mortality [9]. It has been emphasized in previous studies that the quality of life of malnourished patients is worse and thus the

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early diagnosis and treatment of malnutrition is important[10-12]. Recent studies have led to the conclusion that the effects on improving the quality of life as well as on the long-term survival should be considered when evaluating the effectiveness of the treatment in chronic diseases[13]. There was a close relationship between the quality of life, morbidity, and mortality in patients with end-stage renal disease (ESRD). Therefore, treatment options that will increase patients' quality of life should be focused on[14-18].

This study was aimed to evaluate the nutritional parameters, anthropometric parameters, and malnutrition status in order to determine the levels of the quality of life and to determine the relationship between malnutrition and the quality of life in patients with CKD.

METHODS

This study was planned as a descriptive cross-sectional study and was conducted in İzmir Tepecik Training and Research Hospital between May 2016 and August 2016 following its approval by the local ethics committee. No sampling was done for the study; a total of 60 patients, including 50 haemodialysis patients and 10 peritoneal haemodialysis patients, who received routine haemodialysis services at the Hospital, were over 18 years old, and volunteered were included in the study. A questionnaire consisting of three sections was applied to all patients. The first section included the socio-demographic data, anthropometric measurements, and laboratory parameters; the second section included the Mini Nutritional Assessment-Short Form (MNA-SF) scale; and the third section included the European Quality of Life 5-Dimensions (EQ-5D) general quality of life scale.

Mini Nutritional Assessment-Short Form (MNA-SF)

The MNA-SF scale was used to determine the patients' malnutrition levels. MNA-SF is performed using verbal interrogation and anthropometric measurements[19].

The MNA, developed by Guigoz et al.[20], contains eighteen questions. Patients are categorized as normal nutritional status, malnutrition risk, or malnutrition based on the result of evaluation. Several studies have shown that MNA correlates well with nutritional intake, anthropometry, laboratory data, functional status, morbidity, mortality, and length of hospital stay[20,21]. In 2001, Cohendy et al.[22] reviewed the MNA and developed a 6-item MNA-SF, a short form of the MNA, which was found to have high correlation in nutritional evaluation. The validity and reliability test of MNA-SF were done by Kaiser et al. in 2009. The validity and reliability test of the Turkish version was done by Sarikaya[23], in 2013.

European Quality of Life 5-Dimensions (EQ-5D) General Quality of Life Scale

In various diseases, the quality of life can be measured by using general health scales and/or disease-specific scales. The EQ-5D was developed in 1987 by EuroQol, the Western European Quality of Life Research Society. The EQ-5D general health scale has been translated into more than 60 languages, including Turkish, by the EuroQol group. It was first published in 1990 and has maintained the same features (5 dimensions) since 1991. The scale consists of two parts [24].

The EQ-5D index scale consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In each dimension, the answer is one of the three options: there is no problem, there are some problems, and there are major problems. Thus, it is possible to define 243 (3^5=243) different health outcomes with the scale. An index score ranging from -0.59 to 1 is calculated from the five dimensions of the scale. In the score function, a value of 0 indicates death and 1 indicates perfect health while negative values represent living unconscious, dependent on bed, etc. The coefficients produced by Dolan et al. [25] are used in calculating the index score in the EQ-5D[24].

EQ-5D VAS scale is a visual analogue scale where individuals grade their current health status and mark it on a thermometer-like scale. Thus, a quality of life score ranging from 0 to 100 is obtained. Turkish validity and reliability study for the EQ-5D general quality of life scale was conducted by Süt[26], in 2011; Cronbach alpha value of the scale was found 0.86. EQ-5D has been successfully applied in chronic dialysis patients while being a general health measure used in measuring quality of life[27].

All data were transferred to electronic medium and statistically analysed using SPSSv22. The descriptive statistics were given as counts and per-

centages for categorical variables, and as mean and standard deviation for numerical variables. For multiple-independent group comparisons with numerical variables, analysis of variance (ANOVA) was used when the normal distribution was satisfied; Kruskal Wallis test was used when the normal distribution was not satisfied. For two-independent group comparisons, t test was used when the normal distribution was satisfied; Mann Whitney U test was used when not. For the categorical variables, Chi-square test was used for multiple and two-group comparisons when conditions were satisfied. Pearson test was used for correlations between normal-distributed numerical data; Spearman's rho test was used when not. The level of statistical significance was considered to be $p<0.05$.

RESULTS

A total of 60 patients were included in the study, 83.3% were haemodialysis (HD) and 16.7% peritoneal dialysis (PD) patients. Socio-demographics of the patients are shown in Table 1.

The clinical and anthropometric characteristics of the patients are shown in Table 2. The average triceps skin-fold thickness (TSFT) was found significantly higher in the PD group than the HD group (p=0.033). The presence of comorbid disease was significantly higher in the PD group than in the HD group (p=0.037). The frequency of hypertension as a comorbid disease was higher in the PD patients than in the HD patients (p=0.023).

When biochemical parameters were considered, the levels of parathormone (pth p=0.041), alkaline

TABLE 1: SOCIO-DEMOGRAPHICS AND BIOCHEMICAL DATA OF HD AND PD PATIENTS.

		HD (%83, n:50)	PD (%16.7, n:10)	p value
Age (years)		50±18,9	52,4±15,1	0.71
Gender (%)	Male Female	46 54	40 60	0.728
Education (%)	None Elementary Middle School High School	44.0 36.0 16.0 4.0	40.0 30.0 10.0 20.0	
Marital Status (%)	Married Single Widow Separated-Divorced	50.0 26.0 18.0 6.0	70.0 20.0 10.0 0	0.834
Monthly Income (%)	< 1,300 TL 1,300 TL 1,300-2,000 TL > 2,000 TL	76.0 22.0 0 2	50.0 40.0 10.0 0	0.096
Smoking (%)		26	10	0.427
Compliance with Diet (%)		36	80	0,015
Haemoglobin (gr/dL)		10.5±1.24	10.4±0.8	0.900
C-reactive protein (CRP) (mg/L)		19.4±25.2	13.8±13.5	0.641
Urea (mg/dL)		123±30.6	121±16.6	0.761
Creatinine (mg/dL)		7.8±2.0	8.8±1.7	0.168
Calcium (mg/dL)		8.8±0.7	9.8±1.2	0.002
Phosphorus (mg/dL)		5.1±1.5	5.8±0.8	0.141
Parathormone (pg/mL)		421±332	245±105	0.041
Albumin (g/dL)		3.6±0.3	3.4±0.6	0.302
ALP (u/L)		173±110	109±36	0.047
Total protein (g/dL)		6.9±0.5	6.8±0.3	0.365
Total cholesterol (mg/dL)		176±39.5	210±60.2	0.024
High density lipoprotein (mg/dL)		41.9±11.3	48.4±11	0.107
Low density lipoprotein (mg/dL)		98.6±29	120.8±46.2	0.174
Sodium (mmol/L)		135±2.7	135±3.1	0.697
Potassium (mmol/L)		4.9±0.5	4.5±0.4	0.041
TIBC (ug/dL)		188±34	233±41	0.001
Transferrin (mg/dL)		107±27	144±33	0.001

phosphatase (alp, p=0.047), and potassium (p=0.041), were higher in the HD group while the levels of calcium (p=0.002), total cholesterol (p=0.024), total iron binding capacity (TIBC) (p=0.001), and transferrin (p=0.001) levels were higher in the PD group. Patients' biochemical data are summarized in Table 1.

Prevalence of malnutrition

In the HD group, malnutrition risk was 34% and malnutrition was 20% while they were 30% and 10% in the PD group, respectively. The mean MNA-SF score was 10.4 ± 2.8 in the HD group and 10.5 ± 2.9 in the PD group. There was no significant difference between HD and PD groups in terms of malnutrition (p=0.936). The comparison of various aspects of the patients in terms of the malnutrition classification is shown in Table 3. Correlation between malnutrition score and TSFT and BMI show in figure 1. (p<0.001, p<0.001).

Quality of life

The mean EQ5D index score was found 0.60 ± 0.29 (min -0.086, max 1) in the HD group while it was 0.68 ± 0.33 (min -0.166, max 1) in the PD group. The EQ5D VAS score was 66.7 ± 22.3 (min 20, max 100) in the HD group while it was 58.1 ± 13.1 (min30 max 76) in the PD group. No significant difference was found between the HD group and the PD group in terms of quality of life.

When the answers to the EQ-5D scale were examined in terms of comorbidity, it was found that the patients with comorbid coronary artery disease (CAD) had significantly more complaints than the non-CAD patients only in terms of mobility (p=0.007) and usual activities (p=0.028).

There was a negative correlation between EQ-5D score and age (r=-0,459 p<0,001). There was a positive correlation between EQ-5D score and Kt/V ratio (r=0,262 p=0,043). There was no correlation between EQ-5D score and duration of CKD/ duration of dialysis/ haemoglobin/ albumin / phosphorus/ calcium (r=-0.013 p=0.920, r=-0.012 p=0.926, r=-0.108 p=0.413, r=0.189 p=0.147, r=0.202 p=0.122, r=0.203 p=0.119)

Malnutrition - quality of life relationship

The mean EQ5D index score was 0.71 ± 0.22 in the normal-nutrition group, 0.64 ± 0.28 in the malnutrition-risk group, and 0.32 ± 0.33 in the malnutrition group according to the MNA-SF classification. There was a significant difference between the EQ5D index scores of the groups (p=0.001).

The mean EQ5D VAS score was 71.8 ± 17.5 in the normal-nutrition group, 63.5 ± 21.5 in the malnutrition-risk group, and 51.1 ± 23.7 in the malnutrition group according to the MNA-SF classification. There was a significant difference between the EQ5D VAS scores of the groups (p=0.017).

DISCUSSION

Chronic kidney disease (CKD) is an important global public health problem because of the increasing prevalence, high cost of treatment, and its negative impact on the quality of life. As well as being a

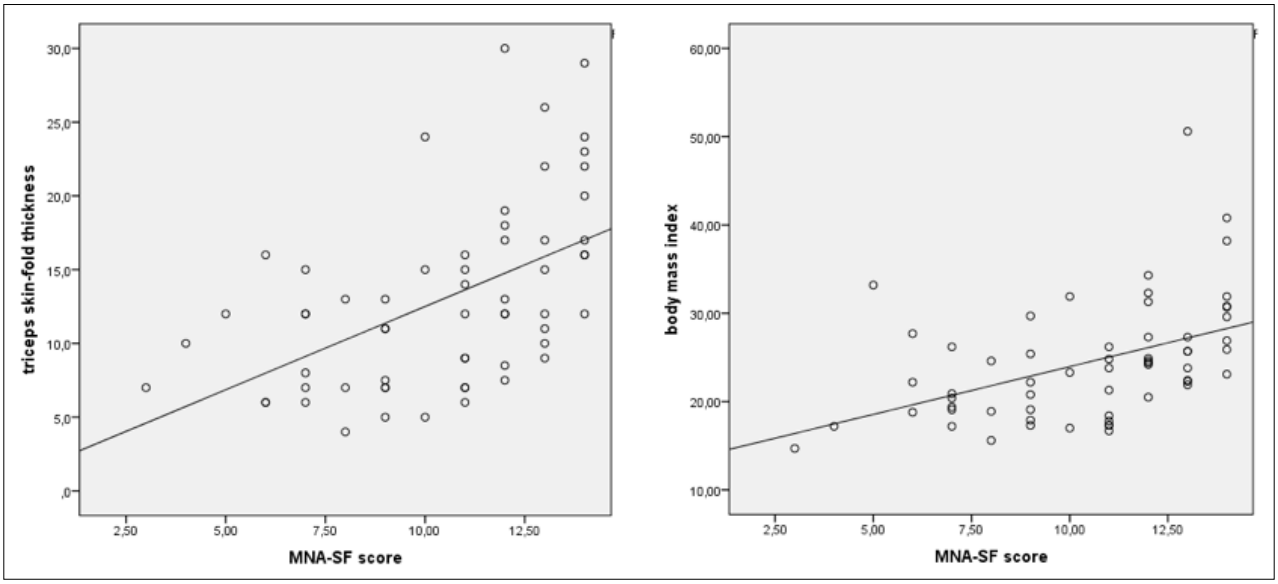

FIGURE 1: CORRELATION BETWEEN MALNUTRITION SCORE AND TSFT AND BMI.

TABLE 2: CLINICAL AND ANTHROPOMETRIC CHARACTERISTICS OF PATIENTS.

		All Groups	HD (%83, n:50)	PD (%16,7, n:10)	P
CKD Duration (months)		68.4±62	68.5±62.9	68±60.6	0.980
Dialysis Duration (months)		51±44.7	53.5±48.3	38.5±14.2	0.338
CKD Etiology (%)	Unknown Diabetes Hypertension Other	66.7 10.0 11.7 11.7	66.0 10.0 10.0 14.0	70.0 10.0 20.0 0	0.592
Presence of Comorbidity (%)	Yes Diabetes Hypertension CAD Other	73.3 23.3 66.7 28.3 8.3	68 24 60 32 6	100 20 100 10 20	0.037 0.023
Skipping Dialysis Sessions (%)	Never Once to Thrice	85.0 15.0	88 12	70 30	0.163
BMI (kg/m2)		24.4±6.6	24.2±7	25.5±4.1	0.572
Waist Circumference (cm)		93.4±16.2	92.3±16.9	98.7±10.7	0.264
TSFT (mm)		12.9±6.2	12.2±5.6	16.8±7.6	0.033
IDWG (gr)			2330±1217		N/A
Kt/V		1.6±0.5	1.4±0.3	2.5±0.6	< 0.001
URR			70.4±6.7		N/A
Systolic BP (mm/Hg)			137±30	145±23	0.471
Diastolic BP (mm/Hg)			80±18	88±17	0.346

Abbreviations: CAD, coronary artery disease; IDWG, interdialytic weight gain; URR, urea reduction ratio; BP, blood pressure;

TABLE 3: COMPARISON OF VARIOUS ASPECTS OF THE PATIENTS IN TERMS OF THE MALNUTRITION RATING.

MNA-SF status	normal nutritional status		malnutrition risk		malnutrition		P
	Mean	SD	Mean	SD	Mean	SD	
BMI (kg/m2)	27.9	6.9	21.4	4.6	21.3	5.4	0.001*
Waist Circumference (cm)	98.3	14.4	88.2	16.8	90	17.0	0.071
TSFT (mm)	16	6.5	10.2	4.8	10	3.5	0.001ϕ
CKD Duration (months)	59.9	57.1	94.4	75.2	43.7	23.7	0.039ω
Dialysis Duration (months)	45.6	40	68.9	47.1	32.6	26.2	0.063
Albumin (g/dL)	3.65	0.3	3.63	0.4	3.45	0.2	0.347
Transferrin (mg/dL)	117.4	31.4	104.1	37	121.9	16.4	0.230
Creatinine (mg/dL)	7.7	2	8.1	2	8.2	1.7	0.710
CRP (mg/L)	17.9	21.1	15.4	29.2	25.6	19.1	0.521
Low density lipoprotein (mg/dL)	105.9	31.5	102.2	36	93	32.7	0.550
Hemoglobin (gr/dL)	10.3	0.8	10.4	1.4	10.9	1.3	0.408
Calcium (mg/dL)	9	0.9	8.4	0.6	8.5	0.6	0.059
Phosphorus (mg/dL)	5.3	1.5	5.3	1.4	4.9	1.5	0.795
Potassium (mmol/L)	4.9	0.6	4.9	0.5	4.5	0.2	0.065

* between normal with malnutrition risk and malnutrition groups. ϕ between normal and malnutrition groups. ω between normal and malnutrition risk groups

common finding in individuals with CKD, malnutrition is associated with increased mortality and morbidity. Malnutrition, in itself, also has a negative impact on the quality of life. Prevention of malnutrition increases the quality and length of life in patients.

The prevalence of malnutrition in patients with CKD is between 18-75% in haemodialysis patients and 10-50% in peritoneal dialysis patients, depending on the criterion that the patient is assessed with. Malnutrition in chronic renal failure is often due to decreased energy intake associated with uremic syndrome and systemic chronic inflammation[2]. In patients who have not started renal replacement therapy, when GFR is lower than 50 mL/dL, oral intake has begun to deteriorate in patients and malnutrition has been established[28].

In our study, 34% of the patients in the HD group were under malnutrition risk and 20% was malnourished; these were 30% and 10% in the PD group, respectively. The relatively low PD patient count is limitation of our study. Studies conducted on large patient populations throughout the world have shown that the MNA test may detect nutritional deficiencies even if the patient's albumin level and body mass index (BMI) are within the normal ranges, and that hypoalbuminemia may be present in patients with normal nutritional status as well as the albumin levels of malnourished patients may be normal[29-34].

In a study by Erdoğan[35], biochemical parameters of patients in various malnutrition categories were compared and it was found that the albumin, creatinine, low density lipoprotein (LDL), haemoglobin levels were lower in the malnourished group but there was not a significant difference in calcium and phosphorus levels.

When biochemical parameters of patients in various malnutrition categories in our study were compared, it was found that the albumin, creatinine, LDL, haemoglobin, calcium, potassium, and phosphorus levels were not significantly different. The study by Girija and Radha[36] also did not find a relationship between malnutrition level and albumin level.

In a study by Rammohan and Aplasca[37], triceps skin-fold thickness (TSFT) was found to be an important anthropometric measure for detecting malnutrition. In a study conducted by Janardhan et al.[38], nutritional score and TSFT were found to negatively correlated. In our study, it was also found that is TSFT was lower in malnourished patients. In a study by Kalantar-Zadeh et al.[39], a negative correlation was found between malnutrition score and BMI; similar results were also obtained in our study.

The quality of life in dialysis patients is related to the biochemical parameters such as haemoglobin, serum albumin level, phosphorus, and calcium; the Kt/V ratio, duration of dialysis, age, and gender[14-18,40,41]. In our study, Kt/V value was found to correlate positively with the quality of life score. However, there was no significant relationship between the quality of life and duration of CKD, duration of dialysis, the levels of albumin, phosphorus, and calcium in this study.

In previous studies, a significant relationship was found between the quality of life and age[41-43]. In our study, a negative correlation was found between the EQ5D index score and age.

There are studies in literature, indicating a better quality of life with HD than with PD as well as the opposite[44,45]. In our study, although the mean EQ5D score was higher in the PD group, this was not statistically significant.

It has been found in some studies that having comorbid disease adversely affects the quality of life[46-49]. A study by Şahin[50] found lower physical component scores for patients with CAD comorbidity. Similarly, in our study, patients with comorbid CAD diagnosis were found to have more complaints related to mobility and usual activities than patients without CAD.

In a study examining the malnutrition levels of the patients were in connection with the EQ5D index score and the EQ5D VAS score, the EQ5D index score and the EQ5D VAS score decreased as the degree of malnutrition increased[51]. Similar results were obtained in our study; the EQ5D index score and the EQ5D VAS score, which are the quality of life scores, were found to decrease with increasing malnutrition. The results obtained in our study were also similar to those of Jiménez-Redondo et al.[52].

CONCLUSION

Malnutrition is common in haemodialysis and peritoneal dialysis patients, and adversely affects the patients' quality of life. It is important to prevent malnutrition and to increase patients' quality of life with early diagnosis and treatment of patients who are at risk of malnutrition. It would be useful to routinely use nutrition and quality of life scores in dialysis monthly evaluations.

RESUMO

INTRODUÇÃO: *O estado nutricional é um dos principais determinantes da qualidade de vida de pacientes com doença renal crônica (DRC) e a prevenção da desnutrição aumenta o tempo e a qualidade de vida nessa população. O objetivo do presente estudo foi determinar a prevalência de desnutrição, a qualidade de vida e a inter-relação entre esses fatores em pacientes com DRC em terapia dialítica.*

MÉTODOS: *Incluímos 60 pacientes com DRC estágio 5 sob terapia dialítica (50 pacientes em hemodiálise [HD] e 10 em diálise peritoneal [DP]). Os pacientes foram analisados com relação aos seus dados sociodemográficos, índice de massa corporal (IMC), circunferência abdominal, dobra cutânea triciptal, pressão arterial sistólica e diastólica pré-diálise, Kt/V e índice de remoção de ureia, parâmetros laboratoriais, miniavaliação nutricional (MNA) e questionário EuroQol-5 Dimensions (EQ-5D).*

RESULTADOS: *Do total de pacientes, havia 27 homens (45%) e 33 mulheres (55%), 83,3% em HD e 16,7% em DP. O MNA médio foi 10,4 ± 2,8 nos pacientes em HD e 10,5 ± 2,9 naqueles em DP, não havendo diferença significativa entre os grupos. O EQ-5D médio foi 0,60 ± 0,29 nos pacientes em HD e 0,68 ± 0,33 naqueles em DP, não havendo diferença estatisticamente significativa entre os grupos. A qualidade de vida foi pior nos pacientes desnutridos (p=0,001).*

CONCLUSÃO: *O diagnóstico e o tratamento precoce da desnutrição são necessários para melhorar a qualidade de vida dessa população.*

PALAVRAS-CHAVE: *Insuficiência renal crônica. Desnutrição. Qualidade de vida. Avaliação nutricional. Inquéritos nutricionais. Inquéritos e questionários.*

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REVIEW ARTICLE

Efficacy and Safety of PARACHUTE® Device: systematic review

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SUMMARY

INTRODUCTION: *Heart failure due to an acute myocardial infarction is a very frequent event, with a tendency to increase according to improvements in the treatment of acute conditions which have led to larger numbers of infarction survivors.*

OBJECTIVE: *The aim of this study is to synthesize the evidence, through a systematic review, on efficacy and safety of the device in patients with this basic condition.*

METHODS: *Studies published between January 2002 and October 2016 were analysed, having as reference databases Embase, Medline, Cochrane Library, Lilacs, Web of Science and Scopus. The selection of studies, data extraction and methodological quality assessment of studies were examined by two independent reviewers, with disagreements resolved by consensus.*

RESULTS: *Only prospective studies without control group were identified. Six studies were included, with averages of 34 participants and follow-up of 13 months. Clinical, functional, hemodynamic and quality of life outcomes were evaluated. The highest mortality rate was 8.4% with 12-month follow-up for unspecified cardiovascular reasons, and heart failure rehospitalization was 29.4% with 36-month follow-up. Statistically significant improvements were found only in some of the studies which evaluating changes in left ventricular volume indices, the distance measured by the six-minute walk test, New York Heart Association functional classification, and quality of life, in pre and post-procedure analysis.*

CONCLUSIONS: *The present review indicates that no available quality evidence can assert efficacy and safety of PARACHUTE® in the treatment of heart failure after apical or anterior wall myocardial infarction.*

KEYWORDS: *Heart failure. Myocardial infarction. Equipment and supplies. Technology assessment, biomedical. Review literature as topic.*

INTRODUCTION

About 40% of cases of acute myocardial infarction (AMI) cases are associated with left ventricular (LV) systolic dysfunction, with the frequency of signs and symptoms of heart failure (HF) after AMI being around 25%. Data indicate that the latter condition is quite frequent and will tend to increase as improvements in the treatment of acute conditions have led to larger numbers of AMI survivors[1].

In 2007, a percutaneously implanted structural cardiac device called PARACHUTE® (PercutAneous Ventricular RestorAtion in Chronic Heart FailUre due to Ischemic HearT DiseasE) was patented (Figure 1). Manufactured by Cardiokinetix, Menlo Park, CA, it was developed for patients with post-AMI HF[2] in order to segregate the dysfunctional LV region, minimizing systolic and diastolic volumes, and con-

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sequently limiting stress on the myocardium and improving hemodynamic as well as its functional capacity[3].

Preliminary studies conducted in Europe and the United States have been driving the performance clinical trials to define the long-term efficacy and safety of PARACHUTE®. Some of these studies have already published their results, emphasizing the relevance in the search and synthesis of the existing clinical results, to carry out the monitoring of the technological horizon and to advise the future decision processes pertinent to the ventricular partitioning device.

The present work was conceived considering that PARACHUTE® is a recent, high cost innovative therapy. In Brazil, experimental research has already begun and the device is being evaluated for sanitary registration in the national regulatory agency, which may lead to future demands for incorporation into the payment schedules of the Brazilian health system. The results of the technology in terms of efficacy and safety have not yet been established, no systematic review of these scopes has been identified and the prevalence of the underlying condition tends to increase due to population aging.

Thus, the objetive of this study was to summarize the evidence, through a systematic review, regarding the efficacy and safety of the ventricular partinioning device in patients with HF after apical or anterior wall AMI.

METHODS

The question of the present systematic review was: "Is the ventricular partitioning device (PARACHUTE®) safe and effective for the treatment of heart failure of ischemic aetiology after apical or anterior wall AMI when compared to the other available treatments?"

In order to answer this question, the following bibliographic databases were searched: Embase, Medline (via PubMed), Cochrane collaboration, Lilacs, Scopus and Web of Science, covering the period from January 2002 to April 2016. There were no restrictions of language in the bibliographic searches. The searches were updated monthly until the completion of the study (October 2016) in order to capture possible scientific productions that had been published later on.

FIGURE 1: PARACHUTE®

In addition, a cross-reference search was made in the articles found and in previously published narrative review articles on the topic. Annals of congresses in the area of Cardiology in the last five years, pages of the medical societies of the areas of Cardiology and Interventional Cardiology, and the databases of ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization and the Brazilian Registry of Clinical Trials were also consulted. Research by evaluations conducted by health technology assessment agencies belonging to the International Network of Agencies for Health Technology Assessment (INAHTA) was made complemented. Finally, we examined the EuroScan International Network, the study base of systematic reviews PROSPERO and the pages of Cardiokinetix, manufacturer of the device.

The search was restricted to humans and the strategy used descriptors, when available, and free words in the title, abstract and text of the manuscripts, related to the disease and the intervention. The complete search strategies used in each database can be made available upon request to the authors.

The selection of the studies was performed based on the initial analysis of the title and abstract, followed by evaluation of the full text by two independent evaluators, with resolution of the disagreements in both stages by consensus. Full-text studies published in languages other than English, Spanish and Portuguese were excluded but registered for the identification of possible language bias. The eligibility criteria used were substantiated by the acronym PICOS. Thus, they had to be randomized or non-randomized controlled clinical trials and observational studies (cohort, case control, and series of cases ≥ 10 patients enrolled) that evaluated the efficacy and safety of the intervention (PARACHUTE®) in the adult patient population (> 18 years old) with HF after apical or anterior wall AMI, in which the comparators, when available, were a ventricular assist device, conventional clinical treatment and surgical treatment; and that had any of the following outcome measures:

mortality from HF, AMI, stroke and non-specified cardiovascular causes, and from any cause; rehospitalization for HF; successful implantation of the device with regard to selected patients; maintenance of the implanted device by time (in months) of follow-up; changes in LV volume index; change in walking distance as measured by the 6-minute walk test; changes in quality of life as measured by the EuroQol five dimension questionnaire (EQ-5D) and Minnesota Living with Heart Failure (MLHFQ) instruments; improved functional classification of the New York Heart Association (NYHA); and frequency of adverse events/complications.

The methodological quality of the studies was also evaluated by the same pair of reviewers, with disagreements resolved by consensus, using the Quality Appraisal Checklist for Case Series Studies tool[4].

Data from the included studies were extracted in duplicate and independently by two reviewers in a standardized electronic collection form, prepared in the public domain EpiData® application. The form was previously tested on selected articles and adjustments were made for adequacy purposes, and it was subsequently reapplied to the entire set of articles.

The results of the studies were analysed using frequency measurements, presenting the continuous mean or median variables, followed by the respective standard deviations. Excel® version 2010 and Stata® version 13 were used to calculate and prepare presentation formats.

The study was approved by the Research Ethics Committee of a federal institute of assistance and education under number 48942915.1.0000.5272, and its protocol was registered on the systematic review base Prospero (CRD42016034179).

RESULTS

Studies selection

This systematic review totalled the inclusion of six studies[5-10] and the flowchart with the results of the selection phases is present in Figure 2.

Characteristics of the studies and participants included in the systematic review

All six studies included in the systematic review are uncontrolled follow-up, corresponding to series of cases with patients enrolled consecutively. The studies were published between 2010 and 2016, one of them developed in China[10] and the others in European centres, one of which was also developed in the United States[6]. Four studies were multicentric[5,6,9,10].

The number of participants effectively submitted to the implantation of the device ranged from 8 to 100 patients, with a mean of 34 patients, median of 23.5 and a standard deviation of 30.9. It should be noted that, in some articles, the number of enrolled participants was higher, but PARACHUTE® was not implanted in all patients recruited, most often as a result of unfavourable anatomy (inadequate ventricular apex dimensions and inappropriate architecture, geometry and trabeculation of the LV).

Functional rating of NYHA from II to IV, age> 18 years old, FEVE between 15% and 40%, and LV anteroapical wall motility disorder were inclusion criteria in 100% of the studies, as well as recent percutaneous coronary angioplasty or myocardial revascularization and valve disease were exclusion parameters in all studies.

The mean age of the patients in the studies ranged from 56.9 to 71.3 years. The vast majority of participants were male, in proportions ranging from 62.5% to 94.4%. The participants' weight and height were reported only in two articles[7,9] and the BMI also in two[9,10], with averages of 27.6 kg/m² (SD ± 3.9) and 25 kg / m² (SD ± 2.2).

Two studies did not present the patients' NYHA functional classification,[6,7] although there is a figure present in Costa et al.[7] which suggests that more than half belonged to class III.

High blood pressure and diabetes mellitus were risk factors for heart disease reported in all studies. Smoking also had high participation rates (from 40% to 80%) in most of the studies.

Previous cardiovascular procedures were described in all studies, mainly revascularization or coronary angioplasty.

Except for two studies, Sagic et al.[5] and Yang et al.[10], all others mentioned participation of patients with comorbidities. Two implants of the device associated with MitraClip as a consequence of severe or moderate/severe mitral valve regurgitation were reported in a manuscript[8].

Previous use of medication by participants was quite diverse. However, in 83% of the studies[5-7,9,10], all patients used antiplatelet or anticoagulant medication (acetylsalicylic acid or warfarin) after the procedure, with the use of diuretics, beta-blockers and ACE inhibitor, in variable proportions (data not included in the table).

TABLE 1 - GENERAL AND CLINICAL OUTCOMES ASSESSED IN THE SYSTEMATIC REVIEW

Author	Follow-up time (m)	% Loss of follow-up* (m)	% Implant Success	% Maintenance of the implanted device* (follow-up months)	% Re-admission due to HF* (follow-up months)	% Mortality due to (follow-up months)	Adverse events/ complications (% of patients)
Sagic et al.(5)	12	13.3 (3 m) 13.3 (6 m) 13.3 (12 m)	86.7	86.7 (3 m) 86.7 (6 m) 86.7 (12 m)	0	Infection 6,7 (3m)	DD (6.7), LC (61.5), VC (6.7)
Bozdag-Turan et al.(6)	3	0 (3 m)	100	100 (3 m)	0	0	0
Costa et al.(7)	36	8.8 (12 m) 20.5 (24 m) 32.3 (36 m)	91.2	91.2 (3 m) 82.3 (12 m) 79.4 (24 m) 67.6 (36 m)	11.8 (12 m) 26.5 (24 m) 29.4 (36 m)	CM - 6.5 (12 m), OC - 3.7 (12 m); cancer - 3.7 (36 m)	Infection (2.9), PE (11.8), VC (14.7), LVC (2.9), DC (2.9)
Schmidt et al.(8)	12†	6.2 (3 m) 12.5 (6 m) 25 (12 m)	93.8	93.8 (3 m) 87.5 (6 m) 75 (12 m)	NI	CVA - 6.7 (6 m), infection - 6.7 (12 m), OC - 6.7 (12 m)	DD (6.2), LC (20), arrhythmia (33.3)
Thomas et al.(9)	12	3 (3 m) 5.1 (6 m) 8.7 (12 m)	97	97 (3 m) 92 (6 m) 84 (12 m)	24.1 (12 m)	OC - 1.0 (6 m), CM - 8.4- (12 m)	DD (1), ECC (3), ET (3.3), PE (1), arrhythmia (1), VC (4), MI (1)
Yang et al.(10)	3	6.4 (3 m)	96.8	93.5 (3 m)	NI	OC (3,2-3 m)	CVA (3.2), VC (3.2), AVE (3.2)

Notes: † - Estimated follow-up time 12 months, three patients died after three months and five have not yet closed the total scheduled follow-up time; * - cumulative percentage. Source: Own preparation. **Key:** CVA - cerebrovascular accident; ECS - emergency cardiac surgery; DC - complication related to the nitidol frame of the device; VC - vascular complications; LVC - left ventricular calcification; DD - displacement of the device; PE - peripheral embolization; TE - thromboembolic events; MI - mitral valve injury; m - months; CM - non-specified cardiovascular mortality; OC - other causes; LC - leakage between the static and dynamic chamber of the left ventricle; NI - not informed. **Name of the review authors:** Roberta da Silva Teixeira, Bruna Medeiros Gonçalves de Veras, Kátia Marie Simões and Senna, Rosângela Caetano

TABLE 2 - FUNCTIONAL, HEMODYNAMIC AND QUALITY OF LIFE OUTCOMES IN THE STUDIED POPULATIONS

Author	Mean NYHA (SD)		Mean walking distance	Quality of life Mean MLHFQ score (SD)		% Mean EFLV (SD)		Mean LVESVi (SD)		Mean LVEDVi (SD)	
	Before	After (m)	Delta* (m)	Before	After (m)	Before	After (m)	Before	After (m)	Before	After (m)
Sagic et al.(5)	2.2 (±0.6)	6 m – 1.3 (±0.5)[1] 12 m – 1.2 (±0.4)[1]	6 m – 27 12 m - 43[2]	21.7 (±18.9)	6 m – 16.7 (±12.3) 12 m – 20.8 (±16.9)	28 (±7)	6 m - 32 (±7) 12 m - 33 (±9)[2]	189 (±45)	6 m -142 (±29)[1] 12 m - 151 (±48)[1]	260 (±47)	6 m - 208 (±33)[1] 12 m - 222 (±58)[3]
Bozdag-Turan et al.(6)	2.8 (±0,7)	3 m – 1.6 (±0.5)[2]	3 m - 190[2]	29 (±13)	3 m - 15 (±10)[2]	NI	NI	NI	NI	NI	NI
Costa et al.(7)	NI	NI	12 m – 16.1	38.6 (±5.1)	12 m – 28.4 (±4.4)[4]	27	6 m – 30 12 m – 29.5 24 m – 27.8 36 m – 23.0	93.9	6 m – 74,1[5]; 12 m – 77,0[5] 24 m – 81.6 36 m – 89.4	127.7	6 m – 105,8[5]; 12 m – 108,7[5] 24 m – 112.8 36 m – 115.5
Schmidt et al.(8)	NI	NI	NI	NI	NI	24.7 (±7.2)	NI	NI	NI	NI	NI
Thomas et al.(9)	2.6 (±0.5)	12 m – 2.0 (±0.7)[1]	12 m - 25[3]	NI	NI	29.2 (±7.9)	12 m - 31 (±7.6)	84 (±24)	12 m – 70.5 (±24)[5]	117.3 (±26,3)	12 m – 99.1 (±27.3)[5]
Yang et al.(10)	NI	NI	3 m – 7.8	NI	NI	30 (±5.4)	3 m – 35.8 (±6.8)[1]	77.5 (±20)	3 m – 53.1 (±17)[5]	110.8 (±26.1)	3 m – 82.1 (±21.3)[1]

Notes: 1 - p <0.001; 2 - p <0.05; 3- p <0.01; 4 - p <0.002; 5 - p <0.0001; * - difference between the average distance travelled per month of follow-up. Key: SD - standard deviation; EFLV - ejection fraction of the left ventricle; LVEDVi - left ventricular end-diastolic volume index; LVESVi - left ventricular end-systolic volume index; m - months of follow-up; MLHFQ - Minnesota Living with Heart Failure Questionnaire; NI - not informed; NYHA - New York Heart Association.

Outcomes assessed in the studies included

For the adequate evaluation of the reported outcomes, it is important to highlight that the follow-up time in the trials ranged from 3 to 36 months, with mean and median 13 and 12 months, respectively.

Analyses of general and clinical outcomes are set forth in Table 1. In turn, functional, hemodynamic, and quality of life outcomes are shown in Table 2.

Changes in quality of life measured by the ML-HFQ instrument were analysed by Sagic et al.[5], Bozdag-Turan et al.[6] and Costa et al.[7]. Yang et al.[10] analysed the improvement of this parameter using the EQ-5D instrument and visual analogue scale (VAS). The VAS value increased by 11.5 points, showing a statistically significant improvement ($p < 0.01$) with three months of follow-up.

Quality of evidence

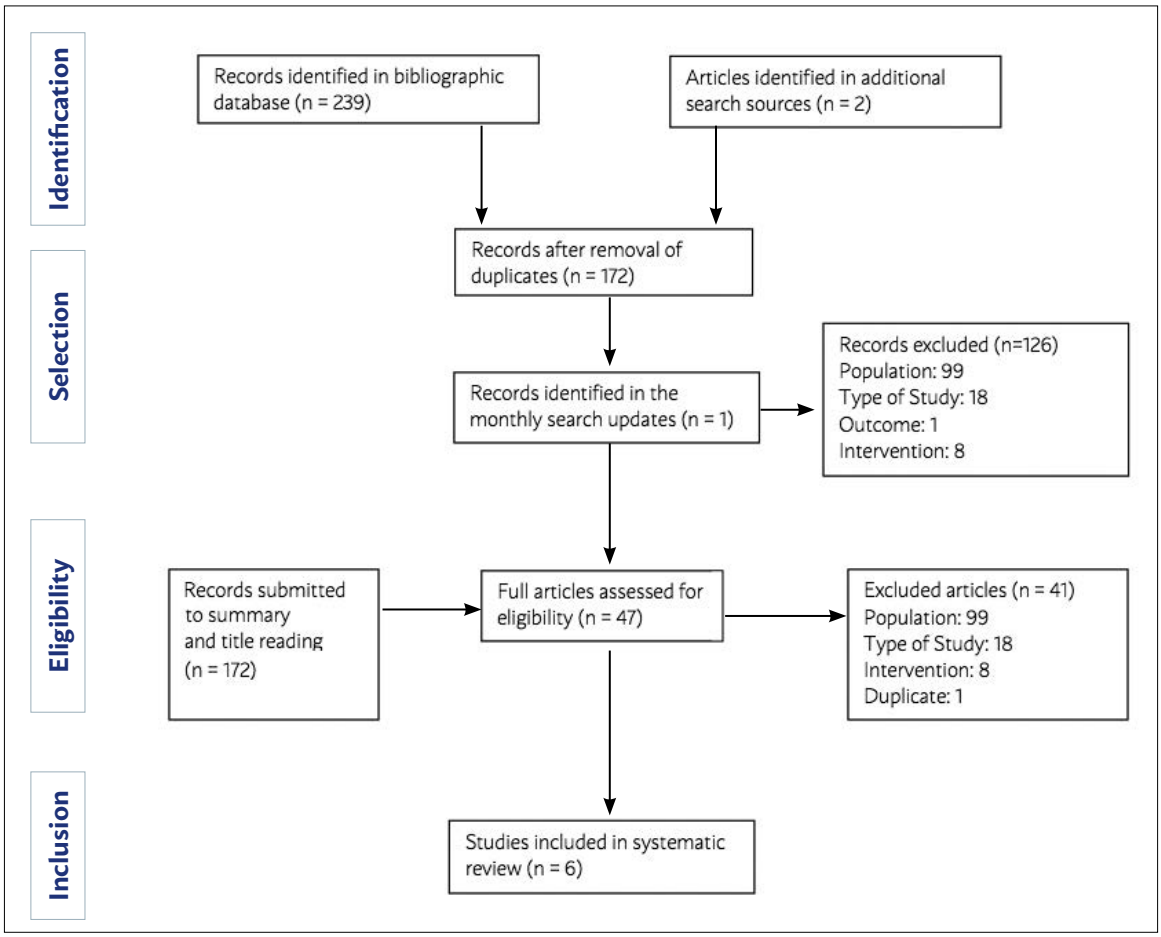
Of the 20 criteria evaluated by the Quality Appraisal Checklist for Case Series Studies tool[4], ten were fully met by all studies in this review.

Two other criteria - a detailed description of the characteristics of the patients included in the studies and the intervention of interest - reached 80% attendance rates. On the other hand, in the criteria "patients started their participation in the study at a similar point of the disease" and "outcome assessors were blinded about the intervention that the patients received", the attendance percentage was less than 40%, and in the criterion "the follow-up was long enough for important events and outcomes", percentage was 20%.

A partial description of co-interventions was performed by all studies, and the percentage of complete care was null for the criterion "the study provided an estimate of the random variability in the analysis of relevant outcome data."

The Costa et al.[7] study was the one with the highest proportion of criteria: 16 out of 20 (80%). The work of Sagic et al.[5], Thomas et al.[9] and Yang et al.[10] also achieved a very good percentage (meeting 15 criteria), with that of Bozdag-Turan et al.[6] presenting the worst individual methodological quality (meeting 60% of the criteria).

FIGURE 2: FLOWCHART OF THE SELECTION OF SYSTEMATIC REVIEW STUDIES



DISCUSSION

This systematic review was based only on uncontrolled follow-up studies, due to the absence of randomized controlled trials (RCTs) published until October 2016.

The quality of evidence available on the efficacy and safety of the device is still rather precarious. Although the case series included present a reasonable quality standard, the findings are derived from a study design that, in essence, does not adopt procedures that allow the control of biases that can influence the results obtained.

A randomized controlled trial - PARACHUTE IV[11] - is currently underway in the United States. This study provides the perspective of supplementing the evidence about the device and establishing its effective utility in the treatment of patients with heart failure of ischemic aetiology.

Observational studies may be a favourable complement in the systematic analysis of adverse events, especially when controlled clinical trials evaluating the efficacy of a technology are scarce[12,13]. In certain situations, even in the absence of RCTs, such studies can provide important information to decision makers, resulting in a complementary source of evidence of low cost, rapid and valuable substitute for technologies in which the diffusion process has already begun[14]. In this scenario, cohort and case-control studies are an alternative to obtain an estimate of the effects of a specific treatment, although the level of evidence from the observational studies is mostly less strong than the RCTs because of the difficulty to control some biases[15].

Case series, due to absence of control group, are prone to biases related to selection, performance, friction and reporting, and to confusion. It is not possible to affirm that its results are attributable to the intervention and do not generate direct statistical comparisons, making it impossible to obtain more robust and unbiased evidence about treatment efficacy[16]. However, this type of study, although less conclusive in terms of evidence, may be the only source of information available to inform health decisions about the implementation of emerging technologies[17,18], as is the case of the device investigated herein. Thus, in the absence of other methodologically more robust types of study, there may be strong assumptions for inclusion of case series in a systematic review or evaluation of a technology in the early stages of development[19].

In this review, the number of papers published is small and, with the limitations set forth, the number of participants in the studies is also very restricted, since only two studies included more than 30 participants. These aspects are further strained by the small follow-up times and the size of the follow-up losses, weakening the analyses of the most relevant clinical outcomes, such as the mortality of patients who underwent device implantation and HF readmissions, as well as the few differences in hemodynamic, functional and quality of life outcomes, assessed before and after the intervention.

It is noteworthy that in the distance-relevant outcome measured by the 6-minute walk test, even considering the 30-meter delta minimum as a reference as the clinically significant minimum difference in the distance travelled,[20] it is observed that in only two studies was evidenced relevance in this regard.

PARACHUTE® has some benefits compared to the other mechanical technologies currently used to treat the clinical situation on the screen. When implanted percutaneously, it prevents the morbidity and mortality of open surgical intervention[21]; it has no external component to the heart, preserving the pericardium and the pericardial space; it can be readily used in patients who do not require myocardial revascularization surgery or other concomitant procedures; and does not prevent the use of other devices adopted in the area of cardiology, such as cardiac resynchronization therapy devices or devices for mitral valve regurgitation[22].

On the other hand, PARACHUTE® is limited in aspects such as the lack of systolic assistance, increased systolic volume and cardiac output, intervening in its ability to act in patients with advanced heart failure[23].

The case report of Ravi et al.[24], in which a patient had deterioration of the functional and hemodynamic outcomes after 24 months of PARACHUTE® implantation, which led to their removal and the implantation of the ventricular assist device, has led to a debate about the efficacy time of PARACHUTE®.

In addition, the findings in the study by Costa et al.[7], included in this systematic review, in which the improvement in LV volumes and LV ejection fraction indexes attained at 12 months of follow-up were not sustained after 36 months of implantation of the device may suggest that this hemodynamic worsening is not by chance, but rather because the device appears to have a relatively short duration of efficacy. Thus, it is possible that the technology could be used

as a link until the implantation of a ventricular assist device or heart transplant[25], instead of working as a definitive intervention in the treatment of patients with heart failure of ischemic aetiology.

After AMI, the prognosis is dependent on left ventricular function[26]. Thus, the exact identification of reversible ventricular dysfunction is essential in the evaluation of patients' treatment[27,28].

The time between AMI and the device implantation procedure needs to be evaluated in the selection of patients. However, it was observed that, among the studies included in the review, only two[5,6] clearly defined this criterion, and two others[7,9] indirectly considered the criterion when establishing that the applicant patients had to be in appropriate clinical treatment of HF in the three months which preceded their selection in the studies.

Thromboembolic events are one of the most important concerns with PARACHUTE®. The percentage of this complication (3.3% of the participants) was described only in one study[9], suggesting that the other studies included in the review reached the goal of reducing these potential events with the use of antithrombotic drugs after device implantation. These findings appear encouraging when compared to thromboembolism rates related to their direct "competitor", the ventricular assist device, whose complication rates are around 20%[29-31]. However, they need to be cautiously interpreted, since their primary studies were not controlled trials and most follow-up times were not very extensive.

The study by Yang et al.[10] showed a better result of systolic function, specifically LV ejection fraction and LV end-systolic volume index, compared to the other studies included in the review. This hemodynamic improvement can be explained by the fact that most patients (93.6%) were treated at the beginning of the progression of HF (NYHA class II). Thus, discussions about the ideal time to implement PARACHUTE® are equally relevant to enhance its benefits to the underlying condition.

Some limitations of this systematic review need to be mentioned. The review identified only observational studies, with a very restricted number of participants and, for the most part, short-term follow-up time. In addition, the measures of outcomes evaluated before and after the implantation of the device did not always reach expressive degrees and, due to the study designs, with absence of control group and blinding, it is not possible to disregard the presence of a potential bias in the adjudication process. The placebo effect in the studies also cannot be disqualified, especially with the use in surrogate and functional outcome studies. Outcomes such as NYHA's functional class, which involve a certain degree of subjectivity in its measurement, may have been misdiagnosed because of the absence of blinding.

CONCLUSIONS

Although PARACHUTE® is an innovative technology, considering the quality of the evidence presented and the results of the measures of outcomes evaluated, it is concluded that there is no available quality evidence that can assert the efficacy and safety of the technology in the treatment of patients with heart failure after acute myocardial infarction or anterior myocardial wall infarction.

The efficacy and safety of PARACHUTE® still need to be evaluated in the future through controlled studies with long-term follow-up and larger sample sizes.

RESUMO

INTRODUÇÃO: *Insuficiência cardíaca após infarto agudo do miocárdio é um evento bastante frequente, que tende a aumentar conforme as melhorias que o tratamento dos quadros agudos têm acarretado a números maiores de sobreviventes de infarto.*

OBJETIVO: *A revisão sistemática sumarizou as evidências relativas à eficácia e segurança do dispositivo de partição ventricular (PARACHUTE®) em pacientes com IC pós-IAM apical ou de parede anterior.*

MÉTODOS: *Foram analisados estudos publicados entre janeiro de 2002 e outubro de 2016 nas bases Embase, Medline, Colaboração Cochrane, Lilacs, Web of Science e Scopus. A seleção dos estudos, a extração dos dados e a avaliação de qualidade metodológica foram realizadas por dois revisores independentes, com as discordâncias resolvidas por consenso.*

RESULTADOS: *Somente estudos prospectivos sem grupo controle foram identificados. Seis estudos foram incluídos, com média de 34 participantes e de follow-up de 13 meses. Foram avaliados desfechos clínicos, funcionais, hemodinâmicos e qualidade de vida. O maior percentual de re-hospitalização por IC foi de 29,4%, com 36 meses de seguimento, e de mortalidade foi de 8,4%, com 12 meses de seguimento, por motivos cardiovasculares não especificados. Melhorias estatisticamente significantes foram constatadas em alguns dos estudos que avaliaram mudanças nos índices de volume do ventrículo esquerdo, distância medida pelo teste de caminhada de 6 minutos, classificação funcional da New York Heart Association e qualidade de vida, em análises do tipo antes e depois do procedimento.*

CONCLUSÕES: *A presente revisão indica que não existem evidências de qualidade disponíveis que permitam afirmar a eficácia e segurança do PARACHUTE® no tratamento da condição de base.*

PALAVRAS-CHAVE: *Insuficiência cardíaca. Infarto do miocárdio. Equipamentos e provisões. Avaliação da tecnologia biomédica. Literatura de revisão como assunto.*

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REVIEW ARTICLE

Ion mobility spectrometry: the diagnostic tool of third millennium medicine

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SUMMARY

Ion mobility spectrometry (IMS) is a fast, low cost, portable, and sensitive technique that separates ions in a drift tube under the influence of an electric field according to their size and shape. IMS represents a non-invasive and reliable instrumental alternative for the diagnosis of different diseases through the analysis of volatile metabolites in biological samples. IMS has applications in medicine in the study of volatile compounds for the non-invasive diagnose of bronchial carcinoma, chronic obstructive pulmonary disease, and other diseases analysing breath, urine, blood, faeces, and other biological samples. This technique has been used to study complex mixtures such as proteomes, metabolomes, complete organisms like bacteria and viruses, monitor anaesthetic agents, determine drugs, pharmaceuticals, and volatile compounds in human body fluids, and others. Pharmaceutical applications include analysis of over-the-counter-drugs, quality assessment, and cleaning verification. Medical practice needs non-invasive, robust, secure, fast, real-time, and low-cost methods with high sensitivity and compact size instruments to diagnose different diseases and IMS is the diagnostic tool that meets all these requirements of the Medicine of the future.

KEYWORDS: *Ion mobility spectrometry. Breath tests. Lung diseases. Carcinoma, bronchogenic.*

INTRODUCTION

Ion mobility spectrometry (IMS) is an atmospheric pressure method that separates ions in the gas phase. IMS is relatively inexpensive, fast, robust, and easy to use. This analytical technique is sensitive to ions of organic or inorganic compounds, and can detect elements, particles and whole organisms from volatile metabolites *in-situ*. IMS is especially sensitive to heteroatoms and organic compounds and can be the method of choice to quickly diagnose different diseases in the emergency room.

INSTRUMENTAL

In IMS, compounds are ionized and accelerated by an electric field in a drift tube and move against a counter-flow of neutral drift gas (air or nitrogen) introduced in the end of the tube (Figure 1). The ions collide continuously against the drift gas, which decelerates them in their way to the detector according to their size and shape; the arrival time at the detector, which depends on the ion's size and shape, allows the ion identification.[1]

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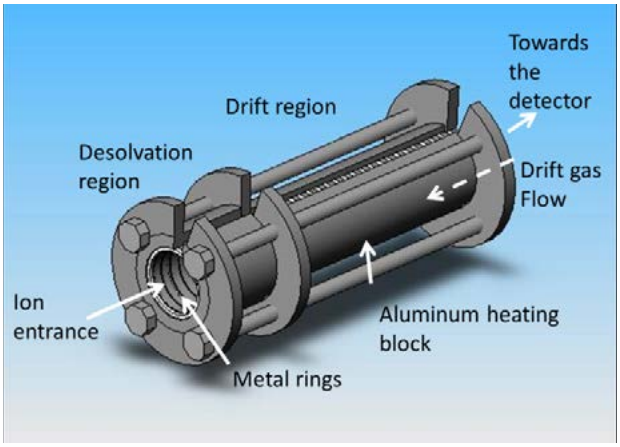

FIGURE 1. Ion mobility spectrometer

Clinical Practice requires fast, safe, low cost, real-time, and non-invasive methods to diagnose different diseases. IMS supplies information on human health through the analysis of volatile organic compounds (VOCs) from exhaled breath, urine, faeces, and other biological samples with all the above requirements for Clinical Practice.

BREATH DIAGNOSIS

Instrumental breath diagnosis is a new area of research with a promising clinical potential with fast real-time analysis of metabolites in exhaled breath. The method is based on the detection of natural volatile metabolites in breath, in healthy states or from diseases, and metabolites from contamination or produced by microbiota in the respiratory system. IMS provides insight on perturbations of the human exposome through breath measurements that can be interpreted as preclinical signals of adverse outcome pathways. Oxidative stress status may be monitored via volatile products of lipid peroxidation, and phenotypic information, important in personalized medicine, is obtained from the measurement of the activity of enzymes such as dihydropyrimidine dehydrogenase.[2] Asthma, bronchial carcinoma, chronic obstructive pulmonary disease, inflammatory lung disease, or metabolic disorders are diseases that may be diagnosed now or in the near future using instrumental breath diagnosis. Vautz et al.[3] coupled IMS to multi-capillary columns (IMS-MCC) for the selective characterization of human breath for early diagnosis as well as medication and therapy control. They demonstrated the complete procedure of breath analyses including the evaluation and interpretation of the data obtained after eating. The signals were compared to a compound database for identification. Hauschild et al.[4] highlighted that the potential of this methodology depends on the successful application of computational approaches for finding relevant VOCs and consequent classification of patients into disease-specific profile groups.

Breath diagnosis includes the detection of drugs,[5] metabolites and volatile organic compounds in the breath of patients as a potential diagnostic tool for chronic obstructive pulmonary disease,[6] bronchial carcinoma,[7] renal failure,[8] colorectal cancer,[9,10] non-alcoholic fatty liver disease[11] and other diseases [12] and conditions such as gut dysbiosis.[13] Additionally, there are promising results in the determination of asbestos-related diseases.[14] Breath analysis was able to identify unique VOCs profiles in patient groups; in 79 volunteers, 1179 different VOCs were detected of which thirteen were sufficient to correctly classify all 79 subjects.[15]

Methodological issues have been detected in breath measurements procedures. Bunkowski et al.[16] studied the variations of eight different compounds over a time period of 11 months in the exhaled breath of the same person in the same room environment and showed that the room air concentration of VOCs must be taken into account to measure the individual variability for medical questions.

Applications of Breath diagnosis in Medicine

Numerous diseases can be determined by the fingerprint of VOCs from breath, urine or faeces. These include sleep apnoea syndrome,[17] renal failure, sarcoidosis, chronic obstructive pulmonary disease, cancer, cystic fibrosis and more.

Pagonas et al.[8] studied breath using IMS and found significant differences in the spectra of 28 patients with or without renal failure. They evaluated 13 compounds that accumulated with decreasing renal function and concluded that impairment of renal function induces a characteristic fingerprint of volatile compounds in breath that can be used for diagnosis. Similar results were obtained by Jazan and Mirzaei.[18]

Sarcoidosis is an inflammatory disease that usually begins with lung inflammation that spreads to other organs, and immune-system cells forming nodes (granulomas) in various organs affecting their function (Figure 2). In one investigation, breath sam-

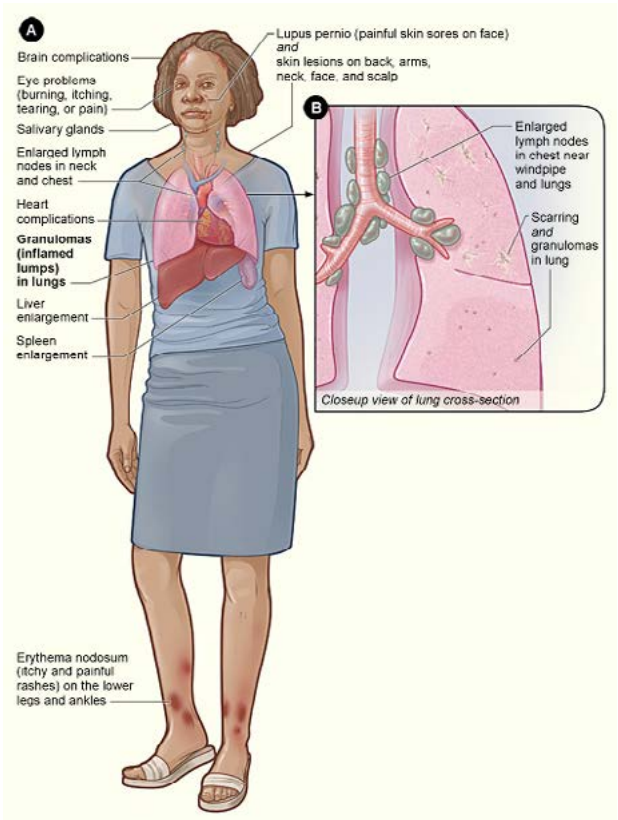

FIGURE 2. Sarcoidosis. From USA National Heart, Lung, and Blood Institute: Lung Diseases: Sarcoidosis: Signs & Symptoms. https://www.nhlbi.nih.gov/health-topics/sarcoidosis

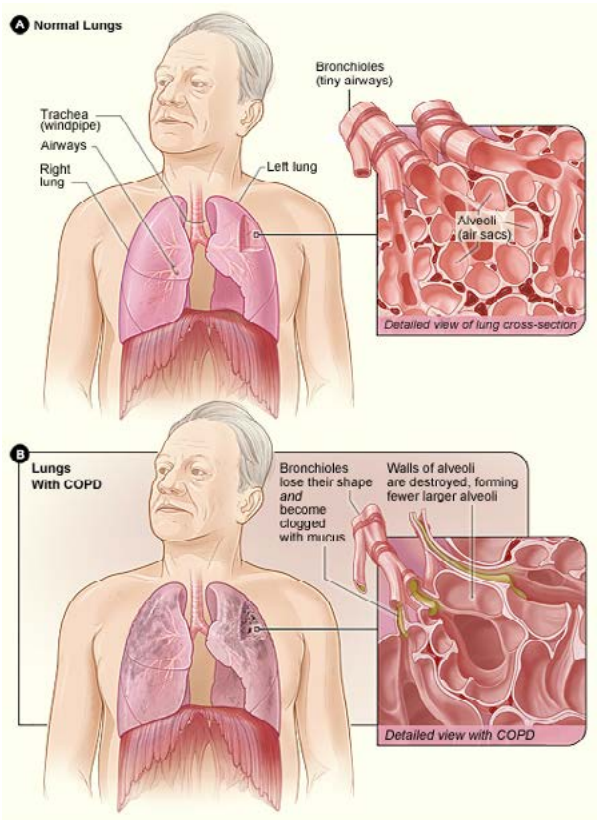

FIGURE 3. Chronic obstructive pulmonary disease (COPD). From USA National Heart Lung and Blood Institute. https://www.nhlbi.nih.gov/health-topics/copd

ples of nine patients with sarcoidosis and suspicion of sarcoidosis, due to mediastinal lymph node enlargement, were investigated by IMS-MCC. Patients with sarcoidosis showed a highly congruent distribution of metabolites in exhaled air, which was different from patients with unspecific mediastinal lymph node enlargement.[19] In another study, IMS-MCC was also used to differentiate these patients by monitoring a single biomarker in breath.[20]

Chronic obstructive pulmonary disease (COPD) is an inflammatory condition characterized by oxidative stress and particular VOCs from lungs (Figure 3).[6] Hauschild et al.[4] analysed breath data by IMS-MCC from 84 volunteers, either healthy or suffering from COPD or bronchial carcinoma and extracted 28-scoring VOCs that allowed differentiating COPD patients. On the other hand, Basanta et al.[21] used differential mobility spectrometry (DMS) to discriminate between individuals with and without COPD. Using gas chromatography-IMS, Allers et al.[22] found three VOCs showing a significant difference between healthy controls and patients with COPD indicating the IMS potential for early detection and differentiation of COPD.

Carbonyls compounds have been defined as cancer markers with significantly higher concentrations in patients with lung cancer distinguishing benign disease from both early and III and IV stages.[23,24] Westhoff et al.[25] used IMS-MCC to study volatile metabolites in human breath of patients with lung cancer. They found typical spectra of patients with lung cancer different from those of the control group demonstrating the usefulness of IMS in medical diagnosis. Analytical methods based on exhaled breath for early detection of lung cancer have been reviewed.[26]

Cystic fibrosis (CF) is an autosomal disorder that thickens mucus clogging lungs, and producing respiratory complications, facilitating the growth of bacteria (Figure 4). CF breath metabolomics investigations using exhaled breath condensate can expose CF metabolic alterations and aid in assessing CF therapies. Traveling wave IMS coupled with mass spectrometry was used to profile metabolites in breath condensates, finding that a panel of three metabolites differentiated between healthy controls and CF patients with excellent cross-validated accuracy.[27]

A comprehensive database of IMS medical appli-

cations has been presented, which combines metabolic maps with heterogeneous biomedical data. The database is a flexible centralized data repository capable of gathering all kinds of information related to the composition of human breath; the platform will support biomarker identification and validation based on IMS-MCC.[28]

APPLICATIONS OF IMS DIAGNOSIS WITH OTHER CLINICAL SAMPLES

Bile acid diarrhoea, inflammatory bowel disease, and renal, liver, and neurodegenerative diseases have been studied with IMS in other biological samples different to breath and the potential of IMS to diagnose these diseases has been shown. An illustration of this potential for disease characterization was an application of IMS-MS analysing blood serum from 60 post-liver transplant patients with recurrent fibrosis progression and 60 non-transplant patients. Significant differential abundances were found in 136 proteins in the serum of transplant patients. Of these, 112 proteins were observed to discriminate between non-progressors (NP) and fast progressors, and 101 between NP and SP (slow progressors) patient groups, with 77 overlapping.[29]

Changes in gut microbiota that affect the health of the intestines and metabolic profile can be determined by IMS or by genomic or faecal analysis. The last ones are too expensive, slow or cumbersome for daily medical practice. The pathogenesis of inflammatory bowel disease (IBD) involves bacterial polysaccharide fermentation producing a fermentation profile traced in urine with electronic nose and Field Asymmetric Ion Mobility Spectrometry (FAIMS).[30] Using FAIMS, Arasaradnam et al.[31] distinguished between complete versus partial bowel cleansing studying the changes in the patient's fermentone and tracked evolving bacterial recolonization.[32] Patients undergoing pelvic radiotherapy often suffer from gastrointestinal side-effects due to products of fermentation caused by gut microflora that can be detected by IMS. Covington et al.[33] investigated electronic nose and FAIMS to identify patients after treatment by their toxicity through IMS

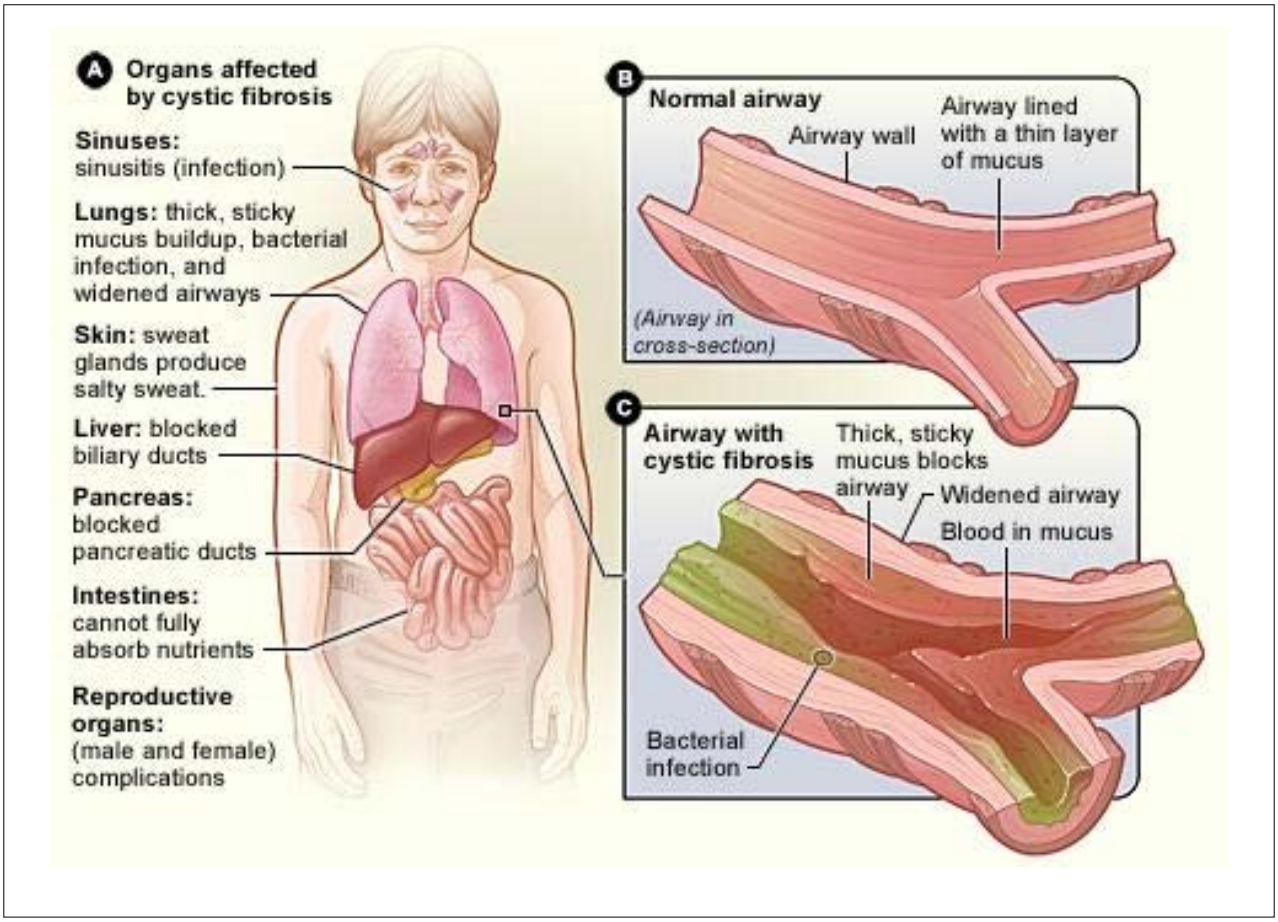

FIGURE 4. Cystic fibrosis. From USA National Heart Lung and Blood Institute. https://www.nhlbi.nih.gov/health-topics/cystic-fibrosis

faecal analysis and informed the treatment pathway for this disease.

Bile acid diarrhoea (BAD) is a gastrointestinal disease diagnosed through imaging techniques. VOCs in urine from patients with BAD and ulcerative colitis were determined in a study. Patients with BAD had 2-propanol and acetamide not present or reduced in ulcerative colitis and control samples. Statistical differences were found between BAD vs. ulcerative colitis and healthy controls.[34] The results indicate the potential of FAIMS for the diagnosis of BAD.

Altered branching and aberrant expression of N-linked glycan are known to be associated with disease states such as cancer. Isailovic et al.[35] examined IMS-MS for characterizing serum N-linked glycan from 81 volunteers, 28 with cirrhosis of the liver, 25 with liver cancer, and 28 apparently healthy. IMS-MS and principal component analysis of the IMS profiles differentiated the liver cancer group from the other samples.[36]

IMS has the potential for the study of neurodegenerative diseases. Zhang et al.[37], studied the striatal metabolomes in a Parkinson's like disease rat model and found metabolic differences with samples and healthy controls using principal component analysis. Intermediate assemblies of amyloid cascades that yield peptide β-sheet fibrils and plaques have been recognized as mediators of neurodegenerative diseases. Bleiholder et al.[38] used IMS to deduce the modulation of peptide self-assembly pathways in the amyloid-β protein fragment *Aβ(25-35)* by two amyloid inhibitors currently in clinical trials for Alzheimer's Disease. They also demonstrated that IMS-MS can guide the development of therapeutic agents and drug evaluation for these processes. The study of amyloid formation using IMS–MS has led to an enhanced understanding of the mechanism by which small molecules modulate amyloid formation.[39]

IMS has also been applied to the determination of different compounds of medical interest in several body fluids.[5] Bocos-Bintintan et al.[40] developed a fast quantitative assay to characterize methanol in human saliva by gas chromatography-DMS in less than three minutes from 25 to 500 mg L^{-1}. Eiceman et al.[41], proposed an alternative simple and cost-effective aspiration condenser to existing anaesthesia monitoring technologies. Common volatile anaesthetic agents (halothane, isoflurane, and enflurane) showed an identification accuracy of 98 % at concentrations higher than 1.0%.

Potential medical applications of IMS

One possible application of IMS breath analysis may be the monitoring of metabolic control in patients with diabetes mellitus (Figure 5). Several studies have been performed trying to relate VOCs in breath with diabetes mellitus. Galassetti et al.[42] found that breath ethanol and acetone would provide a good approximation of the blood glucose profile during a glucose load. Smith et al.[43] reviewed the studies of breath analysis in diabetes, focusing on breath metabolites altered in this disease, highlighting the factors that confound interpretation. They conclude that further work is required in terms of the clinical and analytical validation and which breath metabolites should be monitored. A more recent review on this issue states that it is too early to draw a general conclusion on the relationship between breath acetone and blood glucose from the very limited data in the literature.[44]

The usefulness for the diagnosis of bacterial infections by IMS has been indicated by the determination of bacteria by enzyme-substrate reactions that can have numerous applications in medicine. In a method, o-nitrophenyl-galactopyranoside was introduced in solutions contaminated with bacteria or in cell cultures and bacteria produced o-nitrophenol, detected by IMS.[45] DMS was used for sampling gases produced by bacteria cultures; pattern discovery/

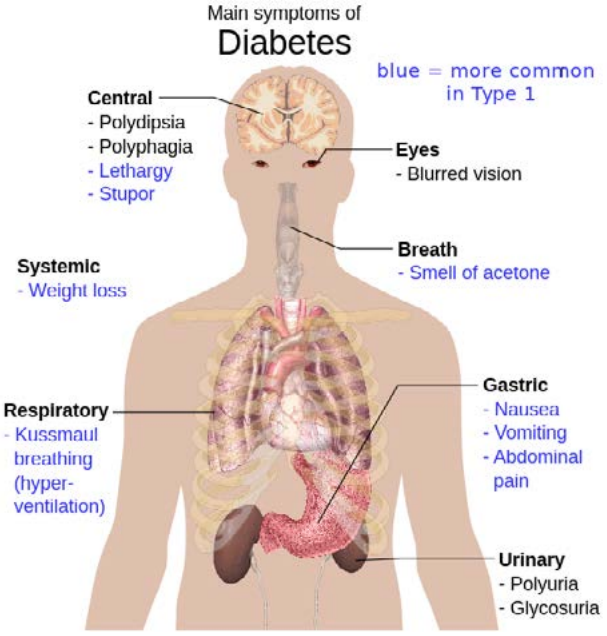

FIGURE 5. Diabetes. From https://commons.wikimedia.org/wiki/File:Main_symptoms_of_diabetes.svg

recognition algorithms were applied to discern multiple species of bacteria in vitro.[46] Other studies with potential applications in medicine investigated biomarkers for Gram-type differentiation of bacteria,[47] proteomes,[48] and metabolomes,[49-51] Medical applications of IMS in breath analysis [52] and FAIMS applications in medical diagnostics[53] have been reviewed.

PHARMACEUTICAL APPLICATIONS

IMS is a fast, low-cost, and sensitive analytical method for quality assessment and control of the production line in the food and pharmaceutical industries, routine screening of batches of raw materials, and the final commercial products. IMS spectra can be obtained in 20–45 ms; IMS instruments can be self-assembled at low cost in the laboratory and maintenance is inexpensive.[54] IMS has been applied to the quantification of propofol,[5] detection of cortisone and betamethasone[55], carbamazepine,[56] and acetaminophen, aspartame, bisacodyl, caffeine, dextromethorphan, diphenhydramine, famotidine, glucosamine, guaifenesin, loratadine, niacin, phenylephrine, pyridoxine, thiamine, and tetrahydrozoline in over-the-counter-drugs and beverages.[57] O'Donnell et al.[58] reviewed the applications of IMS, differential mobility spectrometry, and FAIMS for quality assurance, process monitoring, and maintenance of worker health and safety in the pharmaceutical industry.

IMS represents a low cost, fast and reliable instrumental alternative for the diagnosis of different diseases and metabolic states through the analysis of volatile metabolites found in breath, urine, blood, faeces, and other biological samples. IMS can be used for quality assessment and control in the pharmaceutical industry, and as an alternative to anaesthesia monitoring technologies. Odour analysis in clinical trials is increasing dramatically in a wide range of areas such as several types of cancer, bowel, lung and kidney diseases by sorting through volatile molecules in their breath, sweat, urine, faeces or blood [59] by means of real-time and low-cost analyses and constitutes a non-invasive diagnostic for the Medicine of the third millennium.

RESUMO

A espectrometria de mobilidade iônica (IMS) é uma técnica rápida, de baixo custo, portátil e sensível que separa íons em um tubo de deriva sob a influência de um campo elétrico de acordo com seu tamanho e forma. A IMS representa uma alternativa instrumental não invasiva e confiável para o diagnóstico de diferentes doenças por meio da análise de metabólitos voláteis em amostras biológicas. A IMS possui aplicações em medicina no estudo de compostos voláteis para o diagnóstico não invasivo de carcinoma brônquico, doença pulmonar obstrutiva crônica e outras doenças que analisam respiração, urina, sangue, fezes e outras amostras biológicas. A IMS tem sido usada para estudar misturas complexas, como proteomas, metabólitos, organismos completos como bactérias e vírus, monitorar agentes anestésicos, determinar drogas, produtos farmacêuticos e compostos voláteis em fluidos corporais e outros fluidos. As aplicações farmacêuticas incluem análises de medicamentos sem receita, avaliação de qualidade e verificação de limpeza. A prática médica precisa de métodos não invasivos, robustos, seguros, rápidos, em tempo real e de baixo custo com instrumentos de alta sensibilidade e tamanho compacto para diagnosticar diferentes doenças e a IMS é a ferramenta de diagnóstico que atende a todos esses requisitos da medicina do futuro.

PALAVRAS-CHAVE: *Espectrometria de mobilidade iônica. Testes respiratórios. Pneumopatias. Carcinoma broncogênico.*

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