RAMB

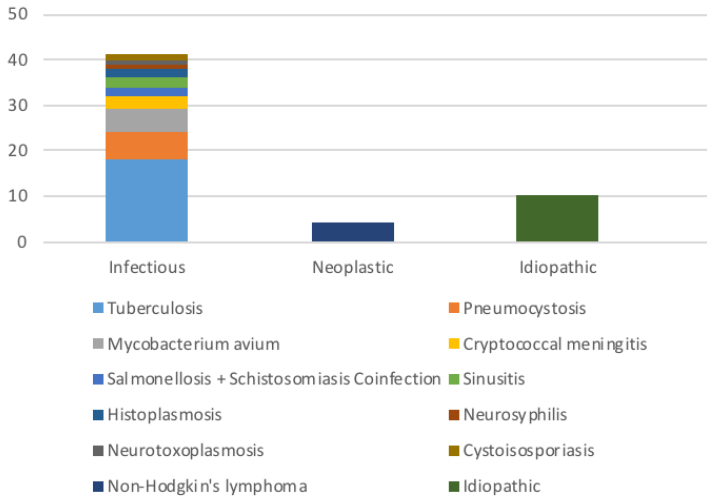
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira

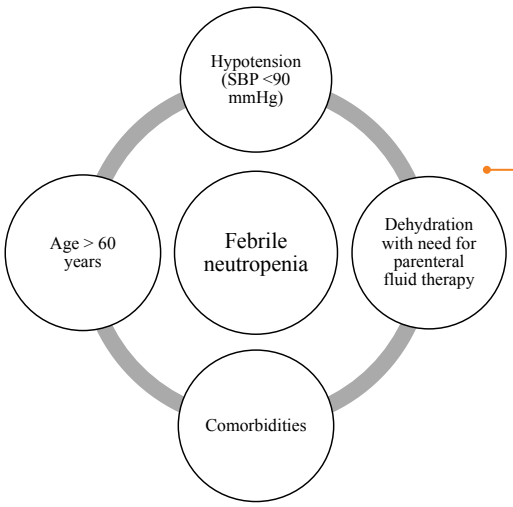
WMA

Volume **65** Number **10** **October 2019**
ISSN **0104-4230**
ISSN **1806-9282** (On-line)

SECTIONS



CAUSES OF FUO ASSOCIATED WITH HIV IN A STUDY CONDUCTED IN BRASIL (1989-1997), ON 55 PATIENTS



FACTORS OF WORSE PROGNOSIS IN NEUTROPENIC PATIENTS WITH FUO

RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

SUMMARY

SECTIONS

ARTICLES

From the measles-free status to the current outbreak in Brasil

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http://dx.doi.org/10.1590/1806-9282.65.10.1129

In 2016, the American continent was declared measles-free as a result of combined actions by countries in the region and the Pan-American Health Organization (PAHO). The disease caused by the virus of the paramyxoviridae family is characterized by being highly transmissible by respiratory route with the possibility of severe evolution with a risk of death, especially in younger age groups with worse social and nutritional conditions. When the vaccine was introduced in 1963, it became possible to control the transmission of the disease and prevent the free circulation of the virus, which led several regions to achieve the measles-free status[1]. In Brasil, the national immunization program incorporated the vaccine in 1970, modifying the schedule of doses over the decades, according to the epidemiological situation of each period.

Shortly after the Americas were declared measles-free, in July 2017, new cases of the disease were reported in Venezuela, where they started to occur endemically. Following migratory flows, cases were reported in Brasil, in the state of Rondônia, as well as in neighboring countries such as Colombia and Ecuador. In 2018, a total of 11 American countries had already reported cases of measles. At the same time, until August 2018 no sustained endemic transmission of measles had occurred in any of these countries, except in Venezuela. At the time, 3,545 cases had been reported in Venezuela, with 62 deaths, and 1,459 cases, with six deaths, had been reported in ten other countries of the region[2]. The presence of the same strain of measles for 12 consecutive months led to the loss of the measles-free status, which, unfortunately, occurred in mid-2018.

In Brasil, after initial cases were reported in Rondônia, other states in the Northern region started notifying more cases, especially the in Amazonas. In July 2018, Roraima and Amazonas declared a state of emergency for 180 days due to the disease. By the end of 2018, 11 Federated Units had notified around 10,000 cases of measles, with 12 deaths. The local vaccination campaigns, especially in the Northern Region, were effective in controlling the outbreak, which was caused by genotype D8 of the measles virus, the same that circulated in Venezuela.

In March 2019, Brasil lost its measles-free status.

In early April of 2019, new cases of measles began to be reported in São Paulo, and the first autochthonous transmission case was confirmed in early May. The initial cases, in April, were considered as imported and came from the island of Malta (arriving by ship through the port of Santos), Israel, and Norway. The genotype involved in the São Paulo cases is the D8.

The most recent data, from the end of August 2019, accounted for 2,753 confirmed cases, 2,109 discarded, and 15,430 under investigation. The distribution includes 13 Brazilian states (São Paulo, Rio de Janeiro, Pernambuco, Santa Catarina, Federal District, Goiás, Maranhão, Paraná, Rio Grande do Norte, Espírito Santo, Bahia, Sergipe, and Piauí)[3]. The state of São Paulo accounts for 98.3% of the confirmed cases, which are distributed through 82.5% of its municipalities, but mostly in the capital. The same state recorded three deaths in patients with no history of vaccination (two children under the age of 1 year and an adult of 42 years)[4].

This latest outbreak leads to important reflections on its causes. There is no doubt that among them, is related to low vaccination coverage. It is recommended that all individuals between the age of 15 months and 29 years receive at least two doses of the vaccine. In recent years, Brasil has registered rates below the 95% coverage target in children. Added to this fact, we have an enormous contingent of adults, especially younger ones, with inadequate immunization due to changes in the vaccination schedule, causing many to have taken only one dose of the vaccine. The dismantling of basic healthcare actions due to the crisis in the country, as well as the increase of anti-vaxxer groups in social media who feed of fraudulent information and untruthful content, contribute to the low coverage in children. It is also known that the average neutralizing antibodies titers in the population have been falling, associated with measles control. This has caused some researchers to discuss the need for a third dose of the vaccine after 15 months of age.

Despite the controversy, all countries that have reached measles-free status did so through consistent immunization campaigns in an attempt to ensure two doses for the entire population[5]. Programmatic and advertising strategies to raise population awareness are key so that we can, once again, become a measles-free country. However, if other countries are not successful as well, the emergence of new outbreaks will always be a reality.

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Peyronie's disease: clinical treatment

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Created on: February 18, 2018

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* This guideline replaces the previous 2016 version.

http://dx.doi.org/10.1590/1806-9282.65.10.1231

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.

Peyronie's disease is an acquired disorder of the connective tissue gained, attributed to repetitive microvascular injury or trauma during sexual intercourse, which leads to the appearance of fibrous plaques or nodules in the tunica albuginea of the penis, reducing local elasticity and curving the penis during an erection. The purpose of this guideline is to provide recommendations that may assist in the decision-making process regarding the clinical treatment for patients with a diagnosis of Peyronie's disease (PD). For this, a systematic review of the literature, was performed, without period restriction, in the MEDLINE database, retrieving 759 papers, of which 37 were selected to respond to clinical doubt. The details about the methodology and the results are set out in Appendix I.

INTRODUCTION

The etiopathogenesis of Peyronie's Disease (PD) is not fully known, but there is a possibility of immunologic genesis[1](D). It is an acquired disorder of the connective tissue gained, attributed to repetitive microvascular injury or trauma during sexual intercourse, which leads to the appearance of fibrous plaques or nodules in the tunica albuginea of the penis, reducing local elasticity and curving the penis during erection[1,2](D). In adults, it is often associated with Dupuytren's contracture (thickening of the palm of the hand that consequently modifies the curvature of the fingers)[3](B), which is not seen in adolescents with PD[4](B).

The diagnosis is based on the medical and sexual history with penile deformity and pain, difficulty during coitus and erectile dysfunction (ED)[2](D). The physical examination includes palpation of the nodules (possible in 70% of cases) and the observation of the curvature of the penis during a natural or induced erection[1](D) or photographs. The penile deformity is the first symptom of the disease in 52% of cases and is present in 94% of affected men[5](D).

The natural history of the PD can vary from spon-

taneous resolution to progressive worsening of the deformity and ED[1](D). The treatment can be clinical or surgical[4](D).

The clinical treatment uses medication via the oral route, intralesional injections, and shockwave therapy[6](D).

Two stages are observed: the acute phase (first six months, characterized by pain and changes in size and/or number of palpable plates and penile deformity), and the chronic or stable phase (between six and 18 months, with possible disappearance of the pain and the stabilization of the size and number of plates)[7](D).

The absence of knowledge on this disease contributes to the diagnostic difficulty, which leads to an estimated prevalence lower than the reality. There is also a greater belief in spontaneous cure more than what actually occurs, and the possibility of the disease existing before the age of 40 years is often ignored; with no investigation of the association of PD in cases of ED and no effective clinical and surgical treatment [8](D).

RESULTS

Oral therapy

Non-steroidal oral anti-inflammatory drugs can be administered to patients with active Peyronie's Disease, which requires treatment for pain[9](D).

Treatment alternatives that use carnitine and tamoxifen[9](B)[10](A) have been abandoned, in addition to para-aminobenzoate potassium (Potaba)[11.12](A), since they have not been associated with significant improvement of pain, curvature, or plaque size.

Vitamin E

Randomized controlled trials (RCTs) that evaluated the use of vitamin E alone or combined with other therapies (intralesional interferon [IFN] α2β or propionyl-L-carnitine) showed no improvement in penile curvature, plaque size, IIEF scores (International Index of Erectile Function) or sexual satisfaction[13.14](A). However, another RCT showed that vitamin E combined with intralesional verapamil (VII) and antioxidants improved the curvature of the penis, plaque size, and IIEF scores[15](B).

A prospective cohort study included 58 men with acute PD (beginning <6 months, without ED and who were treated with vitamin E 800 mg/day orally (OR), and colchicine 1 mg/day OR, for six months. Thirty-six patients were smokers and 22 nonsmokers. With a mean follow-up of 10.3 months, there was a reduction among nonsmokers, in comparison with smokers, for curvature (38% *versus* 54% [p<0.05], respectively) and plaque size (36% *vs.* 50% [p<0.05], respectively). There was no significant difference in response to pain between the two groups [16](B).

It should be noted that vitamin E, in high doses, may increase the risk of cerebrovascular events[17](A).

Intralesional therapy

Collagenase clostridium

Collagenase clostridium histolyticum (CCH) is comprised of a heterogeneous group of seven different enzymes that have shown remarkable specificity for digesting specific proteins, inside the fibers of collagen type I and type III, in physiological conditions.

Two RCTs, Impress ((Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II evaluated results of intralesional infiltration with CCH (0.58 mg) in 417 and 415 patients with PD (penile curvature ≥30 degrees), respectively, with a maximum of four cycles of treatment, compared with a placebo in a one-year follow-up. Each cycle consisted of two infiltrations with an interval of 24-72 hours, weeks apart. All patients underwent modeling (manipulation of the penis in the contralateral direction of the curvature), which was performed by a urologist after each cycle of treatment. The patients were also instructed to perform the modeling at home, three times a day, between the treatment cycles, and try to straighten the penis, during spontaneous erections, once per day. A post-hoc meta-analysis of these two studies (n=832), analyzing data from 74% of this population, showed that CCH, in comparison with the placebo, improved penile curvature (17 degrees *versus* 9.3 degrees; p<0.0001); increased the global response reported by the patient (60.8% *versus* 29.5%; p<0.0001; NNT=4) and increased the risk of adverse events (84.25 *versus* 36.3%; NNH=2). CCH is associated with improvement in the score of PD symptoms (-2.8 ± 3.8 *versus* -1.8 ± 3.5, p=0.0037). The most common adverse events with the use of the CCH were: ecchymosis, swelling, and penile pain. There were six cases of serious adverse events (2.1%) related to treatment with CCH (three cases of corpora rupture and three cases of penile hematoma). No systemic immunological events were reported[18](A).

The effectiveness of the CCH in comparison with the placebo was also assessed, in a 52-week fol-

low-up, for subgroups (curvature of the penis, duration of disease, calcification, and erectile function) of participants of the Impress I/II studies, maintaining consistent results[19](A).

In a before and after study, the safety of intralesional infiltration with CCH in the treatment of PD was evaluated, using a pooled analysis of individual patient data from six studies (n=1,044 men), who received at least one dose of CCH (average number of 7.2 infiltrations/patient). Adverse events (AE) related to treatment (≥1 event) occurred in 85.8% of the 1,044 patients, and most were of mild/moderate severity. The more common AE were: penile hematoma in 50.2%, penile pain in 33.5%, swelling in 28.9%, and pain at the injection site in 24.1%. A total of 0.9% severe adverse events were reported related to treatment, including hematoma in 0.5% and corpora rupture in 0.4%[20](B). These studies did not evaluate the use of collagenase in patients with hourglass deformity or ventral curvature, with calcified plaque or plaque located on the penis base.

The efficacy and safety of CHD in the treatment of PD in the acute phase were evaluated in a historical cohort study. The acute phase was considered the presence of pain and penile plaque, for no more than 12 months. The outcomes evaluated were the change in curvature after CCH treatment, regardless of the number of CCH cycles received, and the frequency of adverse events related to the treatment, comparing a group of patients in the acute phase and another in the chronic phase of PD. A total of 162 patients were included in the study, of whom 36 (22%) were classified as in the acute phase of PD (group 1) and the remaining 126 (78%) as in the stable phase (group 2). There was no significant difference in the change of curvature between the acute and stable group (16.7 versus 15.6 degrees, respectively; p=0.654). There was also no difference in the frequency of adverse events related to the treatment between the acute phase group (four patients, 11%) and the stable phase group (12 patients, 10%, p=0.778). Therefore, the use of CCH in the acute phase of DP is effective and safe[21](B).

Interferon α-2β

A multicenter RCT (reported by Hellström et al.[22] and Kendirci et al.[23]) evaluated intralesional interferon (INF) α-2b and included patients who presented symptoms of PD for more than 12 months and curvature of at least 30 degrees (n=117). The intervention group received intralesional INF α-2β 5 x 10^6 units twice a week for 12 weeks and was compared with a placebo (saline solution). INF α-2b, compared with the placebo, in a three-month follow-up, decreased, on average, the curvature (13 degrees *versus* 4 degrees; p<0.01); reduced, on average, the size of the plaque (54.6% *versus* 19.8%; p<0.001), and increased the number of patients with resolution of pain in during erection (67% *versus* 28%, NNT=3). Penile duplex Doppler ultrasonography showed significant improvements in peak systolic velocity and mean resistive index in the intralesional INF α-2β group, but not in the placebo group. The adverse events of intralesional INF α-2β treatment included penile edema, inflammation, ecchymosis, and flu-like symptoms (fever and arthralgia), which responded well to NSAIDs[22,23](A).

Another RCT compared vitamin E 400 IU twice a day for 24 weeks, intralesional interferon α-2b 5.0 x 10^6 U per week for 12 weeks, and interferon 5 MU per week (for 12 weeks) + Vitamin E 400 IU twice a day (for 24 weeks), in patients with PD in initial stage (average duration of 10.8 months [6 - 18 months]), with at least six months of duration, who presented associated pain, deformity, or penile curvature. Patients with a calcified plaque were excluded from this study. In a six-month follow-up (without losses), there were no statistically significant changes in the objective parameters (degree of penile curvature and plaque size), in comparison with the initial findings in the individual groups or between them (p>0.05 for all comparisons). There was no formation of new plaques or calcification during the study. All patients treated with NPI α-2b had flu-like symptoms (fever, myalgia, and arthralgia)[14].

The effectiveness of intralesional INF-α2b for the PD was evaluated in a before and after retrospective study, reviewing the impact of the moment of therapy from its beginning and the possible predictive variables of the response. A total of 127 patients with pre-treatment curvature (mean ± SD) of 42.4 ± 18.6 degrees received 12 injections (median), fortnightly, of INF-α2B. The PD time of evolution was 2.0 years (median)[24](C).

The response was defined as an improvement of 20% or more in in the curvature. Out of the total number of patients, 54% responded to therapy with an improvement in the global mean by 9.0 degrees (p<0.001). Patients with curvature >30 degrees had a higher probability of response (86% response,

p<0.001); however, an improvement in the pre-treatment curvature was observed in all cases. There was no improvement in the vascular condition of the penis or in ultrasound parameters. Age, pre-treatment curvature, vascular state, ultrasound findings, site of curvature, and IIEF score did not predict the response to therapy. The duration of Peyronie's Disease did not affect the changes in curvature[24](C).

A retrospective cohort compared the results of treatment for PD in men undergoing intralesional INF-α2b, with plaques on different sites. It included 131 patients who received (median) 12 injections (6-24) of intralesional INF-α2b. The patients were stratified in cohorts of ventral plaques (curvature of 44.5 ± 21.5 degrees) and dorsal/side (42.5 ± 18.6 degrees) with a positive response defined as a reduction of the curvature by 20% or more. In total, 91% of the patients responded to the therapy. No significant differences were observed between the two groups in relation to the response rates (54% *versus* 52%, p=0.92) or absolute changes in curvature (8.7 ± 12.6 degrees *versus* 9.3 ± 17.7 degrees, p=0.84). Therefore, there is improvement with intralesional INF-α2b therapy in PD patients, regardless of the site of plaques[25](B).

Verapamil

A placebo-controlled RCT compared intralesional (IL) verapamil with IL saline solution (weekly injections for six months), in patients with PD for an average duration of 16 months (11-24 months) and a volume of plaques, on average, of 1.4 ccs (range of 1.5 to 2.7 cc) before therapy. In comparison with a placebo, IL verapamil (dose ranged from 10 to 27 mg) reduced the size of plaques (57% *versus* 28%, respectively, p<0.04) and improved the quality of erection (43% *versus* 0%, respectively, p<0.02). There was no difference in the improvement of the curvature between the two groups (p>0.05). As an adverse event, there was ecchymosis at the injection site[26](B).

Another RCT included 80 patients with PD (without plaque calcification) who were randomized into IL verapamil 10 mg diluted in 10 ml of distilled water (onset of the disease 20.60 ± 4.2 months) *versus* saline injection (onset of the disease 22.00 ± 4.8 months), two times a week for 12 weeks. In a 24-week follow-up to, there was no difference between the groups in the reduction of the size of the plaque, in pain reduction, reduction of curvature, and improvement of erectile function (p>0.05 for all comparisons)[27](B).

In a before and after study, the administration of IL verapamil in 156 patients with PD resulted in an objective decreased of the curvature in 60% of patients (mean of 30 degrees, ranging from 5 to 90 degrees) and improvement in sexual function in 71% of patients, with an average follow-up of 30.4 months[28](C).

The efficacy of IL verapamil (V) in comparison with intralesional hyaluronic acid (HA) in PD patients (n=140) in the initial phase of the disease (disease duration <12 months associated with a soft nodule or plaque and/or painful erection and/or recent change in penile curvature) was evaluated in a double-blind, multicenter RCT with 12 weeks of follow-up. One group received intralesional treatment with verapamil (10 mg in 5 mL of NaCl 0.9%) per week for 12 weeks (n=70), while the other received intralesional treatment with HA (sodium hyaluronate [sodium salt of hyaluronic acid] 0.8% highly purified,16 mg/2 mL) weekly for 12 weeks (n=70). The difference between the size of the plaque post and pre-treatment was -1.36 mm (SD±1.27) for the IL V group and -1.80 mm (SD±2.47) for the IL HA group (p = not significant [NS] between the groups). There was no difference in penile curvature in the IL verapamil group, while at the IL AH group the curvature of the penis decreased from 4.60 degrees (SD±5.66) from the baseline (p<0.001) and from IL V (p<0.001). Erectile function improved (IIFE-5) in both groups, but without any difference between them (p=NS). There was a global improvement reported by patients (Patient Global Impression of Improvement [PGI-I]), which was greater in the IL AH group (4.0 *versus* 2.0; p<0.05). No adverse events were reported. Therefore, IL HA showed greater efficacy in terms of penile curvature and global improvement, reported by the patient, in comparison with the IL verapamil[29](A).

Topical pharmacological agents

3.1 H-100 Gel

A recent double-blind RCT evaluated the safety and efficacy of the H-100 gel, a combination of nicardipine, superoxide dismutase, and emu oil, applied topically to treat the acute phase of PD, defined as a disease with 12 months duration. Twenty-two patients in the acute phase of PD were randomized to receive H-100 (n=11) or a placebo (n=11) in two daily applications, for three months. After three months, all patients in the study received three months of treatment with H-100. The patients could not use a treatment for PD in the six months prior to the randomization. H-100 showed

significant improvement in all parameters of PD in six months: average increase of the length of the penis taut (22.6%, p=0.0002), an average reduction of curvature (40.8%, p=0.0014) and an average reduction of the level of pain (85.7%, p=0.004). The placebo group showed no significant improvement, except for an average increase in the length of the penis taut (6.8%, p=0.009). The patients who crossed over from the placebo to H-100 showed significant improvement in all parameters: average increase of the length of the penis taut (17.5%, p=0.000007), an average reduction of curvature (37.1%, p=0.006), and an average reduction of the level of pain (40%, p=0.17). The drug was well-tolerated, and a cutaneous rash was the only adverse event[30](B).

Iontophoresis with verapamil

A nonblind RCT with a loss of 25% of the population included randomized 96 patients with PD to receive verapamil 5 mg and dexamethasone 8 mg (n=47) or lidocaine 2% (n=49), by means of transdermal therapy by iontophoresis, in sessions of 20 minutes four times a week for six weeks. The verapamil and dexamethasone group, in comparison with the lidocaine group, had decreased, on average, penile curvature (22 degrees *versus* 0 degrees; p<0.0001) and plaque volume (476 mm^3 *versus* 4.8 mm^3, p<0.0001). There was no difference in pain reduction between both groups[31](B).

Another double-blind, placebo-controlled RCT evaluated the efficacy of verapamil administered by iontophoresis. A total of 42 men with PD were randomized to receive verapamil 10 mg in 4 cm^3 of saline solution (n=23) or 4 cm^3 of saline solution (n=19) administered by iontophoresis, twice a week for three months. To better assess the effectiveness, the total number of patients with significant improvement in curvature (20 degrees or more) was calculated and compared. There was no difference in the reduction of penile curvature between the groups (30.4% in the verapamil group and 21.1% in the placebo group; ARI = 9.3%, 95% CI -0.356 to 0.170; NNH=NS)[32](B).

Extracorporeal shockwaves

A systematic review examined the results from three RCTs that evaluated the efficacy of extracorporeal shockwave therapy, but the mechanism of action is not yet understood. The studies included 238 patients. Hatzichristodoulou et al. and Chitale et al. included patients in the stable phase of the disease, while in the study of Palmiere et al., patients who had symptoms present for a period of fewer than 12 months were eligible. Therefore, the last study may have included patients in the acute phase of PD. The patients in the Hatzichristodoulou et al. study were treated pharmacologically without effect before the inclusion, while the other two studies used ESWT (Extracorporeal Shockwave Therapy) as the first-line treatment. The follow-up ranged between four weeks and six months between the studies. The RCTs showed improvement in pain with extracorporeal shockwaves therapy, but there were no significant reductions in objective measures of the severity of PD (penile curvature and plaque size). Hatzichristodoulou et al. showed that, although the ESWT can improve pain, this is the only symptom of PD that often resolves itself over time, without intervention[33](A).

Results of a meta-analysis revealed that ESWT can be an effective and relatively safe choice for PD patients with plaques and painful erection. They included in this meta-analysis six comparative studies (a total of 443 patients). Three studies, including a total of 225 patients, evaluated the size of the plaque. The pooled data from these studies revealed a significant reduction in the size of the plaque in the ESWT group compared with the control group (OR 2.07, 95% CI 1.11-3.85, I^2=0%; p=0.02). The data describing the improvement of the penile curvature were grouped (three studies), including 198 men, and showed no difference between the groups (OR 1.88, 95% CI: 0.97-3.65, I^2=0%; p=0.06). There was no difference in sexual function between the ESWT and placebo groups (six studies and 296 patients; OR 2.22, CI 95% 0.69-7.11; I^2=62%, p=0.18)[34](A).

This meta-analysis showed that the ESWT group, in comparison with the control group, had more patients with pain relief (three studies and a total of 212 patients; OR 4.46, CI 95% 2.29-8.68, I^2=15%, p<0.0001) and a larger number of patients with complete remission of the pain (three studies and 164 patients; OR 5.86, CI 95% 2.66-12.92, I^2=56%; p<0.0001), but no improvement of the curvature or sexual function. The results were similar for sensitivity analysis and publication bias when only RCTs were included. In this study, ESWT was well tolerated, in general, although there was an incidence of some complications that do not require intervention, such as penile bruises and urethral bleeding[34](A).

ESWT may be considered in men with significant pain due to PD, but they should be informed that it

is unlikely to improve penile curvature and that, in many cases, the pain is resolved over time without intervention.

Radiotherapy (rt)

A non-randomized clinical trial compared two doses of radiotherapy (one treatment of 2.2 to 5.5 Gy *versus* two treatments with a total of 4.4 to 10.4 Gy) with an untreated control group. With regard to the effects on the curvature, the rates of improvement were similar in the two RT groups (50% and 39%) and in the untreated control group (52%). Regarding plaques, the rates of improvement in the RT groups (55% and 44%) were equal to those of the untreated control group (58%). The improvement rates for pain were similar in both RT groups (100% and 92.3%) and in the untreated control group (100%)[35](B).

Recommendation

• In combined therapy (e.g., IL verapamil and antioxidants, colchicine), vitamin E can bring some benefits, but alone, like other oral treatments, it should not be used to improve penile curvature or plaque size. (B)

• Intralesional collagenase clostridium is effective and safe both in the acute and stable phases of PD. (B)

• Intralesional injections of collagenase clostridium decreases the curvature and plaques in patients with curvatures >30º and <90º, with minimal severe adverse events. (B)

• Injections of intralesional interferon α2b can improve the curvature, decrease the size of uncalcified plaques, and pain. (B)

• There is a discrete improvement with intralesional INF-α2b therapy in PD patients, regardless of the site of plaques. (B).

• Intralesional injections of verapamil may result in a reduction of penile curvature and plaque size. (B)

• IL hyaluronic acid showed greater efficacy in terms of penile curvature and global improvement, reported by the patient, in comparison with the IL verapamil. (A)

• There is controversy regarding the use of iontophoresis with verapamil in the treatment of PD. (B)

• Extracorporeal shockwaves can improve pain; however, that symptom of PD is often resolved over time, without any intervention. (A)

• Extracorporeal shockwaves do not improve penile curvature in PD nor the size plaques. (A)

• Radiotherapy should not be indicated for the treatment of PD.

ANNEX I

Clinical question

What are the clinical therapy practices for Peyronie's Disease?

Eligibility criteria

The main reasons for exclusion were: they did not respond to the PICO and study design.

Narrative reviews, case studies, series of cases, studies with preliminarily results presentations were, initially, excluded.

Search for papers

Database

The scientific databases consulted were Medline (via PubMed), Central Cochrane, and references of the selected studies.

Identification of descriptors

P	Peyronie's Disease
I	Clinical treatment
C	Another clinical treatment, placebo, or no treatment
O	Benefit or damage

Research strategy

Searches conducted until February 12, 2018.

Medline via PubMed

#1 (Peyronie's Disease OR Peyronies Disease OR Peyronie Disease OR Penile Induration) AND (Therapy/Broad[filter] OR systematic[sb])

#2 (Peyronie's Disease OR Peyronies Disease OR Peyronie Disease OR Penile Induration) AND (Random* OR Comparative study OR Comparative studies OR systematic[sb])

#1 OR #4 = 759 studies

Central (Cochrane)

(Peyronie's Disease OR Peyronies Disease OR Peyronie Disease OR Penile Induration) = 140

Others

Peyronie's Disease = 77

Critical evaluation

Relevance - clinical importance

This guideline was prepared by means of a clinically relevant question in order to gather information

in medicine to standardize approaches and assist in decision-making.

Reliability - Internal validity

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the databases consulted were independently and blindly conducted, in total accordance with the inclusion and exclusion criteria. Finally, studies with potential relevance were separated. When the title and the summary were not enlightening, we sought for the full article.

Only studies with texts available in its entirety were considered for critical evaluation.

No restriction was made regarding the year of publication.

Languages: Portuguese, English, and Spanish.

Results application - External validity

The level of scientific evidence was classified by type of study, according to Oxford[36](Table 1).

TABLE 1. GRADES FOR RECOMMENDATION AND LEVELS OF EVIDENCE

A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lower consistency.
C: Uncontrolled case/study reports.
D: Opinion deprived of critical evaluation, based on consensus, physiological studies, or animal models.

The selected evidence was defined as a randomized controlled clinical trial (RCT) and submitted to an appropriate critical evaluation checklist (Table 2). The critical evaluation of RCT allows to classify it according to the Jadad score[37], considering Jadad trials < three (3) as inconsistent (grade B) and those with score ≥ three (3) consistent (grade A).

When the evidence selected was defined as a comparative study (observational cohorts, or non-randomized clinical trial), it was subjected to an adequate critical assessment checklist (Table 3), allowing for the classification of the study according to the Newcastle Ottawa Scale[38], which considered consistent cohort studies with scores ≥ 6, and inconsistent < 6.

TABLE 2. PROCESS FOR CRITICAL EVALUATION OF RANDOMIZED CONTROLLED TRIALS

Study data Reference, study design, Jadad, level of evidence	Sample size calculation Estimated differences, power, significance level, total number of patients
Patient selection Inclusion and exclusion criteria	Patients Recruited, randomized, prognostic differences
Randomization Description and blinded allocation	Patient follow-up Time, losses, migration
Treatment protocol Intervention, control, and blinding	Analysis Intention to treat, analyzed intervention and control
Outcomes considered Primary, secondary, measurement instrument for the outcome of interest	Results Benefits or harmful effects in absolute data, benefits or harmful effects on average

A Measurement Tool to Assess Reviews (Amstar)[39] was used to evaluate the quality of the systematic reviews. This tool provides a global quality rating on a scale from 0 to 11, in which 11 represents a review of the highest quality. Quality categories were determined as follows: low (0 to 3 score), medium (4 to 7 score), and high (8 to 11 score). SRs of low and medium quality were excluded.

Method of extraction and result analysis

For results with available evidence, the population, intervention, outcomes, presence or absence of benefits and/or harmful effects, and controversy will be specifically defined whenever possible.

The results will be presented preferably in absolute data, absolute risk, number needed to treat (NNT) or number needed to harm (NNH) and, eventually, in mean and standard deviation values (Table 4).

TABLE 3. PROCESS FOR CRITICAL EVALUATION OF COHORT STUDIES

Representativeness of the exposed and selection of the non-exposed (Max. 2 points)	Exposure definition (Max. 1 point)	Demonstration that the outcome of interest was not present at the beginning of the study (Max. 1 point)	Comparability on the basis of the design or the analysis (Max. 2 points)	Outcome assessment (Max. 1 point)	Adequate follow-up time (Max. 2 points)	Scores and level of evidence

TABLE 4. SPREADSHEET USED FOR DESCRIBING AND PRESENTING THE RESULTS OF EACH STUDY

Evidence included
Study design
Selected population
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ratio, mean

RESULTS

Studies returned (02/2018)

TABLE 5. NUMBER OF PAPERS RETURNED FROM THE SEARCH METHODOLOGY USED IN EACH OF THE SCIENTIFIC DATABASES

DATABASE	NUMBER OF PAPERS
Primary	
PubMed-Medline	759
Cochrane	140

Application of evidence - Recommendation

The recommendations will be elaborated by the authors of the review, with the initial characteristic of synthesis of evidence, is subject to validation by all authors who participated in creating the Guideline.

The available evidence will follow some principles of exposure: it will be by the outcome and will have as components: number of patients, type of comparison, magnitude, and precision (standard deviation and 95% CI).

Its strength will be estimated (Oxford[36]/Grade[40]) as 1b and 1c (grade A) or strong, and as 2a, 2b and 2c (grade B) or moderate weak, or very weak.

Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information in order to standardize approaches that can aid the physician's reasoning and decision-making process. The information contained in this project must be submitted to the evaluation and criticism of the physician responsible for the conduct to be followed, given the reality and clinical condition of each patient.

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Total and partial laparoscopic adrenalectomy

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http://dx.doi.org/10.1590/1806-9282.65.10.1240

Question: Adrenalectomy (laparoscopic) for patients with subclinical Cushing's syndrome?
(Page 582)

Answer: There are benefits in the surgical treatment (laparoscopic) for reducing the risk of metabolic syndrome (glucose intolerance), hypertension, and dyslipidemia in patients with subclinical Cushing's syndrome (Page 584).

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ORIGINAL ARTICLE

Current status of Brazilian interprofessional education: a national survey comparing physical therapy and medical schools

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http://dx.doi.org/10.1590/1806-9282.65.10.1241

SUMMARY

OBJECTIVES: *To investigate how many Brazilian medical and physical therapy schools have initiatives and courses related to IPE in their curricula, assessing the barriers and factors associated with their implementation and comparing the differences between both programs.*

METHODS: *This nationwide survey was carried out in 2017 and included representatives of all physical therapy and medical schools in Brasil. Offers of interprofessional activities and related opinions and barriers were evaluated.*

RESULTS: *A total of 76 (33.9%) of the medical and 159 (41.4%) of the physical therapy schools answered the questionnaires. At least 68.4% of the medical schools and 79.2% of the physical therapy schools have IPE initiatives, although the number of mandatory courses and clerkships is still low. Despite recognizing IPE's importance in health education, school representatives see the lack of integration of programs, conflicting schedules, and the lack of institutional support as barriers. In physical therapy, there is a smaller perception of barriers and greater incorporation of mandatory programs in the curriculum.*

CONCLUSION: *These results will help in the development of future interventions that can enhance IPE in curricula in developing countries.*

KEYWORDS: *Interprofessional education. Medical students. Physical therapy specialty.*

INTRODUCTION

Interprofessional education (IPE) in health is an approach that promotes an interactive and shared learning process, striving to improve collaboration and the quality of focus on health, providing collaborative professional action[1].

In this context, the curriculum needs to promote key IPE attributes such as clarifying interprofessional (IP) competencies, fostering systematic and longitudinal curricular activities, and using active methods that make students able to have early contact with different professions[3]. In the same way, evidence has emerged that this approach to teaching leads to better outcomes, such as improved perceptions of and attitudes about IPE, changes in attitudes/skills, and improved patient care[3].

Despite growing evidence from research, the teaching of interprofessionality is still very heterogeneous throughout the world, varying from 14% to 80%[4-7]. The

DATE OF SUBMISSION: 16-Apr-2019
DATE OF ACCEPTANCE: 30-Jun-2019
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main barriers to implementing IPE are restrictions in the curriculum, lack of planning, lack of resources, communication among different professions, large class size, and stereotypes[4,5,8].

In this context, little is still known about the presence of IPE in developing countries, including those in Latin America[9] and, to the best of our knowledge, there is still no survey of IPE initiatives in Latin America and, particularly, in Brasil, considered one of the countries with the highest number of healthcare schools[10].

Attempting to fill these gaps, the present study aimed to investigate the number of Brazilian medical and physical therapy schools with initiatives and programs related to IPE in their curricula, evaluate the barriers and factors associated with this implementation, and compare whether there are differences in the inclusion of and opinions about IPE between both programs.

METHODS

Study design and participants:

This is a nationwide online survey carried out in 2017, in which representatives from all Brazilian physical therapy and medical schools were invited to participate. This project was approved by the Research Ethics Committee of the Federal University of Juiz de Fora, Brasil. All participants received a letter presenting the project via email with a direct link to the survey questionnaire and signed an online consent form.

Criteria for eligibility

All Brazilian physical therapy (PT) and medical (MD) schools registered with the Ministry of Education having programs in these areas were invited to participate. Schools that did not fill out the form or had no valid phone/email contacts were not included. In the case of duplicate responses, or when two representatives from the same school responded, we used the response of the person who occupied the highest position.

Concept used

For this study, we assumed that IPE "involves educators and learners from 2 or more health professions and their foundational disciplines who jointly create and foster a collaborative learning environment"[2].

Instrument Used

Data was collected using a 10-minute electronic questionnaire sent by email to the school's coordinator or director, containing:

- Sociodemographic data, respondent's position in the school, number of students graduated per year, type of school (public or private), and the school's geographical location;
- Interprofessional learning activities offered, whether there are mandatory or elective classes and internships, course semesters when activities are offered, main areas and which educational strategies were used. If there were programs related to IPE, the person responsible for the institution was asked to describe the programs' names, syllabus, and characteristics;
- Opinion about IPE and potential barriers to its implementation, a questionnaire with 13 items created by the authors and adapted from published literature[8], evaluating the respondents' perception about IPE's importance and the implementation of IPE in their institution. The questions were answered using a Likert scale that varied from Strongly Disagree (1) to Strongly Agree (5).

Details of the questions asked can be seen in the results section.

Procedures

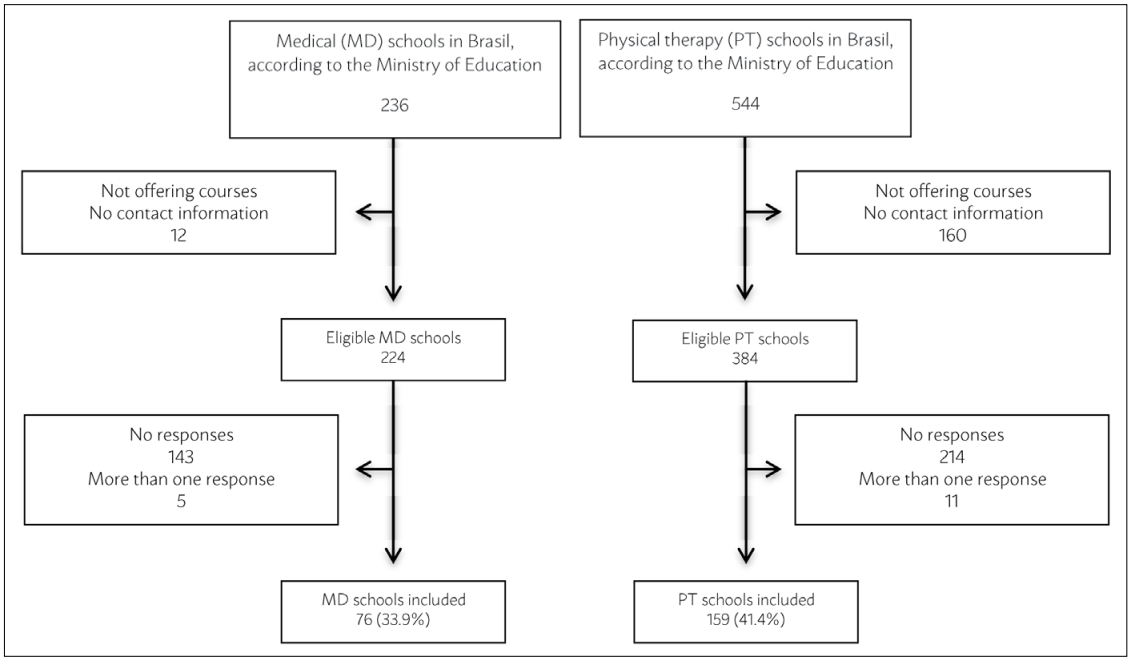
To verify how many medical and physical therapy schools there are in Brasil, we consulted the Ministry of Education's website, from which we compiled the names of the programs and contact information for their leadership. This procedure revealed a total of 224 medical and 384 physical therapy schools to which we were able to send the questionnaires (Figure 1 – supplementary material).

In order to increase responses, the form was sent up to three times to those who had not yet answered it yet, during the year when the data was collected, with a deadline of 60 days each time. We also chose to make contact by telephone to confirm that the email was correct and to remind people to answer the questionnaire.

Data analysis

Descriptive analysis describing the schools' characteristics and the details of IPE activities in MD and PT courses was carried out using frequency, percentage,

SUPPLEMENTARY FIGURE 1. DATA COLLECTION FLOWCHART



mean, and standard deviation. Inferential analysis was then conducted as follows: first, a comparison concerning organizational characteristics and the presence or absence of different IP activities between MD and PT courses was made using chi-square for categorical variables and independent t-test for continuous variables. The same procedures were used to compare the MD and PT representatives' opinions.

Then, stepwise-forward logistic regression models were used to investigate which factors were associated with the presence or absence of IP activities. SPSS version 21 (SPSS Inc.) was used, and a $p<0.05$ was considered significant.

RESULTS

A total of 78 (33.9%) of 224 Brazilian medical schools and 159 (41.4%) of 384 physical therapy schools responded to our questionnaires. A detailed flowchart of this process can be found in Supplementary Figure 1.

Table 1 presents a comparison of these schools' characteristics and the type of IPE programs offered. PT schools were more frequently private institutions (79.9% versus 52.6%, $p<0.001$) while MD schools had more students graduating yearly (87.7 versus 52.7, $p<0.001$). As for IPE programs, 79.2% of PT schools and 68.4% of MD schools reported having IPE activity ($p=0.076$). PT schools offered more mandatory IPE courses (45.3% versus 27.6%, $p=0.010$) and more mandatory IPE clerkships (42.1% versus 17.1%, $p<0.001$), while other IPE courses and activities were offered similarly between courses.

Supplementary tables 1 and 2 show details concerning each IPE activity in both courses. Both usually feature mandatory courses for students in the early undergraduate years and mandatory clerkships for those in late undergraduate years; most courses were related to primary care and public health. The traditional method was still the most used for almost all courses, but other strategies such as problem-posing education, problem-based learning, and team-based learning were also frequently used.

The opinions of the MD and PT school representatives are presented in Table 2. Almost all representatives tended to agree or strongly agree that IPE activities are important and that students should be prepared for interprofessionality (99.1%), that institutional support has an influence on the development of IPE activities (92.8%), and that their institution works with other courses in an integrative manner (59.6%). However, they also agreed that Brazilian schools (16.2%) and the Brazilian health system (23.4%) are not paying enough attention to IPE. Almost half of them reported problems with time/schedule incompatibilities (46.4%) between courses. Comparing schools, PT representatives tend to believe more that their institution works with other courses in an integrative and collaborative manner and that their institution does not have "free time" for their

students. On the other hand, MD representatives tend to believe more that their school curricula are very heterogeneous, hindering an interaction between students and teachers. These results can be seen in Supplementary Table 3.

Stepwise-forward logistic regression (Table 3) revealed that "institutions that work in an integrative and collaborative manner" were more likely to have IPE activities, mandatory IPE courses, and mandatory IPE clerkships. On the other hand, institutions that did not financially support IPE activities had lower chances of having mandatory IPE courses, and institutions that did not academically support IPE activities had lower chances of having IPE activities and mandatory IPE clerkships. Finally, PT courses were more prone to having mandatory IPE clerkships, but not IPE activities and mandatory IPE courses after the logistic regression.

DISCUSSION

In this study, we have outlined the current status of IPE initiatives in Brazilian medical and physical therapy schools' curricula.

In this study, the scenario identified in Brasil, with almost 80% of physical therapy and 69% of medical schools having IPE, is comparable to previous studies in medical schools conducted in New Zealand/Australia (80%)[6] and in the United States (66%)[5]; it is also greater than in Japanese physical therapy schools (14%)[7]. However, it is still different from Canada, where 100% of the schools have this type of initiative4. Despite this

TABLE 1. COMPARISON OF MEDICAL AND PHYSICAL THERAPY SCHOOLS' CHARACTERISTICS AND TYPE OF INTERPROFESSIONALITY COURSES OFFERED.

		Total (n=235)	Medicine (n=76)	Physical Therapy (n=159)	p
Type of University	Public Private	68 (28.9%) 167 (71.1%)	36 (47.4%) 40 (52.6%)	32 (20.1%) 127 (79.9%)	<0.001
Region	South Southeast Center-West Northeast North	59 (25.1%) 97 (41.3%) 19 (8.1%) 46 (19.6%) 14 (6.0%)	16 (21.1%) 35 (46.1%) 4 (5.3%) 16 (21.1%) 5 (6.6%)	43 (27.0%) 62 (39.0%) 15 (9.4%) 30 (18.9%) 9 (5.7%)	0.616
Respondent	Director Dean/coordinator Other professors	11 (4.7%) 199 (84.7%) 25 (10.6%)	5 (6.6%) 61 (80.3%) 10 (13.2%)	6 (3.8%) 138 (86.8%) 15 (9.4%)	0.408
Students graduating yearly		64.0 (44.1)	87.7 (43.3)	52.7 (39.9)	<0.001
Type of IP Activity	Interprofessional Multidisciplinary Both None	81 (34.5%) 41 (17.4%) 97 (41.3%) 16 (6.8%)	24 (31.6%) 15 (19.7%) 28 (36.8%) 9 (11.8%)	57 (35.8%) 26 (16.4%) 69 (43.4%) 7 (4.4%)	0.149
Do you have any IP Activity?	Yes No	178 (75.7%) 57 (24.3%)	52 (68.4%) 24 (31.6%)	126 (79.2%) 33 (20.8%)	0.076
Mandatory IP Courses	Yes No	93 (39.6%) 142 (60.4%)	21 (27.6%) 55 (72.4%)	72 (45.3%) 87 (54.7%)	0.010
Elective IP courses	Yes No	86 (36.6%) 149 (63.4%)	26 (34.2%) 50 (65.8%)	60 (37.7%) 99 (62.3%)	0.665
Mandatory Clerkship	Yes No	80 (34.0%) 155 (66.0%)	13 (17.1%) 63 (82.9%)	67 (42.1%) 92 (57.9%)	<0.001
Elective Clerkship	Yes No	21 (8.9%) 214 (91.1%)	7 (9.2%) 69 (90.8%)	14 (8.8%) 145 (91.2%)	0.919
Other IP Activities	Yes No	172 (73.2%) 63 (26.8%)	50 (65.8%) 26 (34.2%)	122 (76.7%) 37 (23.3%)	0.085
Extension project	Yes No	165 (70.2%) 70 (29.8%)	49 (64.5%) 27 (35.5%)	116 (73.0%) 43 (27.0%)	0.223
Training Project	Yes No	46 (19.6%) 189 (80.4%)	20 (26.3%) 56 (73.7%)	26 (16.4%) 133 (83.6%)	0.080
Undergraduate Research Project	Yes No	112 (47.7%) 123 (52.3%)	31 (40.8%) 45 (59.2%)	81 (50.9%) 78 (49.1%)	0.164
Colloquium/Symposium	Yes No	109 (46.4%) 126 (53.6%)	30 (39.5%) 46 (60.5%)	79 (49.7%) 80 (50.3%)	0.163
Congresses	Yes No	65 (27.7%) 170 (72.3%)	17 (22.4%) 59 (77.6%)	48 (30.2%) 111 (69.8%)	0.275

TABLE 2. THE OPINIONS OF MEDICAL AND PHYSICAL THERAPY SCHOOLS' REPRESENTATIVES CONCERNING INTERPROFESSIONAL EDUCATION

Likert (% of those who agree or strongly agree)	Total (n=235)	Medicine (n=76)	Physical Therapy (n=159)	p
Do you consider Interprofessional Education activity to be important for training professionals in the area of health?	233 (99.1%)	75 (98.7%)	158 (99.4%)	0.543
Do you agree that students should be prepared to act interprofessionally while still in undergraduate school?	233 (99.1%)	74 (97.4%)	159 (100.0%)	0.104
Do you agree that your institution manages to produce undergraduate curriculum for healthcare courses in an integrative and collaborative manner?	140 (59.6%)	32 (42.1%)	108 (67.9%)	<0.001
Do you agree that both institutional and academic institutional support interferes with the development of interprofessional activities in undergraduate health courses?	218 (92.8%)	73 (96.1%)	145 (91.2%)	0.281
Do you agree that undergraduate health courses in Brasil have paid adequate attention to interprofessional work?	38 (16.2%)	9 (11.8%)	29 (18.2%)	0.258
Do you agree that the Brazilian Health System has paid adequate attention to interprofessional work?	55 (23.4%)	23 (30.3%)	32 (20.1%)	0.100
My institution does NOT support interprofessionalism ACADEMICALLY.	28 (11.9%)	13 (17.1%)	15 (9.4%)	0.130
My institution does NOT support interprofessionalism FINANCIALLY.	55 (23.4%)	20 (26.3%)	35 (22.0%)	0.511
Undergraduate course curriculum at my institution is heterogenous, which makes the interaction between students and faculty difficult.	82 (34.9%)	43 (56.6%)	39 (24.5%)	<0.001
My institution does not offer "green zones*" (* shared free time, without activities) in course schedules, thus making the interaction between students and faculty difficult.	86 (36.6%)	19 (25.0%)	67 (42.1%)	0.014
There are difficulties in communication between courses at my institution.	66 (28.1%)	22 (28.9%)	44 (27.7%)	0.877
There are difficulties in time management between courses at my institution.	109 (46.4%)	40 (52.6%)	69 (43.4%)	0.209

TABLE 3. FACTORS ASSOCIATED WITH THE PRESENCE OF INTERPROFESSIONAL ACTIVITIES USING STEPWISE-FORWARD LOGISTIC REGRESSION*

IP activities[a]				
	OR	Lower	Upper	p
Integrated Curriculum	2.68	1.35	5.30	0.005
Not Supported Academically	0.64	0.46	0.89	0.008
Mandatory IP course[b]				
	OR	Lower	Upper	p
Integrated Curriculum	1.52	1.13	2.04	0.005
Not Supported Financially	0.73	0.54	0.97	0.034
Mandatory IP clerkship[c]				
	OR	Lower	Upper	p
Physical Therapy School	2.98	1.46	6.05	0.002
Integrated Curriculum	1.45	1.04	2.02	0.025
Not Supported Academically	0.63	0.43	0.91	0.015

a: Hosmer Lemeshow Chi-square=6.06, p=0.194; Cox & Snell R Square = 0.113, Nagelkerke R Square= 0.154

b: Hosmer Lemeshow Chi-square=10.54, p=0.229; Cox & Snell R Square = 0.102, Nagelkerke R Square= 0.126

c: Hosmer Lemeshow Chi-square=5.18, p=0.738; Cox & Snell R Square = 0.146, Nagelkerke R Square= 0.202

* The variables entered in the model were type of institution (private or public), number of students, course (PT or MD), region (wealthy or poor) and all representatives' opinions.

apparently satisfactory number, most of the initiatives are still sporadic, not longitudinal and non-mandatory in the curriculum, which differs from the reality in countries like Canada, New Zealand, and Australia[6].

As for courses offered in IPE, we found that primary care is the most common field, and the area of Public Health is the one most used. These findings reinforce the idea that IPE and interprofessional practice (IPCP) are enhanced when students and professionals work together with patients and the community in the real world, seeking decision making in complex situations, such as those experienced by family health teams.

SUPPLEMENTARY TABLE 1:. DETAILS CONCERNING EACH INTERPROFESSIONAL EDUCATION ACTIVITY IN MEDICAL COURSES

Mandatory Course – present in 21 (27.6%) medical courses
Period offered: 1st (6), 2nd (9), 3rd (9), 4th (9), 5th (9), 6th (4), 7th (3), 8th (3), 9th (3), 10th (3), 11th (5) and 12th (4)
Most common areas: Health management: 7, public health: 17, clinical areas: 7, health education: 9
Level of focus: Primary: 20, secondary: 5, tertiary: 0
Methods used: Traditional: 7, problem-posing education: 15, PBL: 3, TBL: 9, others: 3
Average number of students involved per semester: 161.6 (SD: 148.9)
Elective Course – present in 26 (34.2%) medical courses
Period offered: 1st (6), 2nd (6), 3rd (8), 4th (5), 5th (6), 6th (6), 7th (8), 8th (6), 9th (4), 10th (3), 11th (3) and 12th (3)
Most common areas: Health management: 7, public health: 17, clinical areas: 13, health education: 11
Level of focus: Primary: 24, secondary: 12, tertiary: 8
Methods used: Traditional: 16, problem-posing education: 17, PBL: 5, TBL: 11, others: 3
Average number of students involved per semester: 79.8 (SD: 110.8)
Mandatory Clerkship – present in 13 (17.1%) medical courses
Period offered: 1st (0), 2nd (0), 3rd (0), 4th (0), 5th (1), 6th (0), 7th (1), 8th (1), 9th (7), 10th (7), 11th (7) and 12th (7)
Most common areas: Health management: 5, public health: 10, clinical areas: 9, health education: 7
Level of focus: Primary: 13, secondary: 7, tertiary: 6
Average number of students involved per semester: 95.9 (SD: 94.5)
Elective Clerkship – present in 7 (9.2%) medical courses
Period offered: 1st (0), 2nd (1), 3rd (2), 4th (2), 5th (2), 6th (2), 7th (3), 8th (3), 9th (3), 10th (3), 11th (3) and 12th (2)
Most common areas: Health management: 2, public health: 6, clinical areas: 4, health education: 1
Level of focus: Primary: 6, secondary: 4, tertiary: 3
Average number of students involved per semester: 26.8 (SD: 20.6)
Other Initiatives – present in 50 (65.7%) medical courses
Extension project: 49/ Training project: 20 / IC Project: 31 / Colloquium/symposiums: 30 / Congresses: 17
Methods used: Traditional: 28, Problem-posing education: 31, PBL: 13, TBL: 18, others: 17

Bold indicates the most prevalent answers

A recent systematic review showed that IPE usually occurs in the community, reinforcing our findings[9].

In relation to educational strategies, our study highlights the prevalence of ongoing use of traditional learning strategies (lectures for large groups that tend to avoid interaction among students), thus, in a sense, violating some of IPE's fundamental precepts. This finding demonstrates that the way IPE is taught in Brasil is still fragile. On the other hand, there is also a high prevalence of using the "problem-posing education" approach developed by Paulo Freire in both medical and physical therapy schools. That is a striking characteristic of IPE in Brasil, as international studies have shown that the main strategies used are problem-based learning, simulation, and case-based discussions[4,11].

Important barriers to incorporating IPE in Brazilian medical and physical therapy schools were also identified. Most school representatives say there is a lack of focus from universities and even Brasil's health system on IPE. Among the main barriers cited are the heterogeneous curriculum, difficulties in administering time, and communication. The incorporation of IPE is significantly influenced by the heterogeneous curriculum and by financial and academic support, results corroborated by previous studies in Canada[4], the United States[11], and New Zealand/Australia[6]. These barriers can help educators jointly rethink their curricula, seeking to create space and shared schedules for students and educators from different areas in structured curricular disciplines to have experiences together[4,9].

Finally, our study found that medical schools perceive more difficulties in incorporating IPE and also offered fewer mandatory courses, which can indirectly reflect and corroborate the fact that medical students are less open to IPE than others. To our knowledge, no study has done this in relation to those who are responsible for these schools. This is important for corroborating data presented with students since those who are responsible for the institutions also have a role in curricular development and consequently in incorporating IPE.

This study has some limitations that should be pointed out. First, it is based upon opinions and information made available by institutions' representatives.

SUPPLEMENTARY TABLE 2. DETAILS CONCERNING EACH INTERPROFESSIONAL EDUCATION IN PHYSICAL THERAPY COURSES

Mandatory Course – present in 72 (45.3%) physical therapy courses
Period offered: 1st (33), **2nd (35)**, 3rd (33), 4th (27), 5th (23), 6th (17), 7th (18), 8th (15), 9th (11), 10th (10)
Most common areas: Health management: 20, **public health: 54**, clinical areas: 23, health education: 42
Level of focus: **Primary: 264**, Secondary: 42, Tertiary: 37
Methods used: Traditional: 42, **Problem-posing education: 45**, PBL: 26, TBL: 22, Others: 15
Average number of students involved per semester: 84.3 (SD: 80.6)
Elective Course – present in 60 (37.7%) physical therapy courses
Period offered: 1st (9), 2nd (8), **3rd (15)**, 4th (11), 5th (13), **6th (17)**, 7th (12), 8th (11), 9th (8), 10th (9)
Most common areas: Health management: 15, public health: 32, clinical areas: 22, health education: 32
Level of focus: **Primary: 50**, Secondary: 33, Tertiary: 28
Methods used: **Traditional: 32, Problem-posing education: 32**, PBL: 23, TBL: 21, others: 10
Average number of students involved per semester: 45.2 (SD: 40.8)
Mandatory Clerkship – present in 67 (42.1%) physical therapy courses
Period offered: 1st (0), 2nd (0), 3rd (1), 4th (2), 5th (5), 6th (10), 7th (17), 8th (24), **9th (26)**, 10th (22)
Most common areas: Health management: 14, **public Health: 52**, clinical areas: 47, health education: 29
Level of focus: **Primary: 50**, secondary: 33, tertiary: 28
Average number of students involved per semester: 37.9 (SD: 30.7)
Elective Clerkship – present in 14 (8.8%) physical therapy courses
Period offered: 1st (0), 2nd (0), 3rd (0), 4th (0), 5th (0), 6th (3), 7th (5), 8th (6), **9th (6)**, 10th (5)
Most common areas: Health management: 1, public Health: 8, **clinical areas: 13**, health education: 6
Level of focus: Primary: 11, **Secondary: 12**, tertiary: 7
Average number of students involved per semester: 40.5 (SD: 31.1)
Other Initiatives – present in 122 (76.7%) physical therapy courses
Extension project: 116 Training project: 26 IC Project: 81 Colloquium/symposiums: 79 Congresses: 48
Methods used: **Traditional: 80**, Problem-posing education: 69, PBL: 41, TBL: 36, others: 21

Bold indicates the most prevalent answers

SUPPLEMENTARY TABLE 3.

Likert (1 strongly disagree to 5 strongly agree)	Total (235)	Medicine (76)	Physical Therapy (159)	p
Do you consider Interprofessional Education activity to be important for training professionals in the area of health?	4.74 (0.50)	4.67 (0.61)	4.77 (0.43)	0.170
Do you agree that students should be prepared to act interprofessionally while still in undergraduate school?	4.78 (0.49)	4.69 (0.67)	4.83 (0.37)	0.112
Do you agree that your institution manages to produce undergraduate curriculum for healthcare courses in an integrative and collaborative manner?	3.53 (1.10)	3.17 (1.12)	3.70 (1.05)	<0.001
Do you agree that both institutional and academic institutional support interferes with the development of interprofessional activities in undergraduate health courses?	4.38 (0.72)	4.39 (0.67)	4.38 (0.74)	0.913
Do you agree that undergraduate health courses in Brasil have paid adequate attention to interprofessional work?	2.45 (0.91)	2.34 (0.84)	2.51 (0.94)	0.157
Do you agree that the Brasilian Health System has paid adequate attention to interprofessional work?	2.64 (0.94)	2.76 (0.93)	2.59 (0.94)	0.191
My institution does NOT support interprofessionalism ACADEMICALLY.	2.15 (1.00)	2.28 (1.05)	2.09 (0.97)	0.163
My institution does NOT support interprofessionalism FINANCIALLY.	2.54 (1.09)	2.59 (1.07)	2.52 (1.10)	0.646
Undergraduate course curriculum at my institution is heterogenous, which makes interaction between students and faculty difficult.	2.80 (1.17)	3.27 (1.09)	2.57 (1.14)	<0.001
My institution does not offer "green zones*" (* common free time, without activities) in course schedules, thus making interaction between students and faculty difficult.	2.82 (1.30)	2.51 (1.24)	2.98 (1.30)	0.010
There are difficulties in communication between courses at my institution.	2.63 (1.16)	2.72 (1.11)	2.59 (1.18)	0.437
There are difficulties in time management between courses at my institution.	3.12 (1.10)	3.39 (0.99)	2.99 (1.13)	0.006

Second, our response rate varied from 32 to 42%, meaning that not all Brazilian schools responded to the questionnaire. Nevertheless, these rates were similar to the national IPE survey in the United States (38% of 126 schools), a country with a number of schools that most closely resembles Brasil's. Third, our study is unable to evaluate the quality of the IPE initiative, thus making it impossible to know if all of these initiatives follow the precepts of IPE.

CONCLUSIONS

In conclusion, we have estimated that at least three-quarters of Brazilian medical and physical therapy schools have IPE initiatives, although there are still a small number of mandatory courses and clerkships. Despite recognizing IPE's importance, school's representatives present significant barriers to incorporating IPE in Brazilian schools such as low political/financial support; the lack of faculty development and clarification of IP competencies; the few IPE moments in the curriculum and work environment; and the lack of integration among courses and schedule incompatibilities. Physical therapy has a lower perception of barriers and greater incorporation of mandatory courses in the curriculum. These results, not yet explored in Brasil's reality, will serve for future interventions that can enhance IPE in the curriculum in Brasil and other developing countries.

RESUMO

OBJETIVOS: *Investigar quantas escolas médicas e de fisioterapia brasileiras possuem iniciativas e cursos relacionados à EIP nos currículos, avaliando as barreiras e fatores associados com essa implementação e comparando as diferenças entre esses dois cursos.*

MÉTODOS: *Essa pesquisa nacional foi conduzida em 2017 e incluiu representantes das escolas médicas e de fisioterapia no Brasil. As ofertas de atividades interprofissionais, assim como as opiniões e barreiras para implementação, foram avaliadas.*

RESULTADOS: *Um total de 76 (33,9%) escolas médicas e 159 (41.4%) escolas de fisioterapia respondeu aos questionários. Pelo menos 68,4% das escolas médicas e 79,2% das escolas de fisioterapia possuem iniciativas de EIP, embora o número de cursos obrigatórios e estágios ainda seja baixo. Apesar de reconhecer a importância da EIP na educação em saúde, os representantes das escolas percebem como barreiras a falta de integração entre os cursos, associada a cronogramas incompatíveis e uma falta de suporte institucional. Na fisioterapia, existe menor percepção de barreiras e uma grande incorporação de cursos obrigatórios no currículo.*

CONCLUSÃO: *Esses resultados auxiliarão no desenvolvimento de futuras intervenções que promovam a EIP no currículo dos países em desenvolvimento.*

PALAVRAS-CHAVE: *Educação interprofissional. Estudantes de medicina. Fisioterapia.*

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ORIGINAL ARTICLE

Clinical aspects of congenital microcephaly syndrome by Zika virus in a rehabilitation center for patients with microcephaly

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http://dx.doi.org/10.1590/1806-9282.65.10.1249

SUMMARY

OBJECTIVE: *In this study, we intend to identify the prevalence of clinical variables in children with microcephaly.*

METHODS: *This is a cross-sectional and observational study with data collected from medical records of patients admitted to the microcephaly outpatient clinic of a referral center in Teresina-PI. Demographic (gender and age) and clinical data (presence of epilepsy, dysphagia, irritability, and associated comorbidities) were collected. The frequency of Zika virus as a probable etiology was determined from computed tomography patterns and the exclusion of other etiologies by serological tests.*

RESULTS: *A total of 67 patient records were evaluated, of which 31 were male and 36 were female, with a mean age of 1 year and 10 months. The most prevalent clinical variables were epilepsy, present in 47 children (70.2%), and irritability in 37 (55.2%). Also with a high frequency, 22 had dysphagia (32.8%), and 13 had musculoskeletal comorbidities (19.4%). Only three patients in the sample had cardiac abnormalities (4.5%), and no endocrine comorbidity was found. A total of 38 children in the sample (56.7%) presented ZIKV as a probable etiology and, in these cases, there was a higher frequency of epilepsy and dysphagia compared to other etiologies, although not statistically significant.*

CONCLUSION: *Epilepsy, irritability, dysphagia, and musculoskeletal comorbidities were the most frequent clinical variables in children with microcephaly. There was a high prevalence of congenital ZIKV microcephaly syndrome in this sample.*

KEYWORDS: *Microcephaly. Zika virus. Epilepsy. Deglutition disorders.*

DATE OF SUBMISSION: 11-Mar-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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INTRODUCTION

Microcephaly is a condition defined as a cephalic perimeter that is more than two standard deviations below the population mean, adjusted for sex and age (z-score <-2); it can be classified as primary (when present at birth) or secondary (when it appears later). When the cephalic perimeter is smaller than three standard deviations, microcephaly is defined as severe. Although the cephalic perimeter itself only measures the size of the skull, it typically reflects brain volume; therefore, abnormal values are important risk factors for intellectual disability, cerebral palsy, epilepsy, and other abnormalities[1].

Causes of microcephaly are diverse and include genetic syndromes, chromosomal abnormalities, metabolic disorders, infections, exposure to teratogens, and injuries sustained during prenatal, perinatal, or postnatal care. Despite this, even after imaging, genetic testing, and serological tests, no etiology is often identified[2]. In the years 2015-2016, there was an increase in the frequency of congenital microcephaly in Brasil, especially in the states of the Northeast Region. The association with ZIKV was elucidated by a series of clinical, epidemiological, and experimental evidence[3].

In the pre-Zika era, the major congenital infections associated with microcephaly were those of the TORCH group: Toxoplasmosis, Other infections (Syphilis, Varicella-Zoster, Parvovirus B-19), Rubella, Cytomegalovirus (CMV) and Herpes virus. Recently, however, Zika virus (ZIKV) infections in pregnant women have been associated with microcephaly and other severe brain abnormalities[2].

Therefore, the objective of the present study is to clinically characterize a sample of children with microcephaly treated at a referral center in an epidemic area in the context of the outbreak of ZIKV infection.

METHODS

Retrospectively, the medical records of patients born with a confirmed diagnosis of congenital microcephaly according to a protocol by the Brazilian Ministry of Health[4] were analyzed. Children aged from 0 to 3 years old were included at the time of data collection, which was performed between October 2017 and January 2018. The sample was obtained from the microcephaly outpatient clinic of the Integrated Rehabilitation Center (CEIR) in Teresina - PI, Brasil. Patients who did not undergo regular medical follow-up (defined as a monthly consultation within the last six months of data collection) were excluded.

From the sample selected, a medical record analysis was performed through a collection form that included demographic (gender and age) and clinical variables, as defined below:

- Epilepsy proven through an interview with a specialist physician and an electroencephalographic report;
- Dysphagia determined through clinical evaluation by speech therapist specialized in swallowing, with evidence of alteration in the oral and/or pharyngeal phases of swallowing;
- Irritability, crying, and/or restlessness throughout the medical history;
- Cardiovascular comorbidities such as congenital heart disease, patent ductus arteriosus, and atrial septal defect;
- Endocrine disorders such as thyroid disorders, diabetes, and adrenal disorders;
- Musculoskeletal pathologies characterized by muscular weakness, muscular group atrophy, postural alteration, and tendinopathy, mainly in the lower limbs.

The etiology of microcephaly was determined according to computed tomography (CT) patterns, to which the patients were submitted to, and from serological tests and CSF markers, allowing differentiation between the two groups: those with congenital microcephaly syndrome by Zika Virus (ZIKV) as probable etiology and those with non-ZIKV causes of microcephaly. From this categorical classification, the statistical differences in the frequencies of clinical comorbidities were analyzed.

Ethical Aspects

The information collected had guaranteed confidentiality conferred by the Informed Consent Form signed by the legal responsible, which ensures the privacy and anonymity of the subjects involved in the research. This research was approved by the Local Research Ethics Committee, process number 76823317.7.0000.5211.

Statistical analysis

The information obtained was used in a statistical analysis in Microsoft Excel and then entered and processed in SPSS (Statistical Package for the Social

Sciences version 20.0) to generate frequency tables with the purpose of verifying the elements relevant to the research. Fisher's exact test was used to compare the frequency of categorical variables (gender and cause of microcephaly). Significant values of p <0.01 were used to establish the significance of the association between variables.

RESULTS

A total of 67 patient charts were evaluated in the outpatient clinic, of which 31 (46.3%) were male and 36 (53.7%) female, with a mean age of 1 year and 10 months. Of all microcephaly patients, the diagnosis of ZIKV as a probable etiology occurred in 38 children, corresponding to 56.7% of all cases of microcephaly. In this group, 14 (36.8%) of the children were male, and 24 (63.2%) were female, with a mean age of 2 years.

In the total sample of children with microcephaly, the most prevalent clinical variables were epilepsy, present in 47 children (70.2%), and irritability in 37 (55.2%). Also, with a high frequency, 22 presented dysphagia (32.8%), and 13 musculoskeletal comorbidities (19.4%). Only 3 patients in the sample had cardiac comorbidities (4.5%), and no endocrine comorbidity was found.

Regarding gender, there was no significant difference between the clinical variables (Table 1). Despite this, the frequency of dysphagia was considerably higher in females. When the gender distribution was specifically assessed in the ZIKV group, this trend was also observed (50% of the children with dysphagia were female and 28.6% male), although, once again, it was not significant (p = 0.309).

The other 29 children who did not have congenital microcephaly syndrome by Zika Virus as a probable etiology were included in a non-Zika group, the vast majority of which were unidentified.

There was no statistically significant difference when comparing the clinical variables for the cause of microcephaly, that is, ZIKV as a probable etiology or the non-Zika group (Table 2). In spite of that, in the sample, the prevalence of epilepsy and dysphagia was much higher in the ZIKV group.

DISCUSSION

In our study, the high prevalence of musculoskeletal abnormalities, epilepsy, and irritability were noted in both the ZIKV and non-ZIKV groups. Several studies have sought to identify the comorbidities and functional outcomes most frequently associated with microcephaly, both before and after the Zika virus outbreak (pre-Zika study).

An Israeli pre-Zika study conducted with a sample of 1393 children with developmental disorders showed that children with microcephaly of the most diverse causes compared to those with normal head circumference had a higher prevalence of several neurological findings such as hypotonia (31,2% of children with microcephaly), spasticity (18.6%), weakness (6.5%), intellectual disability (38.1%), cerebral palsy (21.4%) and epilepsy (28.3%). Hyperactive behavior was found in about 20% of all children, with no significant difference between the normocephaly and microcephaly group[5].

In a large pre-Zika German study that included 680 children with microcephaly, epilepsy was diagnosed in 43% of patients and intellectual disability in 74%. Abnormalities outside the central nervous system were identified with varying frequencies, including ocular disorders (30%), cardiovascular disorders (14%), renal and urinary tract disorders (13%), skeletal disorders (13%) and oropharyngeal disorders (13%). The

TABLE 1. DISTRIBUTION OF CLINICAL COMORBIDITIES BY GENDER IN ALL PATIENTS WITH CONGENITAL MICROCEPHALY ASSESSED FROM RECORDS OF THE INTEGRATED REHABILITATION CENTER, TERESINA (PI).

Clinical Variables	Gender		p
	Male (31)	Female (36)	
Epilepsy	20 (64.5%)	27 (75%)	0.426
Irritability	18 (58.1%)	19 (52.8%)	0.806
Dysphagia	6 (19.4%)	16 (44.4%)	0.038
Musculoskeletal Comorbidities	5 (16.1%)	8 (22.2%)	0.556
Cardiovascular Comorbidities	2 (6.5%)	1 (2.8%)	0.592
Endocrine Comorbidities	0	0	1

TABLE 2. DISTRIBUTION OF CLINICAL COMORBIDITIES BY ETIOLOGY IN ALL PATIENTS WITH CONGENITAL MICROCEPHALY ASSESSED FROM RECORDS OF THE INTEGRATED REHABILITATION CENTER, TERESINA (PI).

Clinical Variables	Microcephaly Etiology		p
	Zika (38)	Não-Zika (29)	
Epilepsy	30 (78.9%)	17 (58.6%)	0.106
Irritability	20 (52.6%)	17 (58.6%)	0.805
Dysphagia	16 (42.1%)	6 (20.7%)	0.073
Musculoskeletal Comorbidities	7 (18.4%)	6 (20.7%)	1
Cardiovascular Comorbidities	1 (2.6%)	2 (6.9%)	0.574
Endocrine Comorbidities	0	0	1

diversity of systemic changes emphasized the need for multidisciplinary care[6].

Compared with clinical characterization studies of patients with microcephaly that described cognitive and intellectual alterations, the nondescription of cognitive impairment in our sample was a limitation, justified by the mean age of the patients. However, all the children analyzed presented neuropsychomotor development delay (such as social smile, head support, the age for sitting up, following family members, and eye contact).

Other more recent studies have identified and quantified common neurological outcomes in children with evidence of congenital infection by ZIKV. In one of them, Moura da Silva et al.[7], in a sample of 48 children with probable infection by ZIKV, based on protocols from the Ministry of Health, identified that 86.7% presented microcephaly, with more than half of them presenting severe microcephaly. Of all children, 85.4% had irritability, the most common symptom described, followed by pyramidal and extrapyramidal symptoms (56.3%), epileptic seizures (50.0%), and dysphagia (14.6%)[7]. As for the series by Alves et al.[8], which included 106 children with congenital ZIKV syndrome, 37.7% of the children had epileptic seizures in the observation period, with a median of 192-day crisis occurrence until the first report, from the date of birth. 43.3% of the seizures were characterized as spasms, 22.7% generalized tonic attacks, 20.5% were partial, and 4.5% were other types of seizures.

In fact, in this sample, irritability and epilepsy were found in more than 50% of children with microcephaly by ZIKV. We did not aim to explore all possible pyramidal and extrapyramidal motor neurological disorders in our study, so that the prevalence of musculoskeletal disorders was significantly lower (18.4%).

Our results did not show any statistically significant differences when comparing the frequency of demographic and clinical variables between the groups of children with ZIKV microcephaly and those with non-ZIKV microcephaly. This indicates that, in patients with microcephaly, the mere presence of variables such as epilepsy or dysphagia should not serve as an indicator that suggests the diagnosis of ZIKV infection. However, it is possible that in larger samples, the same analysis confirms the significance of the differences between the groups in relation to such comorbidities.

Regarding the possible greater occurrence of dysphagia in the female gender, both when analyzing all causes of microcephaly and when analyzing only the ZIKV subgroup, no studies were found evidencing such correlation. Indeed, this data is not easily found in the literature of series of congenital microcephaly cases, which generally only exposes percentages of individual characteristics of the sample, such as the frequency of children with dysphagia and frequency of male children, rather than frequency of male children with dysphagia.

Regarding cardiac comorbidities, Orofino et al.[9] reported echocardiographic alterations in 120 children with intrauterine exposure to ZIKV. Of the total, 40% had cardiac defects noted on echocardiography, most of which were physiological changes or minor defects of little clinical relevance, in most cases patent foramen ovale (72.8%). Only 13 children (10.8%) had major cardiac defects, such as ventricular septal defect. Although at a much higher frequency than in the general population, in none of them was the defect severe enough to require immediate treatment in the first few days or months of life. Therefore, the author suggested that the guideline for the performance of echocardiography in patients with ZIKV syndrome should be the same as in the general population.

In our study, only one child with ZIKV microcephaly had cardiac abnormalities, a much lower frequency than in the study by Orofino et al.[9]. However, this data suggests that the importance given to the research of cardiac comorbidities in patients with ZIKV should be lower than other comorbidities, such as neurological ones.

The aspects of the microcephaly epidemic in the state of Piauí during the years 2015-2016 have been analyzed. During the pre-epidemic period (January to August 2015), the mean monthly incidence rate of congenital microcephaly was about 0.18 cases / 1000 live births, reaching, at the epidemic peak in November, 6.33 cases / 1000 live births (an increase of more than 35 times). Teresina, the state capital, faces serious problems of sanitation, infrastructure, waste management, and vector control, which helps explain the fact that it has concentrated around 44% of the cases of congenital microcephaly in the state. Moreover, in the semi-arid country area, precarious water reserve systems may have contributed to the proliferation of vector mosquitoes[3].

A limitation of our study is the lack of a normocephalic control group, which makes it difficult to interpret the results of some variables, such as irritability. Another limitation is the high probability of selection

bias since children with more severe illnesses are those typically found in a rehabilitation center.

CONCLUSIONS

The cases of microcephaly presented a discrete numerical difference in relation to gender. In addition, epilepsy, irritability, and dysphagia are the most frequent clinical findings in these patients, whereas abnormal cardiac manifestations account for less than 5% of the cases. More than half of the patients with microcephaly presented ZIKV as a probable etiology, and in those cases, there was a higher prevalence, mainly of epilepsy and dysphagia, compared to other microcephaly etiologies.

The diversity of manifestations found in the clinical profile of patients with microcephaly emphasizes the need for an interdisciplinary approach to minimize the impact of the various comorbidities on the quality of life and development of the child.

RESUMO

OBJETIVO: *Pretende-se, neste estudo, identificar a prevalência de variáveis clínicas em crianças com microcefalia.*

MÉTODOS: *Trata-se de um estudo transversal e observacional com dados coletados de prontuários de pacientes admitidos no ambulatório de microcefalia de um centro de referência em Teresina (PI). Foram coletados dados demográficos (gênero e idade) e clínicos (presença de epilepsia, disfagia, irritabilidade e comorbidades associadas). A frequência de Zika vírus como provável etiologia foi determinada a partir de padrões da tomografia computadorizada e da exclusão de outras etiologias por exames sorológicos.*

RESULTADOS: *Foram avaliados 67 prontuários de pacientes, sendo 31 do sexo masculino e 36 do sexo feminino, com idade média de 1 ano e 10 meses. As variáveis clínicas mais prevalentes foram epilepsia, presente em 47 das crianças (70,2%), e irritabilidade, em 37 (55,2%). Também com elevada frequência, 22 possuíam quadro de disfagia (32,8%) e 13 apresentavam comorbidades osteomusculares (19,4%). Apenas três pacientes da amostra tinham quadro de alterações cardiológicas (4,5%) e nenhuma comorbidade endocrinológica foi encontrada. Trinta e oito crianças da amostra (56,7%) apresentaram ZIKV como provável etiologia e, nesses casos, houve maior frequência de epilepsia e disfagia em comparação com outras etiologias, embora não de forma significativa estatisticamente.*

CONCLUSÕES: *Epilepsia, irritabilidade, disfagia e comorbidades osteomusculares foram as variáveis clínicas mais frequentes em crianças com microcefalia. Houve uma prevalência alta de síndrome de microcefalia congênita por ZIKV nessa amostra.*

PALAVRAS-CHAVE: *Microcefalia. Zika vírus. Epilepsia. Transtornos da deglutição.*

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ORIGINAL ARTICLE

Basal insulin persistence in Brazilian participants with T2DM

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http://dx.doi.org/10.1590/1806-9282.65.10.1254

SUMMARY

OBJECTIVE: *Real-world effectiveness of basal insulin therapy is affected by poor treatment persistence, often occurring soon after initiation. This analysis is part of an international cross-sectional study conducted in T2DM patients and is intended to describe the reasons behind non-persistence to insulin therapy in Brasil.*

METHODS: *Responders to an online survey in seven countries were classified as continuers (no gap of ≥7 days), interrupters (interrupted therapy for ≥7 days within first 6 months, then restarted), and discontinuers (terminated therapy for ≥7 days within first 6 months, and did not start it again before the survey). We present the results from the Brazilian cohort.*

RESULTS: *Of 942 global respondents, 156 were from Brasil, with a mean age of 34 years and a mean of 5.8 years since T2DM diagnosis. Reasons contributing to insulin continuation (n=50) were improved glycemic control (82%) and improved physical feeling (50%). Common reasons for interruption (n=51) or discontinuation (n=55) were, respectively, weight gain (47.1%, 43.6%), hypoglycemia (45.1%, 38.2%), and pain from injections (39.2%, 49.1%). However, not all patients who reported weight gain and hypoglycemia as a reason for interruption or discontinuation experienced these: 16/24 (66.7%) and 22/24 (91.7%) participants had weight gain, and 13/23 (56.5%) and 15/21 (71.4%) had hypoglycemia, respectively. The most important reason for possible re-initiation for interrupters and discontinuers, respectively, was persuasion by the physician/HCP (80.4%, 72.7%).*

CONCLUSION: *The benefits of basal insulin therapy motivated continuers to persist with the treatment; experienced or anticipated side effects contributed to interruption and discontinuation. Physician and patient training is key in the treatment of diabetes.*

KEYWORDS: *Diabetes Mellitus, Type 2. Insulin. Medication Adherence.*

INTRODUCTION

An unprecedented increase in the incidence and prevalence of diabetes is seen globally.[1] The condition has an estimated prevalence of 8.7%, and 12.5 million individuals between 20 and 79 years of age have diabetes in Brasil, which places the country in fourth place worldwide, behind China, India, and the USA. Out of that total, 5.7 million individuals (46%) have undiagnosed diabetes.[2,3]

Many patients in Brasil do not achieve appropriate glycemic control in real-life settings despite advances in treatment options and increased awareness of the risk of diabetes complications related to higher hemoglobin A1c (HbA1c).[3-10] In a multicenter study, 73% patients with type 2 diabetes mellitus (T2DM) in Brasil had HbA1c ≥7%; when considering only patients who use insulin, this number increased to

DATE OF SUBMISSION: 07-Jun-2019
DATE OF ACCEPTANCE: 11-Jun-2019
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90%.[9] An online survey found that only 25% of Brasilian physicians would initiate a combination therapy at the start of the treatment despite acknowledging the scientific evidence behind early introduction of combination therapy.[4] Although insulin has shown the highest efficacy among all antihyperglycemic medication options for lowering blood glucose (BG) levels,[11] it still remains a challenge to overcome possible barriers throughout the milestones in insulin treatment: the initiation, persistence, adherence, and intensification.[12]

Major barriers to insulin therapy from a Brazilian physician's/health care professional (HCP)'s perspective reported in the literature are as follows: fear for their patients' safety, including weight gain and hypoglycemia, limited time and financial resources, and lack of proper training to translate this complex disease management to patients and families.[3-5,13] From a patient's perspective, possible barriers to insulin therapy are fear and risk of potential side effects (hypoglycemia and weight gain), negative perception of treatment and perceived lack of efficacy, negative impact on lifestyle and injection phobia, and worsening of diabetes reflecting in personal failure.[4,13,14] Physicians and patients are often reluctant to initiate and intensify insulin therapy. This leads to poor adherence and persistence of insulin therapy resulting in poor glycemic control and increased complications of diabetes.[4,9,15-17]

What motivates patients to start and continue on insulin, and what are the reasons behind interrupting and discontinuing insulin therapy? Knowledge of those aspects could help physicians/HCPs take adequate measures at the start of and during insulin therapy to help patients overcome barriers and achieve glycemic control.

We conducted an online survey in patients with T2DM from seven countries to evaluate participants' insulin initiation experience and the reasons behind different persistence patterns (continuers, interrupters, and discontinuers).[12,18] Since socioeconomic factors, besides others, differ between countries, we report in this manuscript the country-specific results from Brasil.

METHODS

Participants and Study Design

A cross-sectional online survey was conducted with 942 respondents from Brasil and six other countries (Germany, France, Japan, Spain, the UK, and the USA) between July and September 2015. Overall, the study design, inclusion criteria, patterns of persistence, and results have been outlined in detail elsewhere.[12,18] In brief, participants from Brasil were identified from the Branded, Survey Sampling International (SSI) and Toluna market research panels of volunteers who agreed to be contacted about studies. Participants enrolled in the survey were asked to describe if there had been a period of 7 or more days, within the first 6 months of starting on basal insulin, when they did not use it. According to their patterns of treatment persistence, they were classified into three cohorts: C*ontinuers* were participants with no interruption of at least 7 days in the basal insulin treatment between treatment initiation and participation in the survey. *Interrupters* were participants who interrupted basal insulin for at least ≥7 days within the first 6 months after initiation and had restarted by the time of the online survey; and *discontinuers* were participants who stopped basal insulin use within the first 6 months after treatment initiation and did not restart on any basal insulin before the survey.

Data Collection

The survey investigated participants' concerns and experiences with insulin initiation and use, and the reasons contributing to their different patterns of persistence. Eligible participants responded on demographic and socioeconomic characteristics, disease and treatment history, basal insulin initiation experience (e.g., concerns before initiating insulin, experience, and challenges while taking basal insulin, impact of insulin on different aspects of disease control and life), resources available during initiation and use such as training, support/assistance, and reasons for different persistence patterns. No information regarding personal identification was collected as part of the study to minimize risks to participants. Exemption from ethical review was granted by the Western Institutional Review Board, Puyallup, WA, USA, due to minimal risk to participants.

Statistical Analysis

All data evaluated for the Brasil subpopulation were analyzed either collectively or separately for the three cohorts of persistence patterns, ie., continuers, interrupters, and discontinuers. Statistical

analyses were exploratory only. Pairwise comparisons between persistence groups were made using t-tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. Given the moderate sample size and the nature of the exploratory analysis, the p-values generated were only used to assist in the identification of potential differences between cohorts and were not adjusted for multiple comparisons. All data are presented descriptively only. Analyses were performed using SAS v.9.3 (Cary, NC) software.

RESULTS

Participant Characteristics

Overall, 156 individuals from Brasil participated in the online survey and were younger, more educated, and in larger number compared to individuals in the global cohort (Supplemental Table 1). The mean duration of T2DM was 5.8 years, and almost half of the participants initiated basal insulin treatment between 7 and 12 months before the survey. Continuers and interrupters were more likely to be male ($p<0.05$ for both).

Insulin Initiation and Use Experience

Motivators to start basal insulin therapy

Most commonly, Brazilian respondents were motivated to start basal insulin because of encouragement by HCP, concerns about developing diabetes complications, and the expectation for improved glycemic control (69.2%, 46.2%, and 42.9%, respectively). More than half of the participants (55.8%) noted that their views were very/fully considered when initiating insulin, while 26.3% of participants felt they were somewhat considered, and 17.9% felt they were slightly/not at all considered, with no notable differences between groups (Table 1).

Participants' feelings when considering insulin

Most of the respondents agreed/strongly agreed that insulin would help manage diabetes, shared fear of developing complications from diabetes, and felt that insulin recommendation indicated that their diabetes was worsening (87.2%, 78.8%, and 71.8%, respectively). Although similar proportions among the persistence groups agreed to those feelings, interrupters were more likely to believe that insulin was not necessary compared to continuers (49.0% vs. 24%; $p<0.05$). In addition, interrupters and discontinuers were more likely to feel a sense of failure compared with continuers (39.2%, 38.2%, and 20%; $p<0.05$ for both; Table 1).

Participants' concerns before and after one week of insulin

The main concerns before starting insulin therapy were related to the proper storage of insulin (73.1%), potentially frequent hypoglycemia (71.2%), and becoming insulin-dependent (69.2%). Continuers were less likely to be concerned about monitoring BG levels compared to discontinuers and about injecting insulin in front of others compared to interrupters (50% vs. 69.1% and 74.5%, respectively; $p<0.05$ for both). Continuers had fewer concerns about paying for insulin therapy compared with interrupters (36.0% vs. 60.8%, $p<0.05$).

After one week of insulin therapy, the number of concerns decreased throughout, and the order of importance of concerns changed. Now, the most common concerns were about weight gain (55.8%), frequent hypoglycemia (54.5%), insulin dependence (51.9%), mistakes in self-injection, injection in front of others, and need to visit physician/nurse more often (all, 47.4%). Continuers consistently had fewer concerns compared to interrupters and discontinuers, except for body weight ($p<0.05$). Overall, the mean number of concerns decreased after one week of insulin treatment from 8.8 to 6.4, among the persistence groups. Before the treatment, interrupters reported more concerns compared to continuers ($p=0.0285$). After one week of treatment, interrupters and discontinuers reported more concerns compared to continuers ($p=0.0002$ and $p<0.0001$; Table 1).

Challenges during the first week of insulin use

More than a third of the participants perceived injecting insulin, titration, and remembering to inject regularly difficult/very difficult (38.5%, 35.9%, and 32.7%, respectively). Further, the following were considered difficult/very difficult during the first week of insulin use: dealing with emotions about needing insulin (29.5%), proper storage (28.8%), feeling confident about treating hypoglycemia (28.2%), making time to inject and worries about family/friends' reaction (26.3%, each) and more frequent BG levels monitoring (25.6%). The mean number of challenges overall and among persistence groups was 2.7, with no notable differences (Table 1).

TABLE 1. INSULIN INITIATION AND USE EXPERIENCE.

	Brasil cohort				P-value		
	Over-alla (n=156)	Con-tinuersb (n=50)	Inter-ruptersc (n=51)	Discon-tinuersd (n=55)	Con-tinuers vs Inter-rupters	Continu-ers vs Discon-tinuers	Inter-rupters vs Discon-tinuers
Respondents motivations for starting insulin, %							
Encouragement from a physician/healthcare provider	69.2	58.0	78.4	70.9	*		
Improved glycemic control	42.9	48.0	49.0	32.7			
Concern about developing complications of diabetes	46.2	48.0	41.2	49.1			
Preference for injections over pills	17.9	6.0	23.5	23.6	*	*	
Inability to tolerate other antihyperglycemic medications	4.5	4.0	3.9	5.5			
Sources of recommendations to start insulin, %							
Primary care physician	57.1	54.0	52.9	63.6			
Another individual in physician's office	1.9	0.0	3.9	1.8			
Endocrinologist	31.4	38.0	35.3	21.8			
Diabetes educator	9.0	8.0	5.9	12.7			
Respondent	0.6	0.0	2.0	0.0			
Provider's reasons for recommendation to start insulin, %							
Improved glycemic control	74.4	72.0	78.4	72.7			
Prevention of complications of diabetes	61.5	64.0	52.9	67.3			
Inability to tolerate other antihyperglycemic medications	9.6	8.0	5.9	14.5			
Degree to which the respondent felt views were considered, %							
Not at all/slightly	17.9	20.0	21.6	12.7			
Somewhat	26.3	30.0	15.7	32.7			
Very/fully	55.8	50.0	62.7	54.5			
Feelings when considering insulin, % agree/strongly agree							
Sense of failure	32.7	20.0	39.2	38.2	*	*	
Reassurance that insulin would help manage diabetes	87.2	86.0	92.2	83.6			
Belief that insulin was not necessary	34.6	24.0	49.0	30.9	*		
Feeling that insulin indicated that diabetes was worsening	71.8	74.0	72.5	69.1			
Fear of developing complications of diabetes	78.8	80.0	80.4	76.4			
Concerns before starting insulin, % agree/strongly agree							
Worry that insulin would not provide glycemic control	50.0	38.0	56.9	54.5			
Fear of self-injection	59.6	52.0	64.7	61.8			
Fear of making mistakes during self-injection	68.6	64.0	72.5	69.1			
Worry that scarring or bruising would result from injections	59.6	50.0	68.6	60.0			
Worry about proper insulin storage	73.1	66.0	82.4	70.9			
Concern about carrying insulin around	67.3	66.0	74.5	61.8			
Worry that regular insulin use would interfere with daily activities	63.5	56.0	72.5	61.8			
Concern that he/she would need to visit physician/nurse more often	60.3	50.0	64.7	65.5			
Concern that he/she would need to monitor blood glucose more often	62.2	50.0	66.7	69.1		*	
Concern about potentially frequent hypoglycemia	71.2	68.0	72.5	72.7			
Concern about becoming insulin dependent	69.2	72.0	64.7	70.9			
Concern about the ability to pay for insulin therapy	48.7	36.0	60.8	49.1	*		
Worry about potential weight gain	61.5	58.0	62.7	63.6			
Worry about injecting insulin in front of other people	62.2	50.0	74.5	61.8	*		
Number of concerns before starting insulin, mean (SD)	8.8 (4.3)	7.8 (4.0)	9.6 (4.3)	8.9 (4.4)	*		
Concerns after one week of using insulin, % agree/strongly agree							
Worry that insulin will not provide glycemic control	42.3	18.0	54.9	52.7	*	*	
Discomfort regarding self-injection	46.8	24.0	51.0	63.6	*	*	
Fear of making mistakes during self-injection	47.4	28.0	47.1	65.5	*	*	
Bothered by scarring or bruising resulting from injections	46.2	28.0	51.0	58.2	*	*	
Burdened by proper insulin storage	42.3	24.0	52.9	49.1	*	*	
Burdened by carrying insulin around	39.7	26.0	49.0	43.6	*		

	Brasil cohort				P-value		
	Overalla (n=156)	Continuersb (n=50)	Interruptersc (n=51)	Discontinuersd (n=55)	Continuers vs Interrupters	Continuers vs Discontinuers	Interrupters vs Discontinuers
Feeling that regular insulin use interferes with daily activities	35.9	22.0	41.2	43.6	*	*	
Burdened by the need to visit physician/nurse more often	47.4	30.0	56.9	54.5	*	*	
Burdened by the need to monitor blood glucose more often	38.5	26.0	47.1	41.8	*		
Bothered by frequent hypoglycemia	54.5	40.0	60.8	61.8	*	*	
Concern about becoming insulin dependent	51.9	36.0	58.8	60.0	*	*	
Burdened by paying for insulin therapy	44.9	30.0	54.9	49.1	*	*	
Bothered by weight gain	55.8	48.0	62.7	56.4			
Discomfort injecting insulin in front of other people	47.4	32.0	58.8	50.9	*	*	
Number of concerns after one week of using insulin, mean (SD)	6.4 (4.8)	4.1 (3.2)	7.5 (5.3)	7.5 (4.8)	*	*	
Challenges during the first week of insulin use, % difficult/very difficult							
Injecting insulin	38.5	40.0	37.3	38.2			
More frequent blood glucose monitoring	25.6	28.0	25.5	23.6			
Titration	35.9	44.0	33.3	30.9			
Proper insulin storage	28.8	26.0	31.4	29.1			
Remembering to inject insulin regularly	32.7	32.0	35.3	30.9			
Making time during the day to inject insulin	26.3	26.0	25.5	27.3			
Feeling confident about treating hypoglycemia	28.2	26.0	29.4	29.1			
Dealing with emotions about needing insulin	29.5	28.0	27.5	32.7			
Worry about the reaction to insulin use from friends/family	26.3	20.0	25.5	32.7			
Number of challenges during the first week of insulin use, mean (SD)	2.7 (2.8)	2.7 (2.7)	2.7 (3.0)	2.7 (2.8)			
Adverse events experienced while taking insulin, %							
Uncontrolled high blood glucose	23.1	14.0	39.2	16.4	*		*
Symptoms of hypoglycemia	43.6	42.0	43.1	45.5			
Weight gain	45.5	36.0	49.0	50.9			
Injection site reaction	33.3	32.0	31.4	36.4			

a Within-country results were not weighted **b** Continuers had no gaps of ≥7 days in basal insulin treatment. **c** Interrupters interrupted basal insulin for ≥7 days within the first 6 months after initiation and since restarted basal insulin. **d** Discontinuers stopped using basal insulin for ≥7 days within the first 6 months after initiation and had not restarted basal insulin by the time of the survey **e** p-values were calculated using t-tests for continuous variables and chi-square tests for categorical variables without adjustment for multiple comparisons. P<0.05 was considered statistically significant and marked with an asterisk (*).

Impact of insulin use at specific aspects of life

Overall, most participants stated that insulin use had a somewhat or a very positive impact on physical well-being (77.6%), daily activities (73.1%), glycemic control (72.4%), and having to stay physically active (72.4%; Figure 1). The impact of insulin was similar across the persistence groups except for three aspects: continuers were more likely to report that (a) insulin had a positive impact on their physical well-being than discontinuers (82.0% vs. 69.1%) (b) it had a neutral impact on budget than interrupters (38.0% vs. 11.8%), and (c) their perception of themselves as a healthy person (36.0% vs 9.8%; p<0.05).

Available resources on training and support

Most respondents, up to 98%, received training on insulin therapy, diabetes in general, self-injection, titration, and diet/exercise before initiating and also while being on insulin therapy. The availability, use, and helpfulness of the training were found to be similar across persistence groups. Training before insulin use was provided mainly by physicians (78.2%) followed by nurse/physician's assistants (44.9%), diabetes educators (28.8%), and pharmacists (26.9%). The vast majority of participants preferred in-person training (71.8%) to other formats, that is, videos (58.3%), websites (54.5%), and written material (42.9%). Almost all participants (97.4%) perceived the support of medical personnel as helpful. Other training channels, such as telephone hotline and smartphone applications, were less preferred.

On the degree of self-confidence before first insulin self-injection, overall, 53.2% of participants rated themselves as being confident or very confident, 32.7% as somewhat confident, and 14.1% as not at all confident. Moreover, most participants felt confident

or very confident about self-injection before the first use, regardless of the persistence group.

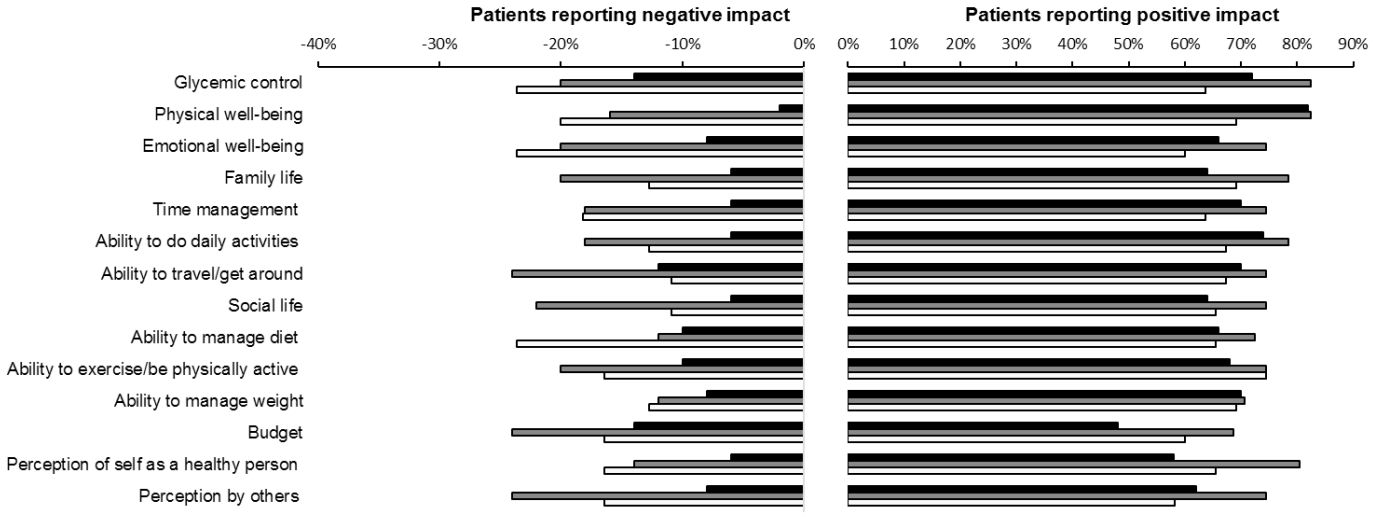
Persistence Patterns: Continuers, Interrupters, and Discontinuers

The most common self-reported reasons for continuing basal insulin therapy were improved glycemic control, physical feeling, the belief that insulin is best for reducing the risk of complications, and improved emotional well-being (Figure 2a). Most participants (74%) stated more than one reason for continuing.

The most common reasons contributing to interruption were weight gain and hypoglycemia, followed by pain from injections (Figure 2b). However, not all participants who reported weight gain or hypoglycemia experienced these. Among interrupters who reported weight gain as a reason to interrupt, 16 (66.7%) out of 24 actually experienced weight gain. Similarly, for hypoglycemia, among interrupters who reported hypoglycemia as a reason to interrupt, 13 (56.5%) out of 23 actually experienced hypoglycemia. Although side effects such as weight gain and hypoglycemia were most often noted as reasons for interruption or discontinuation, those rates were not different between continuers, interrupters, and discontinuers (weight gain: 36.0%, 49.0%, and 50.9%, respectively; symptoms of hypoglycemia: 42.0%, 43.1%, and 45.5%, respectively). Most participants (76.5%) chose more than one reason for interruption, and 72.5% had more than one interruption; 58.8% interrupted insulin therapy for a week, and 41.2% participants had an interruption longer than one week. During the interruption of basal insulin, 49.0% of participants reported higher BG levels than before, despite changes in lifestyle such as exercise (74.5%) and diet (68.6%) and use of oral antidiabetics (51.0%) and noninsulin injectables (29.4%).

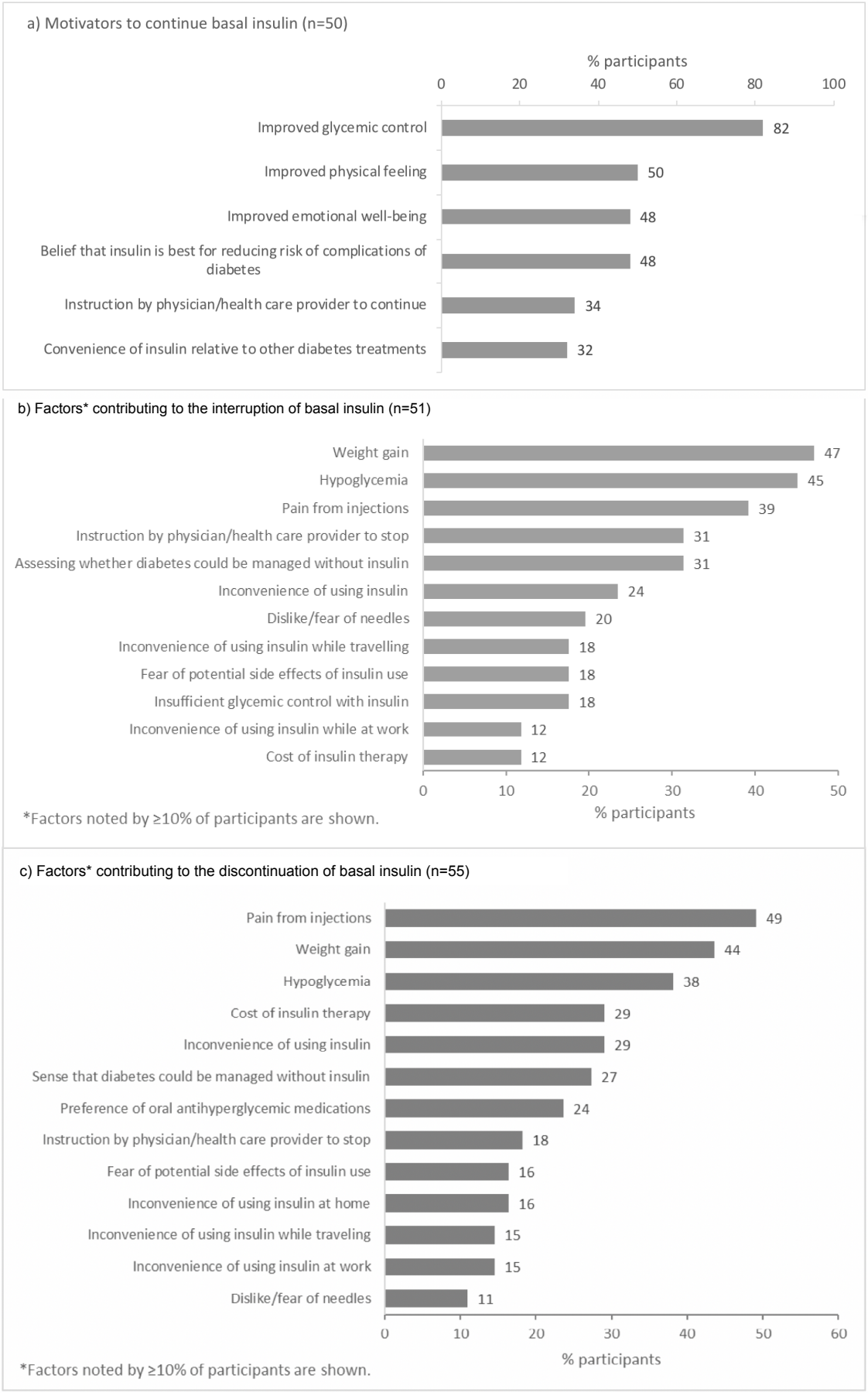
The most common reasons contributing to discontinuation of basal insulin therapy were pain from injections, weight gain, and hypoglycemia followed by the cost of insulin therapy and inconvenience of using insulin (Figure 2c). Similar to what was found among patients who had interrupted insulin, not all participants who reported weight gain or hypoglycemia as a reason to discontinue insulin therapy experienced these. Among discontinuers who reported weight gain as a reason to discontinue, 22 (91.7%) out of 24 actually experienced weight gain. Similarly, for hypoglycemia, among discontinuers who reported it, 15 (71.4%) out of 21 actually experienced hypoglycemia. For 72.7% of participants, multiple reasons led to discontinuation. After discontinuation of basal insulin, 25.5% of participants reported higher BG levels than before discontinuing it despite changes in lifestyle (diet 78.2%, exercise 70.9%) and use of oral antihyperglycemic medications (38.2%) and other noninsulin injectables (21.8%).

FIGURE 1. IMPACT OF BASAL INSULIN USE ON SPECIFIC ASPECTS OF PARTICIPANTS' LIVES.



Based on the question: "How has using basal insulin positively or negatively affected the following? For each statement, please choose one of the options." Possible answers: "Very negatively," "somewhat negatively," "neutral/no effect," "somewhat positively," "very positively". Data shown are the percentages of participants rating the effects as "very" or "somewhat" negative for negative impact and "very" or "somewhat" positive for positive impact. Abbreviations: n, number of participants per cohort.

FIGURE 2. A) MOTIVATION TO CONTINUE (N=50), B) FACTORS CONTRIBUTING TO INTERRUPTION (N=51), AND C) FACTORS CONTRIBUTING TO DISCONTINUATION (N=55) OF BASAL INSULIN.



Reasons and potential reasons for restarting basal insulin among interrupters and discontinuers

The most common reasons contributing to restarting basal insulin therapy among interrupters were persuasion by physician/HCP (80.4%), persuasion by friends/family (47.1%), insufficient glycemic control without insulin (37.3%), and resolution of the issues that led to interruption (13.7%). Nearly half of early interrupters (45.1%) chose more than one reason for restarting insulin. Similarly, the most common reasons for potentially restarting basal insulin among discontinuers were persuasion by physician/HCP (72.7%), insufficient glycemic control without insulin (61.8%), and persuasion by friends/family (43.6%). Overall, 56.4% of discontinuers chose more than one reason for potentially restarting basal insulin.

Adverse Events

Weight gain (45.5%) and hypoglycemia (43.6%) were reported most frequently followed by injection-site reactions (33.3%) and uncontrolled high blood glucose (23.1%). Continuers and discontinuers were less likely to report uncontrolled high blood glucose than interrupters ($p<0.05$).

DISCUSSION

This online survey enrolled 156 participants with T2DM, from Brasil, starting on basal insulin therapy, and intended to provide insights into patient-reported factors on insulin initiation and use. Overall, the literature suggests poor glycemic control among patients with T2DM in Brasil, majorly due to delay in initiating insulin therapy and poor adherence to the treatment.[3,9,19] Carefully understanding the factors that contribute to inadequate glycemic control may help change this scenario.

One of the most relevant findings was the importance of the patient-physician/HCP relationship documented in several parts of the study. Support from medical personnel and in-person training were considered very helpful by most participants and were the preferred format of training before and during insulin treatment. Most participants reported that their physicians encouraged and motivated them to initiate insulin treatment. Further, instruction by a HCP was often a reason for continuing (34.0%), interrupting (31.4%) and resuming (80.4%), discontinuing (18.2%), and potentially resuming(72.7%) insulin therapy. From other studies, it is known that physician recommendations are critical factors in patient decisions[14,20] and likely to be underestimated. Some reported reasons might have been physician-driven without mentioning the physician in particular[12] (e.g., interruption to assess whether diabetes could be managed without insulin [31.4%], insufficient glycemic control with insulin [17.6%]). Mendes et al.[9] found that health care delivered by a multi-professional team was associated with improved glycemic control compared to a primary care physician. Furthermore, a recent pilot study of a Community Health-Agent-led self-management training program using motivational interviewing-based approaches in a primary care setting in Brasil demonstrated overall improvements in patients' self-management of diabetes and in the quality of received diabetes care and clinical risk factors.[21] Diabetes self-management education programs are essential strategies to improve health behaviors.[9] Usually, a primary care physician undertakes the initial evaluation of a patient with diabetes.[3] This was also observed in the current study, with more than 50% of primary care physicians recommending to start basal insulin therapy. In contrast, a recent online survey in Brasil by Vencio et al.[4] noted that fewer patients were initially seen by a primary care physician (34%) and more patients recall initial diabetes counseling by a specialist (53%).

In our study, up to 98% of participants from Brasil reported to have had training possibilities, mainly provided by physicians, and in-person training was preferred over other channels. More than half of the participants felt their views were considered when starting treatment, allowing the positive experience of shared decision making on later treatment persistence with insulin therapy. The shift from advice-giving to encouraging patients to define their own goals[21] may translate into better adherence and persistence to insulin therapy. In another study, 50% of Brazilian patients believed not having had time to explain their fears and concerns.[4] Furthermore, to improve patient engagement, physicians should focus on the quality of life-based discussions on complications rather than mortality-based discussions.[4]

Across all three persistence patterns (continuers, interrupters, and discontinuers), the vast majority of participants agreed that insulin would help manage diabetes, and, interestingly, more individuals in the interrupters cohort agreed on that. However, overall,

continuers had fewer concerns regarding the treatment before and after one week of insulin therapy compared to interrupters and discontinuers. Before treatment, patients throughout the persistence groups reported more concerns than one week after treatment initiation. These highlight insufficient education, confidence, and autonomy at the time of insulin prescription. Further, before treatment, more interrupters compared to continuers had more concerns, which may be due to stressful initial situation influencing treatment persistence. Nevertheless, participants, irrespective of their persistence group, experienced the same mean number of challenges (2.7) and the same typical challenges such as injection, titration, and management of hypoglycemia during the first week of treatment. Interestingly, continuers seemed to be convinced by improvements due to insulin treatment (e.g., improved glycemic control, improved well-being physically and emotionally, among others) and was the main motivation to remain on insulin therapy. Instructions and motivation by HCP were less likely a reason for continuing in this group. It could be speculated that this discrepancy between continuers and interrupters/discontinuers could also be due to a more positive attitude/mindset towards treatment through better training and information on diabetes management.

Before and after one week of treatment, the fear of making mistakes during self-injection, among common concerns, was in fourth place. It is likely that training, information, and experienced self-injection over time were not paired with gained confidence in self-injection.

Actual experienced or anticipated side effects such as weight gain and hypoglycemia were often noted as factors for interruption or discontinuation. However, a substantial proportion of patients who cited fear of weight gain or hypoglycemia as reasons to interrupt or discontinue insulin did not actually experience these events. This discrepancy indicates that whether weight gain or hypoglycemia were experienced or only anticipated, its fear seems to be the same.[22] The proportion of patients that experienced weight gain and hypoglycemia did not differ among continuers, interrupters, and discontinuers. Patient attitudes contributing to resistance to insulin treatment have been identified in several studies; including the belief that taking insulin leads to poor outcomes, such as hypoglycemia, weight gain, and other complications.[14] Better education and training by HCPs may help patients be prepared with realistic expectations and enable them to treat side effects accordingly and continue the treatment. However, a recent online survey in Brasil demonstrated a high level of disconnect between what physicians thought they had discussed and what patients were able to recall, suggesting an urgent need to identify the deficits in education.[4] Educational measures should also target the "trainer," such as training physicians and HCPs on insulin benefits and administration, promoting events on the topic, and improving HCPs' awareness about the importance of having good communication with their patients.[5,13] For physicians/HCPs and patients alike, education and training on T2DM disease management should be the cornerstone in insulin therapy to address the individual needs – challenges, concerns, and feelings.[13]

Limitations

Several limitations apply to this online survey in Brasil. The persistence category was reported by participants. The participants were evaluated only for 3 to 6 months; thus, there is the possibility of misclassification; for example, continuers may stop later, or discontinuers may restart. In addition, clinical information about the diagnosis or severity of the illness was not captured; therefore, the relationship between clinical measures and basal insulin persistence remains unknown. The sample was not representative of the general diabetes population in Brasil. In particular, younger participants were overrepresented in the survey (mean age 34.2 years),[4,6,10] higher education and employment status, as were patients for whom the basal insulin was their first antihyperglycemic treatment (39.1%). Prior to the survey, pre-treatment with other non-insulin injectables was more common in the interrupter and discontinuer cohorts; this is in contrast to findings in the literature which reported a higher likelihood of persistence with prior use.[15,17,18] Results might have been affected by selection bias, recall bias, and social desirability bias, as with all data based on surveys. Concomitant oral treatment or comorbidities as additional factors affecting treatment persistence were not evaluated. There are limitations to the study design as a cross-sectional study with a descriptive design, and there is no adjustment for plausible confounders. Overall, there may be many additional factors influencing the treatment that were not captured in the survey. For example, it was not assessed

how often the participants inject and/or at what time of the day; this could have an influence on the persistence patterns.

CONCLUSION

This study showed the real-world experiences of T2DM patients with different persistence behaviors after initiating basal insulin in Brasil. Fewer concerns were reported by continuers before and after insulin initiation than interrupters and discontinuers. The benefits of basal insulin therapy motivated continuers to persist with the treatment; experienced or anticipated side effects contributed to interruption and discontinuation. It was observed that physicians/HCPs interactions have an important role in initiating and ensuring adherence to insulin therapy. Further, patient training, including discussing their challenges and fears, and setting realistic expectations of insulin, may motivate patients to initiate and adhere to insulin therapy.

Acknowledgments

The authors would like to thank Irene Hadjiyianni, MD, Eli Lilly, Germany, for the contributions to the study design and advice with this publication. The authors also thank Sara Fonseca Jung, MD, Eli Lilly Brasil, for revisions of this publication.

Simone Wille, MA, from Eli Lilly and Company provided medical writing assistance. This study was funded by Eli Lilly and Company.

Conflict of Interest

Denis Reis Franco serves as an advisor for Abbott, Eli Lilly, and Sanofi, as a speaker for Abbott, Eli Lilly, Medtronic and Sanofi, and receives research grants from Eli Lilly, Novo Nordisk, and Sanofi. Magaly Perez-Nieves, Dachuang Cao, and Marcela Saturnino Caselato Vaz are full-time employees and hold shares of Eli Lilly. Jasmina I Ivanova is a former employee of Analysis Group, Inc, which received research funding for this study from Eli Lilly.

RESUMO

OBJETIVO: *Dados de vida real sobre como a eficácia da terapia com insulina é afetada pela baixa persistência ao tratamento que ocorre logo após o início da terapia. Esta análise é a parte brasileira de um estudo transversal internacional conduzido em pacientes com DM2 que teve como objetivo descrever as razões relacionadas à não persistência ao tratamento com insulina.*

METODOLOGIA: *O estudo realizado em sete países por meio de questionários on-line classificou como pacientes continuadores (aqueles que não apresentaram intervalo ≥7 dias sem uso da insulina), interrompedores (interromperam a terapia por ≥7 dias nos primeiros seis meses de uso, depois recomeçaram) e descontinuadores (interromperam a terapia por ≥7 dias nos primeiros seis meses de uso e não retornaram). Nesta análise descrevemos os dados da coorte brasileira.*

RESULTADOS: *Dos 942 pacientes incluídos, 156 eram do Brasil, com idade média de 34 anos e média de seis anos desde o diagnóstico de DM2. Razões que contribuíram para o uso contínuo da insulina (n=50) foram a melhora do controle glicêmico (82%) e a melhora no estado geral (50%). Razões para a interrupção (n=51) ou para a descontinuação (n=55) foram, respectivamente, ganho de peso (41,7%, 43,6%), hipoglicemia (45,1%, 38,2%) e dor à aplicação (39,2%, 49,1%). Entretanto, nem todos os pacientes que reportaram ganho de peso e hipoglicemia como possível razão para interrupção ou descontinuação realmente apresentaram esses eventos: 16/24 (66,7%) e 22/24 (91,4%) dos participantes apresentaram ganho de peso e 13/23 (56,6%) e 15/21 (71,4%) apresentaram hipoglicemia, respectivamente. A razão mais importante para o possível recomeço entre os interrompedores e descontinuadores foi a persuasão de médicos/profissionais de saúde (80,4% e 72,7%, respectivamente).*

CONCLUSÕES: *Os benefícios do tratamento com insulina basal motivaram continuadores a persistir com a terapia; a experiência ou a antecipação de eventos adversos contribuíram para a interrupção e descontinuação. O treinamento de médicos e pacientes é um dos pilares fundamentais do tratamento do diabetes.*

PALAVRAS-CHAVE: *Diabetes mellitus tipo 2. Insulina basal. Adesão à medicação.*

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ORIGINAL ARTICLE

Multidisciplinary protocol for the management of fibromyalgia associated with imbalance. Our experience and literature review

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http://dx.doi.org/10.1590/1806-9282.65.10.1265

SUMMARY

OBJECTIVE: *We reported our multidisciplinary protocol for the management of fibromyalgia associated with imbalance. Our aim was to verify the effectiveness of a proprioceptive training program as a complementary therapy for a traditional protocol of education, mindfulness, and exercise training for the management of fibromyalgia associated with imbalance.*

METHODS: *Retrospective cohort study on 84 women, with primary fibromyalgia associated to imbalance. A group of patients performed traditional exercise training; in a second group the training was supplemented with proprioception exercises. Each session lasted from 40 to 60 minutes and was performed three times a week for 12 weeks.*

RESULTS: *After three months of training and eight months after the end of the training, the balance evaluation revealed significant differences in the comparison of the Timed Up and Go test, Berg Balance Scale, and Tinetti scale with the baseline, there was a better improvement in the proprioceptive training group ($p<0.05$). A reduction in pain and improvement in functional and muscular performance and quality of life were observed in both groups ($p<0.05$), but with no significant differences between them in the Numeric Pain Rating Scale, Fibromyalgia Impact Questionnaire, and Short Form Health Survey ($p>0.05$). Fifteen months after the end of the program, the effects of training were not maintained.*

CONCLUSION: *The present study revealed that training supplemented with proprioception exercises has beneficial effects on clinical findings and improves balance in patients with fibromyalgia, even if the positive results did not persist after the interruption of the rehabilitative program in the long term.*

KEYWORDS: *Fibromyalgia. Postural balance. Chronic pain. Clinical protocols. Quality of life.*

INTRODUCTION

Imbalance in fibromyalgia

Fibromyalgia (FM) is a chronic musculoskeletal pain syndrome characterized by extensive pain and multiple tender points on physical exam[1,2]. Prevalence of FM is 2% in the general population, predominantly women. It often takes more than two years to make a diagnosis, with an average of 3.7 consultations with different physicians[3]. Patients with FM report a variety of symptoms, including muscle weakness, disabling fatigue, mood disturbance, cognitive impairment, non-restorative sleep, morning stiffness. Lack of balance and falls are part of the symptoms of FM. The balance issue in this disease must not

DATE OF SUBMISSION: 05-Mar-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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be underestimated by clinicians, and the clinical examination of this symptom should not be neglected. Several studies showed increased imbalance and frequency of fall in patients with FM[3-8]. Dizziness was reported by 72% of the patients with FM[5]. A study of 2,596 patients with FM reported balance problems as one of the top 10 most debilitating symptoms with a prevalence of 45%[7]. In another study, 68% of 486 patients with FM had dizziness[8]. Postural instability often leads to further deterioration of postural control, fear of falling, with a negative impact on endurance, muscle strength, flexibility, coordination, and quality of life in patients with FM[4,9].

Recommendations for the treatment of FM

The American Pain Society (APS)[10], the Association of the Scientific Medical Societies in Germany (AWMF)[11] and the European League against Rheumatism (EULAR)[12] developed the recommendations for the treatment of FM. According to these, the treatment should be gradual and start with a group therapy session to improve awareness about the disease, as well as non-pharmacological and pharmacological modalities. Exercises involving different skills, such as strength, endurance, balance, and coordination for the management of FM, reduce the disability of these patients. Thus, the treatment of imbalance must be a prerogative of each therapy for patients with FM.

Purpose

The aim of this study was to verify the effectiveness of a proprioceptive training program as a complementary therapy of a protocol of education, mindfulness, and rehabilitation program (including aerobic and functional exercises, strength, and endurance training) for the management of fibromyalgia associated with imbalance. We reported our multidisciplinary clinical protocol for the follow-up and the management of FM associated with postural imbalance.

METHODS

All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the participants included in the study.

Study Design and Data Collection

We conducted a retrospective study at the Pain Medicine Department of the University of Catania from May 2017 to June 2018. A total of 144 potentially eligible outpatients were screened, 84 of whom met the inclusion criteria. The inclusion criteria were as follows: females aged between 20 and 40 years, height between 1.50 and 1.80 m, weight between 50 and 80 kg and BMI in the range of 18.5 to 29.9 kg/m^2; having a clinical diagnosis of FM according to the American College of Rheumatology's criteria[2], diagnosed in the year previous to the research, referring also to imbalance associated with FM, with similar time from symptom onset (mean duration of the symptoms was 10 ± 2 months). We included patients with a sedentary lifestyle with no or irregular physical activity (patients who did not exercise in the last six months). We excluded from the study patients with a history of inflammatory rheumatic disease, musculoskeletal disorders or deformities, and mechanical problems limiting the capacity for exercise, neurological disorder, peripheral neuropathy, diabetes mellitus, unstable hypertension, severe respiratory and cardiac problems as uncontrolled hypertension, malignant tumours, inner ear disease, hearing and visual problems, patients who used antidepressant, opioid, sedative or other drugs that could interfere with balance or nutritional supplements designed to stimulate brain metabolism, patients who received psychological or physical therapy. We also excluded pregnant women. Dropouts were excluded and not considered in the study (Fig. 1).

Procedures

One group of patients carried out traditional exercises, without proprioception exercises (group 1 n= 42), and a second group (group 2 n=42) with proprioception exercises. None of the patients were aware of the two different types of treatment they were receiving. A physician, totally unaware of the group in which each patient was inserted, was responsible for all evaluations. The rheumatologist carried out the first examination for the differential diagnosis and the confirmation of the disease. The otolaryngologist ruled out an inner ear disease causing dizziness. The physiatrist designed the rehabilitation program for the management of FM, without pharmacological treatment. If the rehabilitation exercises alone were not able to improve symptoms, the pain therapist designed a pharmacological protocol at first with

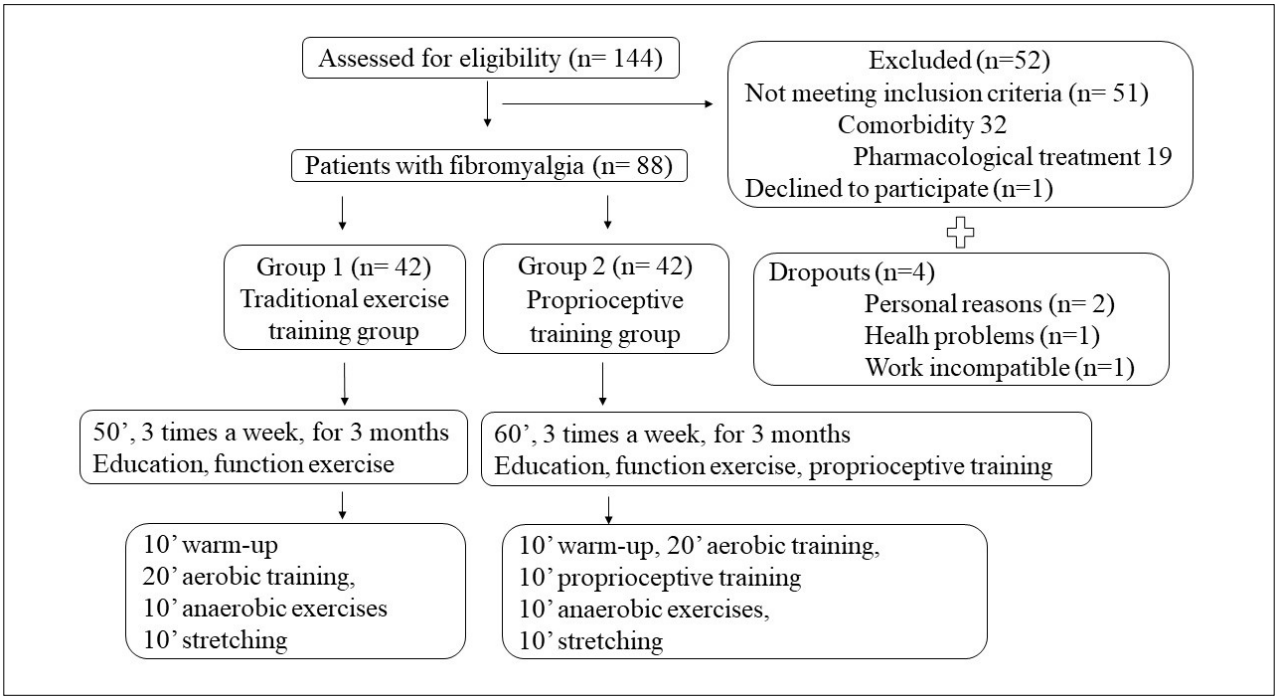

FIGURE 1. FLOW DIAGRAM OF THE PATIENTS

paracetamol, then if the pain was too severe, with non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, antidepressant, opioid, and sedative; in this case the patients were discontinued from the study.

The patients of both groups were evaluated before the training program, after 3 months of treatment, and 8 and 15 months after the suspension of the treatment.

At the first evaluation, before the beginning of the training and during the follow-up, all vestibular tests were normal, without neurological or peripheral vestibular lesions. Neither spontaneous nystagmus with or without visual fixation, nor positional nystagmus were found. Semont and McClure maneuvers, head-shaking test, Halmagyi head thrust maneuver, Fukuda stepping test, and Romberg's test were negative.

Outcome measures

Tenderness was measured with the tender point count; all 18 tender points were assessed according to Wolfe et al.[2].

Quality of life was measured with FIQ and SF-36. We administered the Italian version of the Fibromyalgia Impact Questionnaire (FIQ) to assess FM severity, functional status, and quality of life[13]. This questionnaire measures 10 different features including physical functioning, status of feeling well, inability to work, difficulty in working, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. The FIQ score ranges from 0 to 100; higher scores (>or=59 to 100) indicate a greater impact of the disease on the patients, >or= 39 to <59 a moderate symptomatology, 0 to <39 was found to represent a mild involvement of the functional status of the patients.

The pain was evaluated using the Numerical Rating Scale (NRS) from 0 to 10, with higher values indicating greater intensity[14].

The balance was evaluated using the validated Italian version of the Berg Balance Scale (BBS)[15] and Tinetti scale[16]. The BBS consists of 14 items that evaluate daily functioning. The level of competence in each activity is rated on a 5-point scale ranging from 0 (unable to do) and 4 (able to do independently and safely). The patients were asked to perform all functional parameters; the total score was calculated as the sum of the scores obtained from each parameter. The maximum score that can be obtained from the test is 56; 0–20 points indicate high fall risk, 21–40 points indicate moderate fall risk, and 41–56 points indicate low fall risk. The Tinetti scale has 2 parts: performance-oriented assessment of balance with 16 points (sitting balance, rising from a chair, immediate standing balance in the first 3-5 seconds, standing balance, balance with eyes closed, and turning balance [360°]) and a performance-oriented assessment of gait with 12 points (initiation of gait, step

height, step length, step symmetry, step continuity, path deviation, trunk stability, walk stance, and turning while walking). Less than 19 points means high risk of falls, between 19 and 24 means risk of falls, and between 24 and 28 means no disturbance in gait or balance. Therefore, the cut-off point that predicts a moderate or high risk of falling and disturbance in balance and gait was 24.

Furthermore, the patients reported the number of falls in the last 6 months.

The risk of falling and the disability was measured with the Timed Up and Go Test (TUGT)[17]. The patients were instructed to sit on a chair with back support. A mark was placed on the floor three meters away from the front of the chair. The patients were asked to stand up, walk to the mark on the floor, turn around, walk back to the chair, and sit down. The performance was measured in seconds. Patients with a score of <14 seconds were considered to have a high risk of falls.

Medical Research Council scale (MRC) was used to test hamstring and quadriceps muscle strength[18]. MRC grades muscle power on a scale of 0 to 5.

The validated Italian version of the SF-36 (SF-36)[19] was used to evaluate the activities of daily living (ADL). SF-36 contains 36 items on how daily activities (e.g., walking, shopping, going up some steps) have been limited by health problems. It provides a classification in 8 domains that correspond to the dimensions most related to health indication: role physical health, physical functioning, bodily pain, vitality, social functioning, role emotional, mental health, and general health. These dimensions are evaluated in a standardized 0-to-100 scale, in which the higher the score, the better the representation of health status.

The patients who took NSAIDs, muscle relaxants, antidepressant, opioid, and sedative during the study period were discontinued from the study. The patients who took paracetamol for severe pain were included.

The Rehabilitation Program

This program followed the recommendations of the American College of Sports Medicine (ACSM)[20] for individuals with FM.

The same physical therapists followed the patients and supervised the sessions. For group 1, each session had two stages: a group therapy session and function exercise. This group executed a training program of 50 minutes, three times a week, for 12 consecutive weeks according to the ACSM guidelines[20]. Each session included: 10 minutes of warm-up with walking and warm-water exercise, 20 minutes of aerobic training, 10 minutes of resistance exercises (strength, endurance, and power), 10 minutes of stretching (table 1). Group therapy, conducted by the physiatrist, consisted of education and mindfulness intervention, each session lasted 10 minutes in a week, to encourage adherence to the rehabilitation program. Education made patients more aware of their own pathology and of therapeutic resources. Mindfulness intervention improved concentration, targeting to meet the specific needs of occupational engagement or returning to work, reduced anxiety, improved the awareness of bodily sensations. The training in the pool included 5 min of warming up with slow walks and 5 min of overall mobility using water as resistance and strength exercises. The aerobic exercises included walking on the treadmill at a speed of 6 and no inclination, core stability, the use of major muscle groups in rhythmic activities, and breathing exercises. The intensity of aerobic exercise achieved 64% of predicted maximum heart rate (range 64% to 94% according to the ACSM guidelines[20]). The resistance exercises at an intensity of the Repetition Maximum of each exercise according to ACSM guidelines[20], included bilateral squats (10 sets of 30 seconds with 45 seconds of recovery between sets) and unilateral squat (8 sets of 30 seconds, with 45 seconds of recovery between sets). Stretching exercises included elongation of neck, shoulder, spine, hamstring, quadriceps, gastrocnemius (4 repetitions for each muscle group), in a position of mild discomfort for a duration of 10 to 30 seconds according to the ACSM guidelines[20].

For group 2, each session had three stages: group therapy session, function exercise, and proprioceptive training. Thus, this group performed the same exercise program, with the addition of proprioceptive training for 10 minutes (agility, coordination, and balance). Proprioceptive training included the following exercises: coordination exercises with eyes open and closed, head movement (left, right, up and down) with eyes open and closed, standing on balance pads with eyes open and closed, balancing on both feet and on one foot, tandem exercises, bending exercises, lateral and backward movements, skipping, scissoring gait, rolling and twisting exercises, Freeman board training, walk on unstable ground, like sand, with eyes open and closed, postural biofeedback exercises like catch, speedball, and sky ball.

TABLE 1. DESCRIPTION OF EXERCISES PERFORMED BY BOTH GROUPS DURING A STANDARD SESSION OF TRAINING

Exercise	Description	Progression
WARM-UP 10'		
Walking	Walking	Increase in time and speed
Swimming pool sessions	34°C water	Overall mobility using water as resistance
Core stability	With breathing exercises	
AEROBIC EXERCISES 20'		
Walking on the treadmill	With an initial speed of 6 and no inclination	Increase in time and speed
ANAEROBIC EXERCISES 10'		
Lower limb exercises		
Anterior, lateral, zigzag, and circles straight leg raise	In supine or side-lying	Increase in external resistance (elastic band)
Hip exercise	Side-lying with knee extension. Horizontal hip abduction	Increase in external resistance (elastic band) /isometry at the end of the series (10 s)
Bridge exercise	–	Bipodal and unipodal support
Stand up and sit down	–	Straight back
Mini squats with bipodal and unipodal support	Bilateral squats: 8 sets of 30 seconds with 45 seconds of recovery between sets	Unilateral squat: 5 sets of 30 seconds, with 45 seconds of recovery between sets
Forward lunge	–	Sideway lunge
Up and down stairs	–	Load in the ankle (1 kg)
Calf raises	–	Bipodal and unipodal support
Upper limb exercises		
Shoulders elevation	Shoulder flexion on scapular plane	Increase external resistance (elastic band)
Pull back exercise	Shoulder extension + elbow flexion + scapular adduction	Increase external resistance (elastic band)
Pull down exercise	Shoulder extension with straight elbow	Increase in external resistance (elastic band)
Push up exercise	–	Upper support on step
Trunk exercises		
Elbow plank exercise	Support on knee	Increase in time
One side plank exercise	In side-lying	Increase in time
PROPRIOCEPTIVE TRAINING 10'		
Coordination exercises with open and closed eyes	Movement with the head (head left, right, up and down	Balancing on both feet and one foot
Unipodal balance	Stand on one leg whit opened eyes (3×1 min)	Associate tasks with upper limbs and with contralateral lower limb
Stand up and sit down	–	Bipodal and unipodal support
Standing on balance pads	With eyes open and closed	Balancing on both feet and one foot
Tandem exercises, bending exercises, lateral and backward movements, skipping, scissoring gait, rolling and twisting exercises,	With eyes open and closed	Balancing on both feet and one foot
Freeman board training	Walk on unstable ground, like sand	During dual-task like forward counting
Postural biofeedback exercises	Catch, speedball, sky ball	With more coordination
STRETCHING 10'		
Flexibility exercises	Static stretching of great muscles groups: elongation of neck, shoulder, spine, hamstring, quadriceps, gastrocnemius	6 repetitions for each muscle group. Increase in time (5–10 min)
Breathing exercises	With accessory respiratory muscles	For 3 minutes

The program had a progressive difficulty in execution, such as an increase in external resistance, load, duration and number of exercises, number of series and repetitions, rest time between sets, and speed of movement execution.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS, Version 18.0 for Windows; SPSS Inc., Chicago, IL) was used for data analysis. Quantitative data were expressed as mean and standard deviation and were

compared using the t-test. P<.05 was considered with statistical significance.

RESULTS

One group of patients performed traditional training, without proprioception exercises (group 1 n= 42), and the second group (group 2 n=42) with proprioception exercises. At baseline, the patients of both groups were homogeneous for general clinical features, clinical characteristics, and relevant socio-demographic characteristics (age, body mass index, education, and occupation). The patients with FM associated to imbalance had similar symptoms: sleep disturbances were present in 35%, paraesthesia in 30%, stiffness in 35%, fatigue and dizziness in 100%, headache in 20%, irritable bowel syndrome in 60%, depression in 45%, anxiety in 10%.

No adverse events, exacerbations, or injuries occurred during the treatment in both groups.

Several patients of both groups took paracetamol: 19 of group 1 and 21 of the group 2 (1 mg/day for a mean time of 15 non-consecutive days when they had pain).

At the moment of the diagnosis, the mean number of the FM tender points was 14 out of 18 in both groups (P>.05). At the end of the training and 8 months after program completion, the mean number of FM tender points was 12, without a statistical difference between the two groups (P>.05) (Table 2). Fifteen months after the program completion, the mean number of FM tender points was similar to the results at baseline (Table 2).

At the first evaluation, the initial score of FIQ was 56 in both groups (a moderate involvement of the functional status of the patients). At the end of the training and 8 months after the end of the program, there were significant improvements in FIQ values in both groups (mean FIQ Score 38) (P<.05), showing just a mild involvement of the functional status of the patients, without a significant difference between the two groups (P>.05) (Table 2). Fifteen months after the program completion, the evaluation showed no significant differences in these scale scores, with similar score obtained at the beginning of training in both groups (Table 2).

At the first evaluation, the pain was referred to as very high (9 out 10 in NRS). At the end of the training and 8 months after the end of exercises, there was a significant reduction of pain in both groups (P<.05), without a significant difference in the NRS score between the groups (P>.05) (Table 2). Fifteen months after the program completion, the evaluation showed no significant differences in these scale scores, with a similar score to that obtained at the beginning of training in both groups (Table 2).

Before the beginning of the training, patients of both groups reported a mean of 31 falls over the last twelve months, without a statistical difference between the two groups (P>.05). From the end of the training until 8 months after the end of the training, the patients of group 1 reported a mean of 21 falls, the patients of group 2 reported 8 falls, the mean number of falls was significantly lower in group 2 compared to group 1 (P<.05) (Table 2). Thus, significant relationships were detected between the number of falls and proprioception exercises.

At the beginning of the study, both groups were at risk of falling, according to the TUGT score (mean duration of the best performance was 19 seconds), the BBS score (mean BBS score: 28), and Tinetti (mean score: 26), without a statistical different between the two groups (P>.05). At the end of the training and 8 months after the end of the program, the difference in the values between the two groups revealed a significant statistical difference in the BBS score, in the Tinetti and in the TUGT scores with an improvement of 9 seconds in the group 2 (P<.05) (Table 2). Thus, in TUGT, BBS, and Tinetti scales the effects of training persisted for 8 months after the end of exercises in group 2, with the same scores obtained at the end of the training. Fifteen months after the program completion, the evaluation showed no significant differences in these scale scores, with a similar score to that obtained at the beginning of training in both groups (Table 2).

Compared to the evaluation at the beginning of the study, at the end of the training and 8 months after the end of the program, according to the MRC, there was a statistically significant increase in quadriceps, hamstring, and gastrocnemius strength in both groups (initial mean score: 3; mean score at the end of the program 5) (P<.05), without a significant difference between the two groups (P>.05) (Table 2). Fifteen months after the end of the program, the improvements in strength were not maintained (Table 2).

At the baseline, in both groups, mean SF-36 scores were lower than those of age- and gender-matched population, especially for pain, fatigue, and mobility (mean scores for pain 36, fatigue 35, mobility

TABLE 2. ABOVE THE SCORES OF GROUP 1 AND 2 AT BASELINE, IMMEDIATELY AFTER TREATMENT, AND 8 MONTHS AFTER TREATMENT (PAIRED T-TEST). THEN THE STATISTICAL DIFFERENCE BETWEEN THE TWO GROUPS IMMEDIATELY AFTER TREATMENT, 8 AND 15 MONTHS AFTER TREATMENT (IMPAIRED T-TEST).

Scales	Group 1 Score	Group 1 Score	Group 1 Paired t Test	Group 1 P value	IC-95%		Group 2 Score	Group 2 Score	Group 2 Paired t Test	Group 2 P value	IC-95%	
	At T0	AF and 8m	AF and 8m	AF and 8m	Group 1		At T0	AF and 8m	AF and 8m	AF and 8m	Group 2	
					Lower limit	Upper limit					Lower limit	Upper limit
Tender points	14±2.14	12±0.70	t 1.58	p >0.05	0.62	1.48	14±2.24	31±3.54	t 1.62	p > 0.05	-6.49	4.74
N. falls	31±3.84	21±3.45	t 1.90	p > 0.05	1.61	3.82	31±3.54	8±4.01	t 1.96	p > 0.05	5.08	7.37
FIQ	56 ±5.07	38 ±7.02	t 2.68	p < 0.05	1.11	4.77	56±8.02	38±7.65	t 2.69	p < 0.05	-0.36	4.38
NRS	9 ±1.05	6 ±0.98	t 2.79	p < 0.05	0,29	2.72	9±1.90	5±0.95	t 2.72	p < 0.05	2.12	2.98
TUGT	19 ±1.08	10 ±2.01	t 1.23	p > 0.05	0.93	4.34	19±2.01	10±1.85	t 1.48	p > 0.05	4.11	5.28
BBS	28 ±3.01	35 ±2.89	t 1.52	p > 0.05	-3.31	-1,53	28±4.25	44±6.01	t 1.60	p > 0.05	-4.40	-1.29
Tinetti	26 ±2.85	25 ±3.02	t 1.58	p > 0.05	-0.52	1,26	26±2.74	22±3.01	t 1.43	p > 0.05	0.52	2.29
MRC	3 ±0.04	5 ±0.05	t 2.72	p < 0.05	-44.72	-44.69	3±0.12	5±0.62	t 3.98	P < 0.05	-4.57	4.35
	Group 1	Group 2	Impaired t -Test	P-value	IC-95%		Group 1	Group 2	Impaired t -Test	P-value	IC-95%	
	AF and 8m	AF and 8m	AF and 8m	AF and 8m	AF and 8m		15 m	15m	15m	15m	15m	
					Lower limit	Upper limit					Lower limit	Upper limit
Tender points	12 ±0.50	12 ±0.25	t 0.05	p > 0.05	-0.15	0.08	14 ±0.50	13 ±0.25	t 0.06	p> 0.05	2.41	2.64
N. of falls	21 ±2.01	8 ±1.06	t 2.71	p < 0.05	7.58	8.51	-	-	-	-	-	
FIQ	38 ±1.98	38 ±2.51	t 0.09	p > 0.05	-0.60	0.76	51 ±2.98	52 ±1.51	t 0.10	p> 0.05	-1.33	0.03
NRS	6 ±0.10	5 ±0.19	t 0.65	p > 0.05	6.64	6.72	8 ±0.10	8 ±0.19	t 0.68	p> 0.05	-0.03	0.06
TUGT	19 ±2.01	10 ±1.82	t 2.82	p < 0.05	4.14	5.30	18 ±1.01	17 ±0.82	t 1.82	p> 0.05	0,79	1,35
BBS	35 ±5.01	44 ±4.98	t 2.90	p < 0.05	-3.34	-0.32	30 ±1.02	32 ±0.98	t 1.91	p> 0.05	-2.34	1.74
Tinetti	25 ±3.01	22 ±2.74	t 3.09	p < 0.05	0.14	1.88	26 ±1.01	25 ±1.74	t 1.06	p> 0.05	0.41	1.24
MRC	5 ±0.05	5 ±0.09	t 0.81	p > 005	-0.02	0.03	4 ±0.05	4 ±0.09	t 0.84	P> 005	-0.02	0.03

	Group 1	Group 2	Impaired t -Test	P-value	IC-95%							
SF-36 after treatment					Lower limit	Upper limit						
Pain	50 ±3.84	52 ±4.03	t 0.38	p > 0.05	-1.68	0.70	-	-	-	-	-	-
Fatigue	52 ±2.01	51 ±2.10	t 0.45	p > 0.05	-0.12	1.13	-	-	-	-	-	-
Mobility	39 ±2.86	56 ±4.02	t 2.71	p < 0.05	-5.80	-3.72	-	-	-	-	-	-

Abbreviations: Group 1 exercise training group without proprioception exercises, Group 2 group with proprioception training, ± standard deviation, FIQ Fibromyalgia Impact Questionnaire, NRS Numerical Rating Scale, TUGT Timed Up and Go Test, BBS Berg Balance Scale, MRC Medical Research Council scale, AF immediately after treatment, 8m four months after treatment, T0 at baseline, IC confidence interval, N. numbers. Results reported as mean effect sizes (Cohen's d) (95% confidence interval (95%).

37), without a statistical difference between the two groups (P>.05) (Table 2). At the end of the training and 8 months after the end of the program, a significant improvement was seen in pain and fatigue in both groups; whereas 15 months after the end of the program, the scores were similar to the results at the baseline.

The training protocol we proposed included 10 minutes of warm-water exercise, 20 minutes of aerobic training, 10 minutes of resistance exercises, 10 minutes of stretching, and 10 minutes of proprioceptive training.

DISCUSSION

In this study, we observed that the combination of traditional exercises and proprioceptive training reduced pain and fatigue and increased muscular performance. A proprioceptive training program as a complementary therapy for the management of fi-

bromyalgia associated with imbalance must be part of the rehabilitation program. The results suggested that the benefits provided by the proprioceptive program did not include additional gains in muscular performance. Furthermore, we propose a multidisciplinary clinical approach to guide patients from diagnosis to recurrence of pain. Our diagnostic protocol included the following assessments and scales: vestibular tests, the number of tender points, FIQ, NRS, BBS, Tinetti scale, TUGT, the number of falls in the last 6 months, MRC, and SF-36.

Studies such as ours discuss the benefits of aerobic and resistance exercise in FM patients; we added proprioceptive training in FM patients to improve balance and decrease the fear of falling. The treatment for FM should focus first on non-pharmacological therapies, such as aerobic and strengthening exercises, proprioception exercises, warm-water exercise, for its availability, absence of adverse drug reactions, and relatively low cost[21]. We showed the effects of training for pain, strength, quality of life, and the functional consequences in FM, after 3 months of physical exercises and at 8 and 15 months after the suspension of training. Adding the proprioception exercises, we reported a significant improvement in balance, mobility, and a reduction of the number of falls too.

There is strong evidence that exercise is effective in the treatment of the signs and symptoms of FM, but there are no clear diagnostic and therapeutic protocol[s22,23]. Two studies showed good results in practicing multimodal exercises involving different skills such as strength, endurance, balance, and coordination for pain management, fatigue, and muscle weakness, thus reducing the impact of the disease on the QoL of these subjects[23,24].

To improve the ADL, better outcomes have been obtained from aerobic, strengthening, stretching and flexibility exercises, and water exercises[25-27]. In addition to these classical programs, our protocol was based on proprioception exercises and focused on minimizing fatigue and pain by increasing the level of activity and balance. In another study, the benefits of aerobic training were found to be more significant than balance training[28]. Two studies have found that aerobic exercise is useful to improve the FIQ score, and it is considered the standard treatment for FM[7,29]. A meta-analysis reported that aerobic exercise for patients with FM should be performed at a slight to moderate intensity, two to three times a week, for at least four weeks[22]. Accordingly, in our study, we established that exercise training, three times a week, for three months, led to an improvement in FM symptoms, maintained during the following eight months. Another study showed that uninterrupted training programs should be essential in the management of patients with FM, because training programs had short-term beneficial effects on clinical signs and dynamic balance[30]. Some studies have found improvements in balance and motor control in response to multimodal training programs with strength training in patients with FM[31]. Concurrent strength and endurance training in low to moderate intensity is beneficial to patients with FM, improves the muscle strength and functional performance, and reduces symptoms, fatigue in particular[32]. Several studies have shown that short periods (5–24 weeks) of water exercise improve neuromuscular conditions[33], physical fitness[34], and quality of life[33]. Long-lasting therapy in warm water improves muscle strength, physical problems, emotional problems, mental health, and balance[12]. Meditative movement (yoga, tai chi, qigong, or body awareness therapy) improves sleep and fatigue in the longer term in FM too[12].

In the literature, several studies were conducted on the efficacy of training programs in patients with FM and were focused on symptoms of fatigue and pain[35]. The number of studies on training programs for balance disorders with an accurate description is limited[36]. Even if few studies were directed towards balance dysfunction, imbalance and gait disorders are common symptoms of FM. The increased number of falls in patients with FM is due to imbalance and also to other risk factors, such as pain, muscle weakness, cognitive disturbance, mobility limitations, use of psychotropic drugs. Several drugs, including muscle relaxants, antidepressant drugs, or opioids, which are used commonly by patients with FM, can disturb the balance and are related to falls. Jones et al.[4] reported that 44 to 74 % of patients with FM used such drugs.

Some studies have shown that training improves clinical findings, such as pain, physical function, proprioception, balance, and walking, through stimulation of mechanoreceptors, muscle fibers, and tactile receptors[30,37]. Thus, Gusi et al.[38] reported improvements in balance using a vibratory platform, the whole-body vibration (WBV). Sañudo et al.[29] reported similar results and demonstrated that a traditional

exercise program, supplemented with WVB training, could improve balance in FM[29].

CONCLUSIONS

We recommend that non-pharmacological therapy should be the first-line therapy. The present study showed that traditional exercises (aerobic and resistance exercises and stretching) reduce pain, increase strength, improve exercise capacity, and enhance the quality of life in patients with FM, even if the positive results were not maintained after the interruption of rehabilitative program. The most effective type of exercise for balance is proprioceptive training. Thus, these training programs associated with balance exercises show improvements in FM symptoms (pain, fatigue) and could improve balance and maintain stability, reducing the fear of falling and the number of falls. A balance evaluation is required, and a more specific treatment protocol is needed in patients with FM associated with imbalance. We reported our multidisciplinary clinical protocol for the management of FM associated with postural imbalance.

After three months of training, the balance evaluation revealed significant differences in the TUGT, BBS, and Tinetti scale scores compared to the baseline, with a better improvement in the proprioceptive training group. Eight months after the end of the training, the patients maintained improved performance. After 15 months, the effects of training on balance and on the specific symptoms of the disease were not maintained. It is necessary to maintain proprioceptive ability by continuing the exercises after the end of the physiotherapy program. We recommend repeating the cycle of exercises with our protocol twice a year to maintain the effects of the program.

The theme is relevant, considering that recent studies show that a high proportion of individuals with fibromyalgia present balance problems. We showed the importance of a multidisciplinary clinical approach with a rheumatologist, pain therapist, physiatrist, physiotherapist, and also otolaryngologist to rule out an inner ear disease that might be causing dizziness, to follow the progression of the disease, design a protocol for the management of FM and a program of preventive care.

RESUMO

OBJETIVO: *Relatamos nosso protocolo multidisciplinar para o manejo da fibromialgia associada ao desequilíbrio. Nosso objetivo foi verificar a eficácia do programa de treinamento proprioceptivo como terapia complementar de um protocolo tradicional (exercícios aeróbicos, de resistência e flexibilidade).*

MÉTODOS: *Estudo retrospectivo em 84 mulheres com fibromialgia primária associada a desequilíbrio. Um grupo de pacientes realizou o treinamento tradicional; em um segundo grupo o treinamento foi complementado com exercícios de propriocepção. Cada sessão durou de 40 a 60 minutos e foi realizada três vezes por semana durante 12 semanas.*

RESULTADOS: *Após três meses de treinamento e oito meses após o término do treinamento, a avaliação do equilíbrio revelou diferenças significativas nos testes Timed Up and Go, Escala de Equilíbrio de Berg e Escala de Tinetti em comparação com a linha de base, com uma melhora maior no grupo de treinamento proprioceptivo ($p<0,05$). Redução da dor e melhora do desempenho funcional e muscular e da qualidade de vida foram observadas em ambos os grupos ($p<0,05$), mas sem diferenças significativas entre eles na Escala Numérica de Dor, Fibromyalgia Impact Questionnaire e Short Form Health Survey ($p>0,05$). Quinze meses após o final do programa, os efeitos do treinamento não foram mantidos.*

CONCLUSÃO: *O presente estudo revelou que o treinamento suplementado com exercícios de propriocepção tem efeitos benéficos sobre os achados clínicos e melhora o equilíbrio em pacientes com fibromialgia, mesmo que os resultados positivos não tenham persistido após a interrupção do programa de reabilitação no longo prazo.*

PALAVRAS-CHAVE: *Fibromialgia. Equilíbrio postural. Dor crônica. Protocolos clínicos. Qualidade de vida.*

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ORIGINAL ARTICLE

Gynecological cancer and metabolic screening of 1001 elderly Brazilian women

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http://dx.doi.org/10.1590/1806-9282.65.10.1275

SUMMARY

OBJECTIVE: *The aim of this study was to evaluate gynecological cancer and metabolic screening of Brazilian women aged 65 years or older.*

METHODS: *This retrospective descriptive study was conducted by including 1,001 Brazilian patients of the gynecological geriatric outpatient office of our institution to evaluate the influence of age on gynecological cancer and metabolic screening parameters at the first clinical visit. All patients were divided into three groups: a) 65 to 69 years; b) 70 to 74 years; c) ≥ 75 years. We considered clinical, laboratorial, and image data as variables of this study. The Chi-square test was used to assess the proportion of differences among the age groups, and Kruskal-Wallis was used for quantitative variables.*

RESULTS: *The values of BMI and height in the group over 75 years was lower than that of the 65 to 69 years (p = 0.001). Regardless of the age group, high arterial blood pressure levels were found in 85.45% of participants. Also, many patients had glucose intolerance in the blood. The pelvic ultrasonography showed abnormal endometrial echo thickness (> 5 mm) in 6.14% of patients, but with no significant statistical difference between the age groups. A total of 4.04% of patients had ovaries with high volume values (> 6.1 mL). Abnormal mammography (BI-RADS 3 or 4) was observed in 12.21%.*

CONCLUSIONS: *our data suggest that a great reduction in BMI and stature is more frequent in the group over 75 years. Also, systemic arterial hypertension and carbohydrate disturbance are frequent morbidities in women over 65 years.*

KEYWORDS: *Aged. Women. Menopause. Body mass index. Genital neoplasms, Female.*

INTRODUCTION

The increase of populational longevity concerning people over 60 years old is a reality all over the world. According to the Brazilian Institute of Geography and Statistics (IBGE), the elderly age group increased proportionally more than any other age group in the 20th century, with life expectancy at birth jumping from 42.7 years in 1930 to 74.8 years in 2014[1]. The United Nations World Populations Prospects in 2002[2], estimates that by 2050, the population over 60 years probably will lead 2 billion individuals. These demographic data and others like climate, race, socioeconomic level, health and physical conditions and are very important,

DATE OF SUBMISSION: 29-Apr-2019
DATE OF ACCEPTANCE: 01-Jun-2019
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and more information about[3-7] the female population aged 65 and over is still necessary.

Over the last few decades, there has been increased interest in studying and learning the general conditions of the aging population, particularly women after menopause, which is a particular period with a reduction in estrogen levels and its consequences on the organism, such as vasomotor symptoms. However, a high number of patients present an excessive increase in body mass index (obesity), systemic arterial hypertension, higher fast glucose level, and diabetes mellitus, among other cardiovascular risks, and gynecological cancer during this period[6-10]. This phenomenon is well reported[6-10]. This period finishes at the age of 65 years. However, data on age influence on gynecological and metabolic parameters of women aged over 65 years are scarce. In fact, some guidelines suggest not continuing with cancer screening, such as cervical cancer, in this population[11]. However, life expectancy is rising in Brasil[12], so this is an opportune time to understand the real influence of age on the gynecological parameters for cancer screening, such as pap smears (cervical and vaginal cancer), mammography (breast cancer), ultrasound (endometrial cancer), and physical examination (genital cancer) for starting preventive strategies to reduce morbidity conditions associated to cancer. Also, obesity is an independent factor for cancer (breast and endometrial) as well as metabolic disturbance[5,6,13]. In a recent study on postmenopausal patients, 53% of participants had multimorbidities, including gynecological disturbance, which may have an impact on the quality of life[14]. Also, the gynecological population of Hospital das Clínicas reflects the five macro-regions of Brasil[5]. Those conditions may be worsening with aging. Therefore, the knowledge of this study may provide new information for elaborating strategies for the care of this specific female population.

The aim of the study was to evaluate the influence of the age on clinical and laboratory gynecological parameters for screening morbidities on a large group of Brazilian women aged 65 years or older at the Gynecology Discipline of the Department of Gynecology and Obstetrics at the Hospital das Clínicas, Faculty of Medicine of the University of São Paulo.

METHODS

Study design and subject selection

This was a descriptive, transversal and retrospective study on women without previous chronic comorbidities, aged 65 years or older, conducted by the Gynecology Discipline, at the Department of Gynecology and Obstetrics of Hospital das Clínicas, Faculty of Medicine, University of São Paulo. The length of the study was from 1983 to 2010. We used patient records that included all clinical history, physical examinations, and laboratorial results for evaluating the gynecological and metabolic screening.

Eligibility criteria

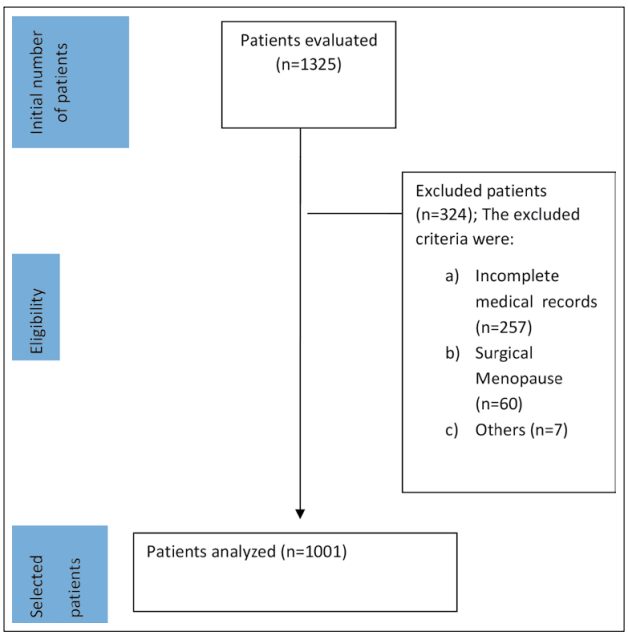
We included patients who were: women aged 65 years old or over, with adequate and complete medical information (medical records of the clinical evaluation, laboratory analysis) to execute and analyze the study variables. Our study included patients invited for gynecological and metabolic screening.

We excluded patients with surgical menopause (ovariectomy or/and hysterectomy), menopause before the age of 40 (premature ovarian insufficiency) and those unable to be examined or who reported previous health problems.

Selection

Initially, 1,325 Brazilian women aged 65 years or older were included in the study. After applying the eligibility criteria, the final number was 1,001 women. Figure 1 summarizes the selection of patients. The main reasons for exclusion were incomplete patient medical data and surgical menopause.

FIGURE 1. PATIENT SELECTION FLOWCHART



To evaluate the influence of age on the gynecological parameters of heath, the patients were divided into the three following groups: a)65 to 69; b)70 to 74; c)≥ 75 years old. The Ethics Committee approved this study for Research Project Analysis of HC-FMUSP (#number 0757/08).

Study variables

Dependent variables: 1) gynecological cancer screening: a) breast; b) cervical; c) ovary; d) endometrium; e)colon cancer (hidden blood in feces); 2) metabolic screening: a) BMI (body mass index, kg/m^2); b) Systemic blood pressure; c) laboratory evaluation (fasting glucose, cholesterol, total and fractions, triglycerides, thyroid-stimulating hormone (TSH), free thyroid hormone (FT4), urea, creatinine).

Independent variables: formal education, sexual partner, religion, skin color, socioeconomic status, alcohol consumption, frequency of alcohol consumption, frequency of physical exercise, mass index (kg/m^2), number of sexual partners over a lifetime. The variable regarding the age of natural menopause was divided into three categories: a) Early menopause (between 40 years and 45 years); b) Adequate menopause (between 45 years and 55 years); c) Late menopause (over 55 years)[15]. The rationale of this classification is that women in early menopause have higher metabolic and cardiovascular risk (longer period in hypoestrogenism) and women in late menopause have higher gynecological cancer risk (larger estrogen window).

Physical examination

The methods for Anthropometric measures were: a) stature was measured with a rounding of 0.1 cm, using a standard stadiometer, with the participants standing and without shoes; b)body weight was measured barefoot on a calibrated precision digital scale (Filizola PL 200, Filizola(r), São Paulo, Brasil) with precision for the nearest 100 grams. Body mass index (BMI) was determined by calculating the ratio of body mass in kilograms to height in square meters.

The gynecologic examination included an examination of the breasts, abdomen, and pelvic organs. The pelvic examination was performed with the patient lying supine on an office examination table with the knees flexed, and with the feet in supporting stirrups. The vagina and cervix were inspected for lesions. Pap Smears were taken for cervical or vaginal cytology with a spatula, and a sample from the endocervical canal was taken with a brush. The material was fixed immediately after obtaining the sample in order to avoid air-drying artifact.

The bimanual examination was performed with the aid of lubricating jelly. The examiner placed two fingers in the vagina and used the opposite hand to palpate the lower abdomen. In some cases, a single digit was placed in the vagina. The examiner palpated the vagina, cervix, uterus, adnexa, and surrounding structures by elevating structures with the vaginal hand and palpating in a downward fashion with the abdominal hand. The posterior cul-de-sac and utero-sacral ligaments were checked for nodularity and masses.

LABORATORY PARAMETERS

Gynecological cancer screening

Mammography screening: all views from the mammogram pairs were evaluated by the radiologists of Hospital das Clínicas. The BIRADS Classification was used for reducing confusion in breast imaging interpretations. If necessary, breast ultrasound was performed for final diagnosis.

Pap smears: the conventional Pap smear was done. The samples were smeared directly onto a microscope slide after collection and evaluated by a pathologist. The classification was described as class I, II, III, IV, and V.

Ultrasound: The participants were placed on the examination table in dorsal decubitus. The evaluation was performed with the HDI-5000 Philips Sono System (Philips Medical Systems, Andover, MA, USA). We followed the parameters: normal uterus volume < 60 cm^3, enhanced volume > 60 cm^3; endometrial echo thickness: the cut-off of normality was 5 mm. The cut-off of the ovarian volume normality was 3 cm^3.

The classic fecal occult blood test was used to check stool samples for hidden blood. Negative exams were defined as normal.

Metabolic screening

The blood was collected for laboratory metabolic analyses: fasting glucose, cholesterol total, fractions and triglycerides, urea, creatinine, thyroid-stimulating hormone (TSH), free thyroid hormone (FT4), testosterone, and androstenedione.

The values for abnormally high levels of fast glucose, LDL-cholesterol, triglycerides, urea, creatinine, testosterone, and androstenedione were >100 mg/dl,

> 130 mg/dl, 150 mg/dl, > 50mg/dl, > 1.30mg/dl, >70 mg/dl, and > 2.8 mg/ml, respectively.

The diagnosis of diabetes mellitus was made when fast glucose was over 125 mg/dl. The low level of HDL-cholesterol was defined at <50 mg/dl. Hypothyroidism was defined when TSH > 4.5 mUI/L and FT4 <0.6 ng/d (if the patients had symptoms).

Statistical analysis

The variables were analyzed, and the representation of data was done by using mean and standard deviation. We used the chi-square test to assess the relationship among the categorical proportion variables mentioned above; p-values less than 0.05 were considered statistically significant. The statistical method of Kruskal-Wallis was used for quantitative variables. After that, Dunn's Multiple Comparison Test was applied for evaluating the differences between the two groups. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, SPSS Inc, Chicago, II, US), version 16.01.

RESULTS

Demographic data

The age of the 1001 women selected ranged from 65 to 98 years (68,56 ± 4,47 years). The composition of the patients seems to mirror the geographic distribution of the Brazilian population: 23.3%, 14.1%, 27.5%, 17.3%, and 17.8%, respectively, were from the North, Northeast, Midwest, Southeast, and South of Brasil. Also, approximately 90% of the patients were of low-level socioeconomic status, and around 10% were of medium socioeconomic status. All variables were similar among the groups (formal education; sexual partner; religion; skin color; socioeconomic status; alcohol consumption; frequency of alcohol consumption; frequency of physical exercise). The age of natural menopause was similar among groups (Table 1).

Metabolic screening data

Table 1 summarizes the BMI, height, and systemic arterial pressure of participants in this study. In the assessment of BMI in different ages, groups were observed that with the increasing of age there is a decrease in BMI, with statistically significant difference (p= 0.001), mainly in the patients with obesity and morbidly obesity over 75 years compared to ones with less 69 years. The height of the patients ranged from 138 cm to 173 cm, with a reduction in stature with a significant statistical difference with the increase of age (p<0.001), mainly in the group over 75 years compared to the one between 65 and 69 years. Regardless of the group, high systemic arterial blood pressure was detected in most women (85.45%), but there was no difference among the age groups (p=0.15).

TABLE 1. NATURAL MENOPAUSE AND PHYSICAL DATA FROM 1001 BRAZILIAN WOMEN PER AGE GROUP

Age Groups	*65-69 years (n = 661)*	*70-74 years (n = 233)*	*≥ 75 years (n = 107)*	*p*
*Menopause**				
Early	*97 (14.67%)*	*31 (13.30%)*	*10 (9.35%)*	*0.59*
Adequate	*510 (77.16%)*	*193 (82.83)*	*91 (85.05%)*	
Late	*54 (8.17%)*	*9 (3.86.66%)*	*3 (2.81%)*	
*Body mass index (kg/m²)**				
≤20	*24 (3.63%)*	*8 (3.43%)*	*9 (8.41%)*	*0.001*
20-25	*159 (24.05%)*	*66 (28.33%)*	*31 (28.97%)*	
26-30	*241 (36.46%)*	*106 (45.49%)*	*48 (44.86%)*	
31-35	*161 (24.36%)*	*43 (18.45%)*	*15 (14.02%)*	
≥35	*76 (11.50%)*	*10 (4.29%)*	*4 (3.74%)*	
*Height ***				
Means (cm)	*1.54 ± 0.05*	*1.53 ± 0.06*	*1.52 ± 0.05*	*< 0.001*
*Blood pressure (maximum and/or minimum, mmHg)**				
Normal (<140 and <90)	*106 (16.04%)*	*28 (12.02%)*	*11 (10.28%)*	*0.15*
High (≥ 140 and/or ≥ 90)	*555 (83.96%)*	*205 (87.98%)*	*96 (89.72%)*	

*Chi-square test, p<0.001 when >75 year-group was compared to the 65-69 year- group; **Kruskal-wallis followed by Dunn test (comparison between the 65-69 year and over 75 years groups).

The laboratory data are summarized in Table 2. There is no difference among groups in relation to the following variables: fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, VDRL-cholesterol, triglycerides, TSH, free T4, total testosterone, and androsterone blood levels. The total testosterone level has high only on 2 patients (values: 111ng/dL and 79 ng/dL), and androstenedione levels were high on one patient (127 ng/dL). High values of TSH (mUI/ml) and low values of free T4 (ng/dl) were detected in women with clinical symptoms of thyroid dysfunction. Creatinine and urea blood levels of patients over 75 years was significantly superior to the 65-69 years group, respectively, p=0.009 and p=0.085.

GYNECOLOGICAL CANCER SCREENING

Gynecological examination

The percentage of patients with normal gynecologic examination, breast, abdomen, external genital organs, vagina and internal genital organs, was, respectively, 82.57%, 95.67%, 32.33%, 26.33%, and 33.45%. Most women had abnormal characteristics with atrophic external and internal genital organs. Also, 17.43% of women with abnormal breast examination presented nodules or papillary discharge. There was no difference among the age groups.

Colon and cervical screening

The positive and negative results of fecal occult blood in 313 women were respectively 17.57% and 82.43%. There was no difference among age groups. Vaginal and cervical oncological cytology results of 818 patients were: a) category I -n=350(42.79%); b)category II – n=464 (56.72%); c) category III – 4 (0.49 %); there was no detection of category IV or V in our study. There was no difference among age groups.

OVARIAN AND ENDOMETRIAL CANCER SCREENING

Pelvic sonography data

Pelvic ultrasonography was performed in 546 women and showed 94.14% and 5.86%, respectively, normal and abnormal values in general. Normal and high volume uterus were detected respectively in 83.47% and 16.53% of the women. In the comparison between the groups, low values of volume were detected in patients over 75 years old compared to the other groups (p=0.03). Endometrial echo thickness was normal in 93.86% of participants (<5mm) and abnormal in 6.14% (> 5.1 mm). The statistical analysis did not detect significant differences among the groups. Ovarian volume was assessed in 173 women; 95.96% and 4.04%, respectively, presented normal and abnormal volume. The ultrasound did not detect the ovarian image in 374 patients. There was no difference between age groups. The abnormal values of ultrasonography were forwarded to a cancer center for final diagnosis.

Mammography data

The mammography evaluation was done using the BI-RADS method in 852 women: 87.80% and 12.21% of patients presented, respectively, BI-RADS 1/2 and BI-RADS 3/4. The patients with suspected breast

TABLE 2. BLOOD LEVELS OF METABOLIC LABORATORIAL SCREENING OF 1001 BRAZILIAN WOMEN PER AGE GROUPS

Age Groups	*65-69 years (n = 661)*	*70-74 years (n = 233)*	*≥ 75 years (n = 107)*	*p*
Fasting glucose (mg/dL)	*103.91±36.56*	*103.21±27.16*	*98.73± 15.66*	*0.369*
Total cholesterol (mg/dL)	*213.62±41.08*	*213.88±44.76*	*218.13±43.55*	*0.637*
HDL-cholesterol (mg/dL)	*56.03±15.98*	*59.13±22.83*	*57.99±18.91*	*0.520*
LDL- cholesterol (mg/dL)	*131.63±35.98*	*128.39±41.64*	*133.81±39.26*	*0.515*
VLDL- cholesterol (mg/dL)	*26.37±13.25*	*25.25±16.05*	*23.47±11.63*	*0.173*
Triglycerides (mg/dL)	*136.46±65.92*	*130.80±86.08*	*128.07±64.03*	*0.177*
TSH (mUI/mL)	*2.61±2.42*	*2.82±4.38*	*2.34±1.80*	*0.872*
FT4 (ng/dL)	*1.21±1.18*	*1.12±0.25*	*1.08±0.30*	*0.154*
Total testosterone (ng/dL)	*20.50±12.43*	*38.10±35.10*	*37.30±36.20*	*0.273*
Androstenedione (ng/dL)	*3.30±7.47*	*1.22±0.75*	*0.60±0.15*	*0.301*
*Creatinine (mg/dL)**	*0.78±0.18*	*0.83±0.19*	*0.87±0.17*	*0.009*
*Urea (mg/dL)**	*34.54±13.25*	*37.65±16.05*	*38.85±11.63*	*0.085*

*Kruskal-wallisfollowed by Dunn test (comparison between the 65-69 group and the over 75 years group).

cancer image were forwarded to the mastology sector for final diagnosis.

DISCUSSION

The elderly demographic has increased in most countries of the world, and one of the main objectives of public health programs is to know the conditions of health and lifestyle that can be controlled in the population to improve the quality of life of elderly individuals. Geriatric women have been studied by many researchers, and this retrospective study conducted at the gynecological geriatric outpatient office at Hospital das Clínicas, College of Medicine University of São Paulo by gynecologists had the opportunity to evaluate 1001 elderly women (aged from 65 to 98 years old) from different Brazilian regions. In general, the data analyzed presented similar features in postmenopausal women (age<65 years)[5-7]. Apparently, health conditions (metabolic and gynecological cancer screening) of geriatric women are not worse than those during the postmenopausal period. Also, our data suggest that the great reduction in BMI and stature is more frequent in the group over 75 years.

In a review study by Palacios[14]et al and others[5-7], age is one factor that increases the risk of cancer and metabolic disturbance. However, obesity, genetic inheritance, and other diseases, such as polycystic ovarian syndrome and diabetes mellitus may play an important role in the development of metabolic disturbances and cancer[4,6,7-10,16]. The detection of BMI reduction in women over 75 years may be valuable information regarding the health condition, but another possibility is that obesity may increase the morbidity and mortality in other age groups (< 75 years), which may be why the percentage of obese women was low over 75 years. This is important data to create new strategies of public and private health programs targeted at individuals younger than 75 years. Perhaps, it could increase the life expectancy in the female population[4-7,10,12-15].

Excess weight is considered a problem for the health and quality of life. It is important to emphasize that most of these factors can be prevented with recommendations for a better lifestyle, including regular physical and intellectual activity, correct nutritional approaches, and others[5,6,12,16]. Excess weight and arterial hypertension in climacteric and postmenopausal women are considered major risks for cardiovascular diseases and metabolic syndrome, and preventive care is recommended for this group of women to reduce morbidity and mortality[5-7,9,17-19]. Also, it partially explains why high levels of systemic arterial blood pressure are also detected in women over 65 years. In addition, this disease needs a unique health care program for this specific population to prevent and reduce morbidity and mortality[5,18-21].

The atrophy of the genital system is frequently found in most patients after menopause. It is related to a hypoestrogenism state[5,6,9,16,22]. However, breast papillary discharge is not common after menopause[5,6,9,16,22]. We found this in approximately 17% of cases. One possibility for this change is the atrophy of mammary ducts[16,22]. However, those women need to maintain an evaluation for warding off other conditions or diseases.

Regardless of the age, the metabolic results of patients did not show great concerns regarding the lipid profile. However, carbohydrate metabolism is a problem due to insulin resistance and glucose intolerance in many women over 65 years[4,6,8,9,21,23]. This seems to be more of an individual problem than an age influence[4,6,8,9,21,23]. Also, this glucose profile may be no worse than that reported by postmenopausal women[5-6]. Androgen production is similar among the age groups, and it reflects the ovarian and, mainly, adrenal production. Previous studies by our group found that 5-10 years after menopause the ovaries are no longer relevant for sex steroid synthesis[24]. Therefore, androgen levels can be used to evaluate adrenal metabolism.

The investigation of occult blood in feces was positive in more than 17% of participants of our study. It is a health concern because this exam is used for screening gastrointestinal tract diseases[5,9]. This test has both merits and weaknesses. Testing does uncover subclinical colorectal cancer, often at a relatively early stage, but whether this actually improves the prognosis remains to be proven. Benign polyps are also detected, which is a limitation of this exam. The test sensitivity for malignancy varies from good to moderate, but it is poor for polyps. Specificity is usually around 97%-98%, yet the predictive value of a positive test for cancer is only about 10%[25]. However, it is cheaper and less complex than a colonoscopy[25]. Colorectal cancer represents the third most common malignancy in high-income countries, where it also ranks third in leading causes of cancer deaths[26]. Although it is not a gynecological cancer, we included this exam due to its prevalence and importance for public health.

Women diagnosed with early-stage ovarian cancer may have a better prognosis. Accordingly, it is imperative to detect and diagnose the disease as early as possible in its development. Unfortunately, there are no biomarkers or ultrasound exams with good accuracy for screening this cancer in early stage[27]. Therefore, the ovarian volume can be used as a way to identify patients with risk of this type of cancer through a physical examination or pelvic ultrasonography[27]. Regardless of age, we found this change in a small number of patients in our study. However, it is a great concern to the high morbidity and mortality of this diesease[27]. Endometrial cancer is more frequent than ovarian, but the most important marker is abnormal uterine bleeding[28], which goes directly to the other sector of our outpatient system in Hospital das Clínicas. It is a limitation of our ultrasonographic results, which found around 6% of our patients had endometrial echo over 5.1 mm. This exam in asymptomatic women will result in unnecessary additional biopsies because of false-positive test results, such as polyps or other affections[28]. However, being overweight or obese, adult weight gain, and diabetes are associated with an increased risk of endometrial cancer[28]. Regardless of age, we found a high number of patients with carbohydrate metabolism disturbance. It is a public health concern that requires special care by public programs to reduce this affection on women over 65 years. Also, those diseases or affections interfere with the quality of life[9,11,29].

The mammography showed 12.21% of patients had abnormal BIRADS classification. This is important because gynecological cancer causes high rates of mortality and morbidity among young and old women[1,18,30,31]. Our study is limited because the final cancer diagnosis is performed in the breast section of our institution to be sure that this high rate of abnormal BIRADS correspondent to a true disease. However, it is a alert due to the risk of breast cancer related to a high score of BIRADS[1,18,30,31].

CONCLUSION

The fact that the female population over 65 years has increased longevity makes this study interesting because we found a metabolic and gynecological cancer profile of those patients. Our data may help public programs for diagnosis, treatment, and advice for a better lifestyle to reduce morbidity and mortality with this specific population. Finally, our data suggest that a great reduction in BMI and stature is more frequent in the group over 75 years. Also, systemic arterial hypertension and carbohydrate disturbances are frequent morbidities in women over 65 years.

Funding: This study was supported by CNPq and CAPES (Brasíla-Br)

Statement: The authors do not have any conflict of interest

Acknowledgments: This study was supported by grants from CAPES and CNPq

Competing interests: The authors declare that they have no competing interests

RESUMO

OBJETIVO: *O objetivo deste trabalho foi estudar retrospectivamente alguns dados clínicos, laboratoriais e imagens de um grupo de idosas brasileiras.*

MÉTODO: *Estudo observacional retrospectivo realizado com inclusão de 1.001 mulheres brasileiras atendidas no ambulatório de geriatria ginecológica de nossa instituição. Foram analisados: a idade dos pacientes na primeira consulta clínica e a idade na menopausa natural; alguns achados clínicos durante um exame ginecológico; resultados de análises laboratoriais. Considerou-se a relação dessas variáveis com o grupo da idade das mulheres. O teste do qui-quadrado foi utilizado para avaliar os dados e para algumas variáveis, Kruskal-Wallis ou Anova.*

RESULTADOS: *A avaliação do IMC e da estatura nas diferentes faixas etárias das mulheres mostrou que, com o aumento da idade, há diminuição do IMC e da estatura (p=0,001). Nível anormal de pressão arterial estava presente em 85,45%. De acordo com o grupo de idade, as medidas laboratoriais foram avaliadas pelo método estatístico Kruskal-Wallis, e a Anova mostrou diferença estatisticamente significante apenas no valor da creatinina, com pequeno aumento com a idade. A ultrassonografia pélvica foi alterada com espessura endometrial normal (>5 mm) em 29 (6,14%), mas sem diferença estatística significativa com os grupos de idade, e os ovários mostraram sete (4,04%) com volume anormal (>6,1). Mamografia anormal (BI-Rads 3 ou 4) foi observada em 104 pacientes (12,21%).*

CONCLUSÕES: *O estudo conclui que, com o aumento da idade, há redução do IMC e da estatura. A hipertensão é morbidade frequente. Os dados laboratoriais e a avaliação de imagens deste estudo são importantes para aumentar o conjunto de informações sobre mulheres idosas e talvez para melhorar a assistência à saúde.*

PALAVRAS-CHAVE: *Idoso. Mulheres. Menopausa. Índice de Massa Corporal. Neoplasias dos genitais femininos.*

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ORIGINAL ARTICLE

The usefulness of Tanita TBF-310 for body composition assessment in Judo athletes using a four-compartment molecular model as the reference method

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http://dx.doi.org/10.1590/1806-9282.65.10.1283

SUMMARY

Body composition assessment at the molecular level is relevant for the athletic population and its association with high performance is well recognized. The four-compartment molecular model (4C) is the reference method for fat mass (FM) and fat-free mass (FFM) estimation. However, its implementation in a real context is not feasible. Coaches and athletes need practical body composition methods for body composition assessment, and the bioelectrical impedance analysis method (BIA) is usually seen as a useful alternative. The aim of this study was to test the validity of BIA (Tanita, TBF-310) to determine the FM and FFM of elite judo athletes. A total of 29 males were evaluated in a period of weight stability using the reference method (4C) and the alternative method (Tanita, TBF-310). Regarding the 4C method, total-body water was assessed by deuterium dilution, bone mineral by DXA, and body volume by air displacement plethysmography. The slops and intercepts differed from 1 (0.39 and 1.11) and 0 (4.24 and -6.41) for FM and FFM, respectively. FM from Tanita TBF-310 overestimated the 4C method by 0.2 kg although no differences were found for FFM. Tanita TBF-310 explained 21% and 72% respectively in the estimation of absolute values of FM and FFM from the 4C method. Limits of agreement were significant, varying from -6.7 kg to 7.0 kg for FM and from -8.9 kg to 7.5 kg for FFM. In conclusion, TBF-310 Tanita is not a valid alternative method for estimating body composition in highly trained judo athletes.

KEYWORDS: *Bioelectrical impedance analysis; tanita TBF-310; 4 compartments model; fat mass; fat-free mass; body composition methods.*

ABBREVIATIONS:

2C – Two-compartment model
4C – four-compartment model
^2H_2O – Deuterium oxide solution dose
BIA – Bioelectrical impedance analysis method
BMC – Bone mineral content
BV – Body volume
BW – Body weight
CV – Coefficient of variation
DFFM – Fat-free mass density
FFM – Fat-free mass
FM – Fat mass
M – Total-body mineral
Mo – Bone mineral
Ms – Total-body soft tissue mineral
SMOW – Standard mean ocean water
TBW – Total-body water
TEM^2 – Squared technical errors of measurement
VO_{2max} – Maximum oxygen uptake

DATE OF SUBMISSION: 13-Feb-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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INTRODUCTION

For athletic populations, body composition has an important role in performance regulation and training programs; that is even more relevant in sports in which weight can greatly affect the performance, or a target body weight needs to be achieved. Judo athletes frequently use dehydration techniques for weight loss since it is a quick way to achieve a target weight, a strategy that impairs performance[1-4]. The assessment of body composition in weight-sensitive sports, such as judo, using bioelectrical impedance analysis (BIA) is still relatively unexplored, and information is scarce in this area[5].

BIA is a method based on a volumetric approach to estimate total-body water (TBW). Based on the assumption that fat-free mass (FFM) comprises 73.2% of water, the mass of this compartment can be calculated from TBW. Then, fat mass (FM) is obtained by subtracting FFM from the total-body mass. In athletes, the water fraction of FFM tends to have a high variability[6-10]. The algorithms used by BIA devices to predict TBW do not take into account the variability of water fraction in the FFM compartment and also the variability of the remaining protein and mineral fractions. Different BIA manufactures and devices also use several different algorithms to estimate TBW and its associated calculation of FFM. Among several types of BIA equipment, foot-to-foot equipment has been used to assess body composition in highly active adults[11-13]. In a large sample of adults, including participants involved in regular sport practice[14], the foot-to-foot BIA equipment (TBF-310) presented higher reproducibility in fat mass determination[11]. Another study involving lean and obese adults used the foot-to-foot BIA equipment (TBF-300A) and concluded that it was an accurate solution for lean but not obese adults when compared to bioimpedance spectroscopy[12]. Swartz et al[13] used a sample of highly active adults and found that the 'adult' mode of a foot-to-foot BIA equipment (TBF-305) accurately estimated group % body fat of individuals engaging in >2.5 h aerobic activity/week, using hydrostatic weighing as the reference. Considering the studies above, using foot-to-foot BIA equipment in highly active adults did not use reference methods for determining the accuracy of body composition measures, specifically by using the reference method at the molecular level, i.e., the four-compartment model (4C model).

At the molecular level, multicompartment models, such as the four-compartment model (4C) take into consideration the variability of the main FFM components (water, protein, and minerals) and are considered the state of the art regarding FM and FFM assessment because they provide more accurate estimates of body composition than the other methods[15].

The performance of the Tanita model TBF-310, a foot-to-foot device for body composition assessment of athletes, is still unknown. The aim of this study was to test the validity of BIA (Tanita, TBF-310) in the determination of FFM and FM in judo athletes using a 4C molecular method as a reference. We hypothesize that the Tanita TBF-310 it is a valid alternative in body composition estimation of judo athletes when compared to a 4C model.

METHODS

Participants

Twenty-nine male judo athletes from the Portuguese national team were evaluated during a period of weight stability. The inclusion criteria were as follows: 1) age of 18 years or over; 2) at least 5 years of training experience; 3) currently training at least 15 h per week; 4) a minimum technical level of 1rst degree black belt; 5) tested negative for doping; and 6) not taking any medications or dietary supplements.

Medical screening indicated no health limitations for study participation. All athletes were informed about the possible risks of the investigation before providing written informed consent to participate.

All procedures were approved by the Ethics Committee of the Faculty of Human Kinetics, University of Lisbon and conducted in accordance with the Declaration of Helsinki[16].

Experimental design

Participants were national top-level judo athletes. Data collection was performed between September and October. The period of weight stability was considered the baseline phase with judo athletes performing their regular regimens of judo training, which typically consists of 2 h in the morning and 2 h in the evening. Two of the morning sessions were used for improving cardiorespiratory fitness and strength, while the other sessions consisted of judo-specific skills, drills, and randori (fighting practice) with varying intensity below and up to 90–95% of maximum oxygen uptake (VO_{2max}), representing a target heart rate below and up to 185–190 beats/min.

Body composition measurements

Participants attended the laboratory after a 12-h fast and refrained from exercise, alcohol, or stimulant beverages for at least 15 h. All measurements were carried out on the same morning. In brief, the procedures were as follows:

Anthropometry

Participants were weighed to the nearest 0.01 kg wearing a bathing suit without shoes on an electronic scale connected to the plethysmograph computer (BOD POD, COSMED, Rome, Italy). Height was measured to the nearest 0.1 cm with a stadiometer (Seca, Hamburg, Germany), according to the standardized procedures described elsewhere[17].

Hydration status

To ensure all athletes were in a neutral hydration state during the period of weight stability, we checked if voided urine was pale yellow. We confirmed with the athletes that their first daily post-voiding body weight on the 3 days before the first visit did not change by more than 1%[18].

Bioelectrical impedance analysis.

Body composition was assessed using the Tanita Body Composition Analyser - model TBF-310 foot-to-foot (Tanita Corp., Tokyo, Japan) which provided a print-out of measured impedance and calculated FM and FFM. FFM hydration is assumed as a constant value of 73.2%. The subjects were barefoot and wearing bathing suits for the evaluation. Based on the test-retest of 10 subjects, the coefficients of variation for both fat-free mass and fat mass were nearly 2%.

Four-compartment model

A four-compartment (4C) model was used as the reference method with total-body soft tissue mineral (Ms) component estimated at 0.0129TBW[19]. The 4C model is described as follows:

$$FM\ (kg) = 2.748BV - 0.699TBW + 1.129Mo - 2.051BM \quad (1)$$

Where FM is fat mass, BV is body volume (L) assessed by air displacement plethysmograph, TBW is total body water (kg) evaluated by the deuterium dilution technique, Mo is bone mineral (kg) obtained by DXA, Ms is total body soft tissue mineral content (kg), and BW is body weight (kg).

Total body mineral (M) was calculated as:

$$M = Mo + Ms \quad (3)$$

Fat-free mass was calculated as body weight minus fat mass.

Calculation of fat-free mass density

FFM density (DFFM) was estimated from TBW, Mo, Ms, and protein (protein is equal to body weight minus fat mass, TBW, Mo, and Ms), contents of FFM (estimated as body weight minus FM from the 4C model) and their densities (0.9937, 2.982, 3.317, and 1.34 gcc) for TBW, Mo, Ms, and protein, respectively:

$$DFFM = 1/[(TBW/DTBW) + (Mo/DMo) + (Ms/DMs) + (protein/Dprotein)] \quad (4)$$

Bone mineral

Dual-energy X-ray absorptiometry (Scan Hologic Explorer-W, fan-beam densitometer, software QDR for Windows version 12.4; Hologic, Waltham, Massachusetts, USA) was used to measure bone mineral content (BMC). The scan positioning, acquisition, and analysis were standardized. Since bone mineral content represents ashed bone, BMC was converted to total body bone mineral (Mo) by multiplying it by 1.0436[20]. The coefficient of variation (CV), based on the test-retest of 10 participants, was 1.6%[21].

Body volume

Body volume was assessed by air displacement plethysmography (COSMED, Rome, Italy) as described elsewhere[22]. Body volume was computed based on the initial body volume corrected for thoracic gas volume and a surface area artifact computed automatically. The CV, based on the test-retest of 10 participants, was 0.5%[23].

Total-body water

Total-body water (TBW) was assessed by the deuterium dilution technique using a stable Hydra gas isotope ratio mass spectrometer (PDZ, Europa Scientific, UK). After a 12-h fast, an initial urine sample was collected and a deuterium oxide solution dose (^2H_2O) of 99.9 atom % D (Sigma-Aldrich Chemistry) at 0.1 g/kg of body weight, diluted in 50 mL of tap water was immediately administered. After a 4-h equilibration period, a new urine sample was collected. Abundances of ^2H_2O in dilutions of the isotope doses were analyzed. Urine

and diluted dose samples were prepared for analysis using the equilibration technique of Scrimgeour and colleagues[24]. The enrichments of equilibrated local water standards were calibrated against the standard mean ocean water (SMOW). Based on delta SMOW, total body water was estimated including a 4% correction due to the recognized amount corresponding to deuterium dilution in other compartments[25]. The CV, based on the test-retest of 10 participants, was 1.3%[26].

Propagation of measurement error

In the present study, we selected air-displacement plethysmography to assess BV, DXA to estimate bone mineral, and BIA to estimate TBW. The propagation of measurement errors associated with the determination of BV, TBW, and bone mineral (Mo) can be calculated by assuming that the squared technical errors of measurement (TEM^2) are independent and additive. Accordingly:

$$TEM = (TEM^2 \text{ for effect of body volume determination on \% } FM + TEM^2 \text{ for TBW on \% } FM + TEM^2 \text{ for MO on \% } FM)\ 1^{0.5}$$

So, using the equation above:

$$TEM = [0.81^2 + 0.36^2 + 0.04^2]1^{0.5} = 0.89 \text{ \% } FM$$

The precision of the 4C model to determine FM was ~1%.

Statistical analysis

Data were analyzed with SPSS software for Windows version 22.0 (SPSS Inc., Chicago, IL). The comparison of group means was performed using paired-sample t-test and Wilcoxon test when normality was not verified. Comparison of group means with the reference population was made using one-sample t-test. Simple linear regression analysis was performed to calculate the relationship between fat-free mass estimated by the reference 4C model and from BIA. The concordance correlation coefficient analysis was performed according to Lin[27] using the software MedCalc (Software MedCalc, Mariakerke, Belgium (2009)). The agreement between methods was assessed by the Bland-Altman method[28], including the 95% limits of agreement. The correlation between the mean of the reference and the alternative method with the difference between both was used as an indication of proportional bias. Also, correlations between the differences between the methods and potential variables that could affect these differences were determined. For all tests, statistical significance was set at $p<0.05$.

RESULTS

The variables representing demographic characteristics and body composition of participants are presented in Table 1.

TABLE 1. CHARACTERISTICS AND BODY COMPOSITION VARIABLES (N=29)

	Total (n = 29)	Range
	Mean ± SD	
Age (years)	23.1 ± 3.4	18 - 31
Weight (kg)	73.5 ± 8.4	56.5 - 100.1
Height (cm)	175.4 ± 5.7	165 - 188.7
BMI (kg/m²)	24.0 ± 2.6	20.2 - 31.2
FM_{4C} (kg)	7.0 ± 3.1	2.9 - 16.7
FM_{4C} (%)	9.5 ± 3.7	3.7 ± 20.6
FFM_{4C} (kg)	66.5 ± 7.8	51.2 - 89.7
FM_{Tanita} (kg) [a]	7.2 ± 3.6	2.8 - 17.4
FM_{Tanita} (%) [a]	9.5 ± 3.8	4.1 - 20.4
FFM_{Tanita} (kg)	65.7 ± 5.93	52.8 - 82.8
Water fraction (%)	71.6 ± 2.1	68 - 77
Bone mineral fraction (%)	4.9 ± 0.3	4 - 5
Soft mineral fraction (%)	0.9 ± 0.03	1 - 1
Residual fraction (%)	22.6 ± 2.4	18 - 27
FFM_D (g/cm³)	1.101 ± 0.007	1.085 - 1.112

Abbreviations: SD, standard deviations; BMI, body mass index; FM, Fat mass; FFM, Fat-free mass; 4C, four-compartment model; FFM_D, Fat-free mass density.

[a] Significantly different from the reference method, $p<0.05$

Tanita overestimated FM by 0.2±3.5kg from the 4C model ($p=0.012$) while for the FFM no differences were found between methods (0.7±4.17kg) (Table 1).

Table 2 shows the results related to the Tanita performance in the evaluation of FM and FFM by regression analysis and the concordance correlation coefficient.

TABLE 2. CRITERIA PERFORMANCE OF TANITA TBF-310 IN THE ESTIMATION OF FM AND FFM FROM THE REFERENCE METHOD

	R	SEE	Slope	Intercept	CCC	Precision	Accuracy
	(kg)					(p)	(Cb)
FM (kg)	0.46	2.75	0.39 [a]	4.24 [b]	0.45	0.46	0.98
FFM (kg)	0.85	4.20	1.11 [a]	-6.41	0.81	0.85	0.96

Abbreviations: R, coefficient of correlation; SEE, standard error of estimation; CCC, concordance correlation coefficient; FM, Fat mass; FFM, Fat-free mass.

[a] Slope significantly different from 1, $p<0.05$

[b] Intercept significantly different from 0, $p<0.05$

The alternative method explained 21% and 72% of the absolute values observed in FM and FFM, respectively, from the reference method.

For both FM and FFM, the slops and the intercepts, differed from 1 and 0, respectively.

Figure 1 displays the agreement between methods using the Bland-Altman technique. For FM and FFM, relatively large limits of agreement (95% confidence intervals) were observed with an under-estimation of -6.7 kg and -8.8 kg or an over-estimation of 7.0 kg and 7.5 kg, respectively for FM and FFM.

DISCUSSION

We evaluated the validity of Tanita TBF-310 for body composition estimation in elite judo athletes, using a 4C model as the reference method. Our findings indicate that this BIA device is not accurate for assessing body composition in highly trained athletes.

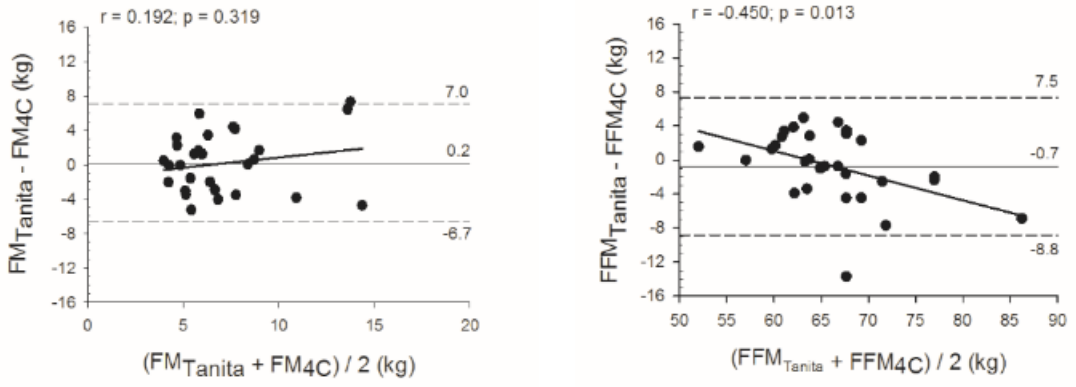
The present foot-to-foot BIA equipment, a simple and low-cost solution for body composition estimation in the field settings, has been used to assess fat and fat-free mass of highly active populations[11-13] with acceptable accuracy, though not extended by our findings.

So far, no studies analyzed the Tanita model (TBF-310) for determining body composition in athletes using the 4C model as criterion. Nevertheless, this foot-to-foot device was validated in other populations[29-31]. In a cross-sectional study using DXA as the reference method, Beeson et al. found that Tanita TBF-310 explained 86% and 93% of FM (%) and FFM (kg), respectively, in Hispanic diabetic participants but with large individual variability[29]. Using a cross-sectional design, Radley et al. reported that Tanita TBF-319 explained 94% and 83% of FM and FFM, respectively, in overweight and obese children with individual differences up to 11.0% for FM and 9.3 kg for FFM compared to DXA[30]. In a longitudinal study with a sample of overweight and obese women, the Tanita TBF-310 explained 77% and 14% of the variability in FM and FFM changes from a 4C model, along with wide limits of agreement[31].

Compared to the aforementioned studies, Tanita TBF-310 showed poor validity, explaining 21% and 72% for FM and FFM, respectively, with a lack of agreement between methods and inaccuracies in estimating body composition at an individual level. It is important to underline that a 4C model was used as the criterion to validate the foot-to-foot BIA device. This state-of-the-art method does not rely on assumptions in FM determination as it accounts for the variability of the FFM components, namely TBW, protein, and mineral.

Conversely, in 2C models using densitometric techniques, the FFM density is assumed to be constant at 1.1 g/cm^3 by considering that a stable contribution of the main FFM components is observed[32]. We observed that TBW, protein, and mineral fractions of the FFM were similar to those observed on cadaver analysis[33]. Brozek et al[32] referred 5.6% of Mo is FFM, and 1.2% of Ms is FFM[32]. We obtained values of 4.8% and 0.92%, respectively, for Mo and Ms FFM fractions. For protein, the assumed contribution is 19.4%, but a higher percentage was found in this study 22.6%. In the majority of mammals, TBW/FFM is constant at 73.2% ± 0.036[33], but in our study we found that athletes

FIGURE 1. BLAND–ALTMAN ANALYSIS OF THE DIFFERENCES BETWEEN TANITA TBF-310 AND THE 4C MODEL FOR FM AND FFM ESTIMATION. THE SOLID MIDDLE LINE REPRESENTS THE MEAN DIFFERENCES BETWEEN ABSOLUTE FAT MASS (FM) AND FAT-FREE MASS (FFM) FROM TANITA TBF-310 AND THE FOUR-COMPONENT MODEL (4-C); THE UPPER AND LOWER DASHED LINES REPRESENT ± 2 SD FROM THE MEAN, I.E. 95 % LIMITS OF AGREEMENT (± 1·96 SD).



showed a mean value of 71.5% ± 2.1%. Therefore, using hydrometric techniques to estimate FFM based on the assumed value of 73.2%, an overestimation of FM and an underestimation of FFM would be expected. These results indicate that the assumption of a stable FFM composition and density is not appropriate in highly trained judo athletes. In fact, densitometric and hydrometric techniques may compromise body composition estimation in this population.

The use of the 4C model is a major strength of this study, as this method is considered the "state of the art" to determine the FM and FFM at the molecular level. The 4C model accounts for the variability of the FFM molecular components thus avoiding assumptions that may not be valid for highly trained athletes.

A few limitations of this study should be highlighted, namely its external validity as results are not generalized for females, non-athletic population, and other devices/models. This study did not assess the validity of this equipment in determining longitudinal changes in body composition. It is also important to mention that the validity of the equipment was tested during a period of weight stability in judo athletes and therefore it is unknown if a similar accuracy would be found if these athletes were assessed prior competition when a target body weight would be required.

Many laboratories and clinical centers still use the Tanita TBF-310 equipment. The point of this validation was to demonstrate the usefulness of this equipment for estimating body composition in athletes whose weight management is determinant. Based on the findings, this equipment provided inaccurate estimations of fat and fat-free mass and must not be used for assessing body composition in elite judo athletes.

CONCLUSION

Considering all the performance criteria, our findings revealed that Tanita TBF-310 is not a valid alternative in body composition estimation of judo athletes when compared to a 4C model. The larger individual variability observed limits its accuracy at an individual level. Thus, Tanita TBF-310 should not be used in judo athletes to assess and monitor body composition over the season as the errors observed when using this device may compromise athletic health and performance.

Acknowledgments

We would like to express our gratitude to the athletes for their time and effort. This work was supported by the Portuguese Foundation for Science and Technology (grant: PTDC/DES/69495/2006).

Conflict of interest

None of the authors had a conflict of interest in any company or organization sponsoring this study.

Authors Contributions

CD: responsible for data pooling, screening, analysis, and manuscript writing; CM: responsible for data analysis and data collection; CE: responsible for manuscript revision and advice; LS: responsible for manuscript revision and advice and AMS: responsible for manuscript writing and provided administrative support, supervision, and advice.

RESUMO

A avaliação da composição corporal ao nível molecular é relevante para a população esportiva e sua associação com o alto rendimento é bem reconhecida. O modelo molecular a quatro compartimentos (4C) é o método de referência para as estimativas de massa gorda (MG) e massa livre de gordura (MLG). No entanto, sua implementação no contexto real não é viável. Técnicos e atletas precisam de métodos práticos de composição corporal para a avaliação da composição corporal e o método de análise de impedância bioelétrica (BIA) é geralmente visto como uma alternativa útil. O objetivo deste estudo foi testar a validade da BIA (Tanita, TBF-310) na determinação de MG e MLG em atletas de elite de judô. Um total de 29 atletas masculinos foi avaliado em um período de estabilidade de peso usando o método de referência (4C) e o método alternativo (Tanita, TBF-310). Em relação ao método a 4C, a água corporal total foi avaliada pela diluição de deutério, mineral ósseo por DXA e volume corporal por pletismografia por deslocamento de ar. Os declives e interceções diferiram de 1 (0,39 e 1,11) e 0 (4,24 e −6,41) para MG e MLG, respectivamente. A MG da Tanita TBF-310 superestimou o método 4C em 0,2 kg, embora não tenham sido encontradas diferenças para MLG. A Tanita TBF-310 explicou 21% e 72%, respectivamente, na estimativa dos valores absolutos de MG e MLG do método a 4C. Os limites de concordância foram grandes, variando de −6,7 kg a 7,0 kg para MG e de −8,9 kg a 7,5 kg para MLG. Em conclusão, a TBF-310 Tanita não é um método alternativo válido para estimar a composição corporal em judocas altamente treinados.

PALAVRAS-CHAVE: *Análise por impedância bioelétrica. Tanita TBF-310. Modelo a quatro compartimentos. Massa gorda. Massa livre de gordura. Métodos de avaliação de composição corporal.*

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ORIGINAL ARTICLE

Edition of Portuguese health journals and its relationship with their visibility: a quantitative analysis

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http://dx.doi.org/10.1590/1806-9282.65.10.1290

SUMMARY

BACKGROUND: *Scientific journals play a fundamental role in the field of health sciences, contributing not only to the dissemination of scientific results but also to the progress of medicine and the training of researchers. The visibility of scientific production in the health area is fundamental to the development of medicine. This study aimed to find the relationship between the editorial quality of a sample of Portuguese scientific health journals and their national and international visibility.*

METHODS: *This is an analytical, transversal and, essentially, quantitative study, based on the analysis of the compliance with Latindex editorial quality criteria in a sample of 46 scientific health journals and ascertaining their national and international visibility.*

RESULTS: *The research showed that the global average of compliance with the criteria by the sample of journals is 91%. The average visibility of the sample is 24%. The hypothesis that the editing criteria are related to the visibility of a sample of Portuguese health journals is confirmed.*

CONCLUSION: *Despite the high rate of compliance with editorial quality criteria, the international visibility of the journals analyzed is still scarce. This reveals the need for the development of complementary competences.*

KEYWORDS: *Periodicals as topic. Scientific and Technical Publications. Health. Portugal. Edition.*

INTRODUCTION

Health scientific journals are fundamental to disseminate results of scientific research. The poor dissemination of research published in scientific journals leads to lack of recognition of the work of the authors who publish and, consequently, the invisibility of scientific research.

The quality of scientific journals is often associated with the databases on which they are indexed.[1] When publishing results of scientific research, It is essential to choose a quality scientific journal, indexed in prestigious databases, which will proceed to conduct peer reviews and ensure the visibility of the work. Publication in what is known as "predatory journals" can have very negative effects on the career of researchers. These journals do not include a rigorous process of peer review and are not governed by standards of international quality. They are often open-access journals that charge the authors processing fees, alluring them with the publication of papers for profit.[2]

DATE OF SUBMISSION: 07-Mar-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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The visibility of scientific production relates to the ability of the publication to be accessed and recognized by the scientific community to which it is intended. The visibility of scientific journals can be assessed by two indicators: direct and indirect dissemination. Direct dissemination relates to the circulation of the publication, including the number of subscribers and its presence in libraries catalogs. Indirect dissemination is the presence of the journal in secondary sources, such as directories of journals, databases, and the internet.[3]

The inclusion in databases is essential to ensure the projection and visibility of scientific journals, as well as of the content they bring and researchers who publish it. Taking into account the importance of the presence of scientific journals in databases, our analysis focused on indirect diffusion, particularly in the presence of the target journals in national and international recognized and prestigious databases.

The responsibility of developing procedures to ensure that health journals are indexed in prestigious databases and satisfy editorial quality criteria is of publishing groups, who are responsible for editing such journals. Editors, particularly the editor-in-chief, play an essential role in the guidelines established for the quality and visibility of journals, as well as in inciting methodological and empirical innovation.[4]

Based on the perception of the importance of visibility of the scientific knowledge produced in the area of health, we sought to investigate the situation of 46 Portuguese scientific journals in the area of health. The main objective of the research is to verify the relationship between the editorial quality of the population of Portuguese health scientific journals and the national and international visibility of these journals.

METHODS

The study can be classified as analytical and cross-sectional, essentially quantitative, based on the analysis of compliance with the Latindex criteria for editorial quality of a population of Portuguese health magazines and the verification of national and international visibility of these journals.

This study took place between 2012 and 2018. The selection of Portuguese scientific journals, with active state, from the health area, was performed on the Ulrich's International Periodicals Directory database, in November 2013.

The study population comprises 46 Portuguese scientific journals in the area of health that are active on the Ulrich's International Periodicals Directory. Between February 2014 and November 2015, we proceeded to research data related to the exhaustive check of compliance with the Latindex criteria for editorial quality of all issues of the years 2012 and 2013 of the journals selected in our study. The visibility of those journals was examined in the same period. By checking their indexing in the Index of Portuguese Medical Journals and SciELO Portugal, we investigated their national visibility. The international visibility was measured by checking their indexing in the Journal Citation Reports, the Medicus/MEDLINE Index, the Latindex System, and the SCImago Journal and Country Rank.

The results obtained from the data search were subsequently analyzed quantitatively. The statistical analysis of the data was done in Microsoft Excel, version 14.0 (32-bit) of Microsoft Office Professional Plus 2010.

RESULTS

The journals analyzed are mostly of quarterly periodicity; they are predominantly of the areas of Clinical Psychology, Nursing, Internal and General Medicine, Psychiatry, Cardiology and Cardiovascular Systems; the main publication language is Portuguese; the place of publication is mainly the district of Lisbon; the entities responsible are mostly scientific/professional societies; the creation dates are mainly between the years of 1994 and 2011; most journals have an electronic edition with free access to full texts and online presence.

The results of the investigation regarding compliance with the Latindex criteria for editorial quality is presented in Table 1.

TABLE 1. AVERAGE OF COMPLIANCE PER TYPE OF LATINDEX CHARACTERISTICS PER POPULATION OF JOURNALS ANALYZED

Compliance with Latindex characteristics by the journal population	
Type of characteristics	% of compliance
Basic characteristics	99.7%
Presentation characteristics	85.0%
Editorial management and policy characteristics	90.6%
Content characteristics	86.6%
Average	91.0%

The analysis of the circulation of the journals on the Index of Portuguese Medical Journals and SciELO Portugal databases allowed us to conclude that the average circulation is higher in the Index of the Portuguese Medical Journals, 46%, in comparison with SciELO Portugal, with an average circulation of 26%. The circulation of the journals on international databases was measured by checking their indexing on the Journal Citation Reports, the Medicus/MEDLINE Index, the Latindex System, and the SCImago Journal and Country Rank databases. The average circulation of the journal population is higher in the Latindex System, reaching 43%. Immediately next is the SCImago Journal and Country Rank, in which the journals circulate, on average, 15%. The two international databases with the lowest circulation were the Journal Citation Reports and the Index Medicus/MEDLINE, both with an average circulation of only 7%.

In Table 2, we can see the average compliance with the Latindex criteria for editorial quality of all journals studied, as well as the visibility of each. The findings allow us to affirm that the degree of visibility of the population of Portuguese health journals, in national databases, is superior to that in international databases.

Based on the scatter plot of Figure 1, we see that the value of the linear correlation of Pearson's r coefficient between the variable of editing criteria and the variable of visibility is r=0.39. For Pestana and Gageiro[5], r values between 0.2 and 0.39 indicate a weak positive linear association. According to these figures, we find there is a weak positive correlation between the variable of editing criteria and the variable of visibility.

FIGURE 1. SCATTER PLOT OF THE AVERAGE COMPLIANCE WITH THE EDITING CRITERIA AND AVERAGE VISIBILITY OF THE POPULATION OF JOURNALS

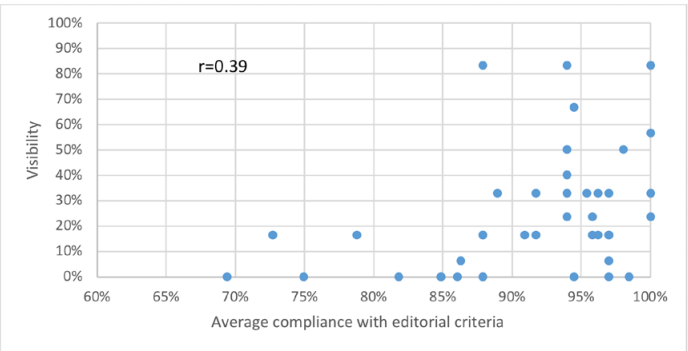

TABLE 2. AVERAGE COMPLIANCE WITH THE EDITING CRITERIA AND AVERAGE VISIBILITY OF THE POPULATION OF JOURNALS

Journals	Average compliance with editorial criteria	Visibility
Acta Médica Portuguesa	100%	83%
Acta Obstétrica e Ginecológica Portuguesa	79%	17%
Acta Pediátrica Portuguesa	100%	23%
Acta Reumatológica Portuguesa	88%	83%
Acta Urológica Portuguesa	97%	17%
Análise Psicológica	94%	50%
Angiologia e Cirurgia Vascular	94%	50%
Archives of Exercise in Health and Disease	86%	0%
Arquivos de Medicina	94%	67%
Cadernos de Saúde	88%	0%
Experimental Pathology and Health Sciences	69%	0%
Factores de Risco	73%	17%
GE - Jornal Português de Gastrenterologia	94%	40%
Jada	88%	0%
JETVCE	85%	0%
Laboratório de Psicologia	96%	17%
Medicina Interna	94%	23%
Nascer e Crescer	98%	50%
Nursing	97%	7%
Oftalmologia	88%	17%
Pensar Enfermagem	92%	17%
Psicologia, Educação e Cultura	97%	17%
Psicologia	95%	33%
Psicologia, Saúde & Doenças	89%	33%
Psi Logos	92%	33%
Psique	98%	0%
Psychologica	91%	17%
Revista de Enfermagem Referência	97%	33%
Revista de Psicol. da Criança e do Adolescente	97%	0%
Revista E-Psi	96%	17%
Revista Investigação em Enfermagem	97%	17%
Revista Motricidade	100%	57%
Revista Portuguesa de Cardiologia	94%	83%
Revista Portuguesa de Diabetes	88%	17%
Revista Portuguesa de Endocrinol. Diabetes e Metab.	96%	23%
Revista Port. de Enfermagem de Saúde Mental	100%	33%
Revista Portuguesa de Farmacoterapia	88%	17%
Revista Portuguesa de Grupanálise	75%	0%
Revista Port. de Hipertensão e Risco Cardiovascular	73%	17%
Revista Portuguesa de Ortopedia e Traumatologia	96%	33%
Revista Sinais Vitais	86%	7%
Salutis Scientia	94%	0%
Sinapse	94%	33%
The Lancet Infectious Diseases	85%	0%
The Lancet Neurology	82%	0%
The Lancet Oncology	85%	0%
Total / %	91%	24%

DISCUSSION

This is the first study to date, in Portugal, which relates the compliance with editorial criteria for quality with the national and international visibility of journals in the area of health.

A study conducted in Spain by Vázquez-Valero et al.[6] that analyzed 275 Spanish journals of health sciences in relation to the Latindex criteria of editorial quality shows a compliance rate of 78.5%.

The research developed by Abejón-Peña and Rodríguez-Yunta[7] evaluated the results and benefits for Spanish journals of Spain participation on Latindex. The criterion relating to the indication of the dates of receipt and acceptance of the originals is identified as one of the least met by Spanish scientific journals. The same criterion is also one of the least met by the Portuguese journals analyzed: only 41% of printed journals and 56% of electronic ones met the criterion concerning the indication of dates of receipt and acceptance of the originals.

Another study conducted in Mexico by Alonso-Gamboa et al.[8] on the contribution of Latindex to the characteristics and editorial quality of Mexican journals showed that the criterion relating to the indication of the dates of receipt and acceptance of the originals is among the less often met characteristics.

The investigation by Ponce-Aura[9] on the circulation of Spanish biomedical journals on national and international databases concluded that Spanish medical journals have considerable circulation on national and international databases.

The results obtained in the study by Colombo[10] on the visibility of 59 Argentinean journals of medicine on international databases found that 45 journals are indexed in multidisciplinary, international databases, but only three are indexed in the Web of Science, and five on Medline.

We found that the results of the research are similar to the data from similar studies from other countries that are part of the reference literature. Despite the high compliance with the Latindex criteria for editorial quality, the journals demonstrated reduced indexation in international databases, which reduces the international visibility of their articles.

CONCLUSION

The study demonstrated that the hypothesis that the editing criteria relate to the visibility of a population of Portuguese scientific health journals is confirmed.

Among the printed journals, the criteria most often not met are: the criterion relating to the indication of the dates of receipt and acceptance of the originals, met by only 41% of the journals; and the criterion regarding the indication of the institutional affiliation of the members of the editorial board, met by 48% of the publications. Both criteria are related to the presentation characteristics in the Latindex System.

The criteria less often met by electronic journals are: the criterion which requires an editorial opening, only 46% of these journals follow this guidance; the criterion relating to the indication of the dates of receipt and acceptance of the originals, met by 56% of electronic publications; the characteristic of provision of value-added services, met by only 62% of the publications; and the presence of search engines, met by only 69% of these journals. These criteria are related to the characteristics of management and editorial policy, characteristics of presentation, and characteristics of content, respectively.

Three journals stood out for registering, simultaneously, an average of compliance with the Latindex criteria for editorial quality above 75% and average visibility greater than 75%: The Acta Médica Portuguesa: the scientific journal of the Order of Physicians; and the Revista Portuguesa de Cardiologia: official publication of the Portuguese Society of Cardiology; and the Acta Reumatológica Portuguesa.

Despite the high compliance with the criteria for editorial quality, the international visibility of the journals analyzed is still scarce, which leads us to consider the need for developing complementary skills that connect several factors, such as the professionalization of editorial management, the attractiveness of the journal, and the development of criteria for scientific quality.

RESUMO

OBJETIVO: *No âmbito das ciências da saúde, as revistas científicas desempenham um papel fulcral, contribuindo — para além da divulgação dos resultados científicos — para o progresso da medicina e para a formação dos investigadores. A visibilidade da produção científica é fundamental para o desenvolvimento da medicina. O objetivo deste estudo foi averiguar a relação entre a qualidade editorial de uma população de revistas portuguesas científicas de saúde e a visibilidade nacional e internacional destas.*

MÉTODOS: *Estudo transversal analítico e essencialmente quantitativo, baseou-se na análise do cumprimento de critérios de qualidade editorial Latindex de uma população de 46 revistas científicas de saúde portuguesas e na verificação da respectiva visibilidade nacional e internacional.*

RESULTADOS: *A investigação revelou que a média global de cumprimento de critérios pela população de revistas situa-se nos 91%. A visibilidade média da população é de 24%. Confirma-se a hipótese de que os critérios de edição se relacionam com a visibilidade de uma população de revistas científicas de saúde portuguesas.*

CONCLUSÃO: *Apesar do elevado cumprimento de critérios de qualidade editorial, a visibilidade internacional das revistas analisadas é ainda escassa, o que aponta a necessidade de serem desenvolvidas competências complementares.*

PALAVRAS-CHAVE: *Publicações periódicas como assunto. Publicações científicas e técnicas. Saúde. Portugal.*

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ORIGINAL ARTICLE

HIF-1α Levels in patients receiving chemoradiotherapy for locally advanced non-small cell lung carcinoma

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http://dx.doi.org/10.1590/1806-9282.65.10.1295

SUMMARY

AIM: *To examine the relationship between treatment response and hypoxia-inducible factor-1 alpha (HIF-1α) levels in patients with locally advanced non-small cell lung cancer (NSCLC) who received chemoradiotherapy (CRT).*

METHODS: *Eighty patients with NSCLC were included in the study and treated at Acibadem Mehmet Ali Aydınlar University Medical Faculty. HIF-1 α levels were measured before and after CRT by the enzyme-linked immunosorbent assay (ELISA) method.*

RESULTS: *Patients' stages were as follows; stage IIIA (65%) and stage IIIB (35%). Squamous histology was 45%, adenocarcinoma was 44%, and others were 11%. Chemotherapy and radiotherapy were given concurrently to 80 patients. Forty-five (56%) patients received cisplatin-based chemotherapy, and 35 (44%) received carboplatin-based chemotherapy. Serum HIF-1α levels (42.90 ± 10.55 pg/mL) after CRT were significantly lower than the pretreatment levels (63.10 ± 10.22 pg/mL, p<0.001) in patients with locally advanced NSCLC.*

CONCLUSION: *The results of this study revealed that serum HIF-1α levels decreased after CRT. Decrease of HIF-1α levels after the initiation of CRT may be useful for predicting the efficacy of CRT.*

KEYWORDS: *Carcinoma, Non-Small-Cell Lung. Chemoradiotherapy. Hypoxia-Inducible Factor 1, alpha Subunit.*

INTRODUCTION

Lung cancer is the primary cause of cancer deaths worldwide in both men and women[1]. Non-small cell lung cancer (NSCLC) elucidates most lung cancers (approximately 85%)[2]. Treatment depends on the cell type (small cell versus non-small cell), the patient's overall medical condition, and the tumor stage in lung cancer. Stage III NSCLC comprises a diverse group of patients with dissimilarities in the extent and localization of disease[3]. For most patients with clinically evident N2 disease, the approach is concurrent chemoradiotherapy, using platinum-based chemotherapy plus full-dose radiotherapy (RT)[4].

Lung cancer is characterized by hypoxia and inflammation. Hypoxia-inducible factor-1 alpha (HIF-1α) takes part in the initiation, appraisal, and prognosis of lung cancer, and starts metastasis and angiogenesis by the transcription of multiple genes[5]. HIF-1α is related to the resistance to chemothera-

DATE OF SUBMISSION: 25-Feb-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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peutic agents[6]. HIF-1α plays a role in the formation of lung cancer according to cigarette smoking, and mechanisms that may be effective on this pathway at the cellular level in the prevention of oxidative damage are studied[7,8]. It is thought that an antimetastatic effect can be achieved by acting on this mechanism[9].

In recent years, some studies have suggested that HIF-1α may be prognostic in lung cancer and be associated with tumor aggression[10-12]. It is thought to be related to chemo-resistance in patients with lung cancer[13]. In the literature, it has been shown that hypoxia-persuaded glutamine metabolism is convoluted in drug resistance in lung cancer, and the hypoxia-induced expression of glutamate dehydrogenase (GDH) depends on the upregulation of HIF-1α[14]. This could be reversed by the death domain-associated protein (Daxx), which negatively regulates hypoxia-persuaded cell invasion by inhibiting the HIF-1α/Histone deacetylase 1 (HDAC1) /Slug pathway[15].

Studies have found that hypoxia is the most common feature in the progression of all solid tumors, and thus it has become a central issue in tumor physiology and cancer treatment. Therefore, we wanted to examine the relationship between treatment response and HIF-1α levels in patients with locally advanced lung cancer who received chemoradiotherapy (CRT).

METHODS

The serum samples of 80 NSCLC patients who were referred to the Acibadem Mehmet Ali Aydınlar University Medical Faculty, Department of Medical Oncology, and Pulmonary Diseases from May to November 2018 were obtained. All patients had histologically confirmed NSCLC diagnosis and had not received any treatment within the last six months. The staging was determined according to the American Joint Committee on Cancer (AJCC) and International Union against Cancer (UICC) staging systems. Stage IIIA and IIIB patients were included in the study; all had taken curative CRT. Patients with another malignancy, early and terminal stage disease, any hypoxic disease, such as diabetes and ischemic heart disease, any infection, and who had had surgery within the last six months were excluded.

Detailed clinical history, physical examination, and a series of biochemistry tests were done before the treatment phase. Those with the Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less and appropriate blood chemistry tests received chemotherapy concurrently with radiotherapy. Chemotherapy and radiotherapy were given concurrently to 84 patients, of whom 45 (56%) received cisplatin-based chemotherapy, and 35 (44%) received carboplatin-based chemotherapy. Concurrent CT regimens were cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 with etoposide 50 mg/m^2 on days 1–5 and 29–33; paclitaxel 50 mg/m^2 weekly with carboplatin dose of area under the curve (AUC) 2 and, for non-squamous tumors, only cisplatin 75 mg/m^2 on day 1 with pemetrexed 500 mg/m^2 on day 1, every 21 days for three cycles. All patients (n = 80) received a total radiation dose of at least 60 Gy (range 50–66 Gy) in 2.0 Gy daily fractions.

Blood samples were obtained from patients in the morning after 12 hours of fasting before the initiation of CRT and after one week of treatment completion. Medical histories of the patients were also recorded on the initiation of therapy. Serum samples were stored at −80°C until final analyses were carried out.

Measurement of serum hypoxia-inducible factor-1 (HIF) levels

and Serum HIF-1a levels were measured using the sandwich-enzyme-linked immunosorbent assay method with the Human ELISA kit (Elabscience, Catalog Number: E-EL-H1277, Wuhan, Hubei Province, China). A preliminary experiment was conducted to verify the validity of plasma samples. The coefficients of intra- and inter-assay variation were 4.8 % (n=15) and 6.1 % (n=15), respectively.

Statistical analysis

Statistical analysis was carried out using SPPS 21.0 software (SPSS Inc., Chicago, IL., USA). Continuous variables were categorized using median values as the cut-off point. For group comparison of categorical variables, One-way ANOVA or Chi-square tests were used, and Mann–Whitney U test or Kruskall–Wallis tests were used for the comparison of continuous variables. All statistical tests were carried out two-sided, and a p-value ≤0.05 was considered statistically significant.

RESULTS

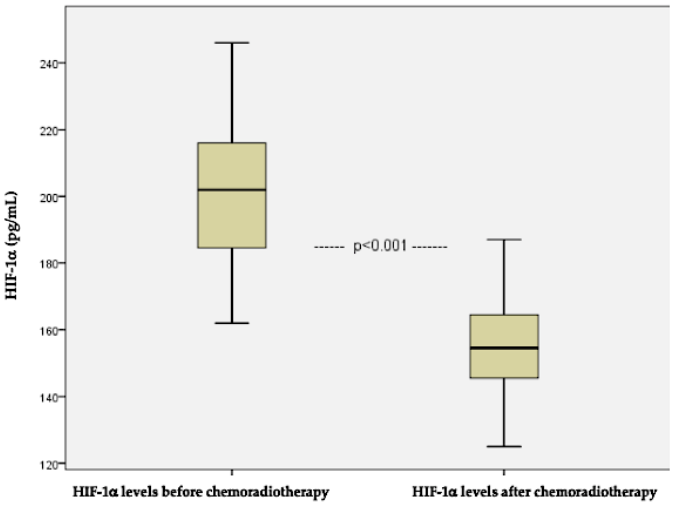
The general data of the 80 NSCLC patients are shown in Table 1. The median age of the patients was 63 (45–79) years. Most of the patients were male

TABLE 1. GENERAL CHARACTERISTICS AND TREATMENT MODALITIES OF NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS.

Characteristic	No. of cases (%)	Plasma HIF-1α level (pg/mL) (Mean ± SD)	*p*
Gender			
Female	18 (23)	62.56 ± 11.30	>0.05
Male	62 (77)	63.42 ± 9.76	
PS			
0	45 (56)	66.27 ± 9.69	>0.05
1	31 (39)	63.09 ± 10.38	
2	4 (5)	61.75 ± 0.83	
cStage			
IIIA	52 (65)	63.00 ± 9.72	>0.05
IIIB	28 (35)	63.38 ± 10.40	
Histopathology			
Adenocarcinoma	35 (44)	61.25±9,12	>0.05
SqCC	36 (45)	67.83±4.81	
Other	9 (11)	63.00±11.21	

NSCLC = Non-small cell lung cancer; PS = performance status; ECOG-PS = Eastern Cooperative Oncology Group PS; SqCC = squamous cell carcinoma; cStage = clinical stage; HIF-1α = hypoxia-inducible factor-1 alpha.

FIGURE 1. CHANGES OF SERUM HYPOXIA-INDUCIBLE FACTOR-1 ALPHA (HIF-1A) LEVELS BEFORE AND AFTER CHEMORADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC).



(77%). Patients' stages were as follows: stage IIIA (35%) and stage IIIB (65%). Squamous histology was 45%, adenocarcinoma was 44%, and others were 11%.

The changes in serum HIF-1α levels before and after CRT in patients with locally advanced NSCLC are shown in Fig. 1. Serum HIF-1α levels (42.90 ± 10.55 pg/mL) after CRT were significantly lower than the pretreatment levels (63.10 ± 10.22 pg/mL, $p < 0.001$) in patients with locally advanced NSCLC.

DISCUSSION

Lung cancer is a highly lethal cancer worldwide. Although different treatments are available, the survival of patients is still poor. Oxygen supply is necessary for the growth of cells and is often diminished, especially inside the tumor mass in solid tumors. Tumor hypoxia contributes to radiotherapy- and chemotherapy-resistance of cancer cells, thus predicting an aggressive behavior by promoting neoangiogenesis[16]. The current study showed that serum HIF-1α levels in patients with locally advanced NSCLC decreased significantly after CRT.

HIF-1 and HIF-2 coordinate the cellular response to hypoxia and are essential nuclear transcription factors for solid tumor growth and survival. When there is hypoxia, HIF-1α heterodimerizes with the HIF-1β subunit within the tumor nucleus and binds to the hypoxia-response element (HRE). This way, HIF-1 stimulates several genes, such as erythropoietin or vascular endothelial growth factors (VEGFs), that are involved in angiogenesis, migration, and survival[17,18]. These genes are found to be explicated in tumor cells and are also involved in tumor progression[19]. Tumor and endothelial cell-specific HIF1α are found to have conflicting roles in thrombosis of cancer patients[20]. Furthermore, during lung injury due to sodium nitrite, antioxidants reverse this injury by downregulating HIF-1α[21].

In cervical and oropharyngeal carcinoma patients who are treated with radiotherapy, HIF-1a overexpression has been associated with poor outcome[22,23]. Hypoxia-induced resistance is multiplex. HIF-1 plays an important role in the conversion of cells into the hypoxic conditions, which precisely brings about the chemo-resistance of tumors[24-33]. Patients with shorter survival in early staged cancers are associated with overexpression of HIF-1α[34]. Cisplatin and doxorubicin are the drugs for which hypoxia-induced drug resistance has been reported for lung cancer[26]. Furthermore, it has been shown that multidrug resistance in colon cancer can be reversed by HIF-1 inhibition[35], and when compared with wild-types, HIF-1α knockout cells are more sensitive to cytostatic and irradiation[36].

Cancer stem cells (CSC) are thought as drivers of tumor growth and are responsible for unresponsiveness to therapy, recurrence, and metastasis. In hypoxia, CSCs are shown to be regulated by HIF-1α and HIF-2α for survival and protection of tumor growth[37]. The expression of a CSC marker which is called CD133, in both small cell lung cancer (SCLC)

and NSCLC cells, was correlated with the hypoxia-induced up-regulation of HIF-1α[38]. Moreover, Hu et al.[39] have tested F-fluoroerythronitroimidazole PET/CT to evaluate the prognosis in NSCLC patients as an assessment for tumor hypoxia. A clinical study showed a decline in HIF-1 protein and mRNA levels in some of its target genes in tumor cells[40]. Additionally, Kummar et al.[41] proved that a chemotherapy drug called topotecan decreases the expression of HIF-1α and some HIF-1 genes in different solid tumors.

Furthermore, Zonta et al.[42] indicated that the regulatory signaling of melatonin is mediated via its receptor MT1, suggesting melatonin as an adjuvant strategy against angiogenesis in ovarian cancer (OC). Regarding reproductive cancers, overexpression of HIF-1a has also been linked to poor prognosis in OC, and treatment with melatonin reduced the levels of HIF-1α, VEGF, and VEGF receptor (VEGFR2).

He et al.[43] have shown that the plasma HIF-1α levels in NSCLC patients are higher than in healthy volunteers. The current research and this study all found that the plasma levels of HIF-1α in NSCLC patients were higher than those of healthy people[43]. The reason for this might be that tumor tissues with high HIF-1α protein expression experienced tissue necrosis, which resulted in a huge amount of HIF-1α entering the bloodstream, or that there was a special regulation mechanism in the hematological system of NSCLC patients, such as CSCs[43-49].

Since hypoxia is closely associated with chemo- and radio-resistance, we investigated HIF-1a levels during CRT in patients with stage III NSCLC. We found that the levels of HIF-1a decrease during CRT. If these levels start to increase after CRT, following hypoxia and tumor progression, this means that HIF-1a levels can be used to detect tumor progression and metastasis. Decreased HIF-1α levels after the start of CRT may also be useful for predicting the efficacy of CRT. New hypotheses can be produced, and future studies are needed to prove this theory.

Conflict of interest: All authors declare no conflict of interest.

RESUMO

OBJETIVO: *Examinar a relação entre a resposta ao tratamento e os níveis de fator 1 induzida por hipóxia (HIF-1α) em pacientes com câncer de pulmão de células não pequenas localmente avançado (NSCLC) que receberam quimiorradioterapia (CRT).*

MÉTODO: *Oitenta pacientes com NSCLC foram incluídos no estudo e foram tratados na Faculdade de Medicina da Acibadem Mehmet Ali Aydınlar University. O nível de HIF-1α foi medido antes e depois da TRC pelo método de ensaio imunoenzimático (ELISA).*

RESULTADOS: *Os estágios dos pacientes foram os seguintes; estágio IIIA (65%) e estágio IIIB (35%). A histologia escamosa foi de 45%, o adenocarcinoma de 44% e o outro de 11%. Quimioterapia e radioterapia foram dadas simultaneamente a 80 pacientes. Quarenta e cinco (56%) pacientes receberam quimioterapia à base de cisplatina e 35 (44%) receberam quimioterapia à base de carboplatina. Os níveis séricos de HIF-1α (42,90 ± 10,55 pg / mL) após a TRC foram significativamente menores do que os níveis pré-tratamento (63,10 ± 10,22 pg / mL, p <0,001) em pacientes com NSCLC localmente avançado.*

CONCLUSÃO: *Os resultados deste estudo revelaram que os níveis séricos de HIF-1α diminuíram após a TRC. A diminuição dos níveis de HIF-1α após o início da TRC pode ser útil para prever a eficácia da TRC.*

PALAVRAS-CHAVE: *Carcinoma Pulmonar de Células não Pequenas. Quimiorradioterapia. Subunidade alfa do Fator 1 Induzível por Hipóxia.*

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ORIGINAL ARTICLE

Basic Life Support: an accessible tool in layperson training

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http://dx.doi.org/10.1590/1806-9282.65.10.1300

SUMMARY

OBJECTIVES: *1) To evaluate the efficiency of a new method of training laypeople on cardiopulmonary resuscitation (CPR). 2) To assess previous knowledge of the participants.*

METHODS: *Instructors were trained according to the 2015 American Heart Association Guidelines, with emphasis on CPR. Dummies made with PET bottles were used, and a questionnaire was applied to the participants before and after training. Statistical analysis was performed in the R commander program. Participants with incomplete documents were excluded from the study.*

RESULTS: *Out of 101 participants, 96 were included: 69 lay people, 17 health professionals, and ten health students. There was an improvement in the overall performance after training (mean pre: 62.7%, mean post: 75.8%, p <0.01), also present in the following main concepts: "mouth-to-mouth breathing is not necessary" (p <0.01), "risk of contamination" (p <0.01), "compression technique" (p <0.01). The concepts "recognition of severity" and "what is chest compression" did not improve, but had good pre-test means, 96.8% and 81.2%. There was no statistical difference in the knowledge between the groups (laypeople vs. health professionals and students, pre=0,06 e post=0,33).*

CONCLUSION: *The tools used in training were efficient. However, further studies are necessary to assess the long-term impact of this intervention.*

KEYWORDS: *Cardiopulmonary Resuscitation. Out-of-Hospital Cardiac Arrest. Education. Manikins.*

INTRODUCTION

Cardiovascular diseases have a high prevalence. According to the WHO, 19% of deaths worldwide in 2012 were due to cardiovascular diseases[1]. It is estimated that Brasil has 200 thousand cases of cardiac arrest (CA) annually, half of those in an extra-hospital environment, i.e., in homes and public places[2]. In these cases, the success rate is, on average, 10%[3]. In this context, it can be argued that laypeople will often witness a CA. Several studies point to the important role of cardiopulmonary resuscitation (CPR) executed by a spectator, which can increase the chances of survival of the victim by more than two times[4]. In view of this purpose, lay people can be trained without necessarily having to undergo extensive hours.

DATE OF SUBMISSION: 10-Mar-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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There are studies that show satisfactory learning of basic life support (BLS) using videos and/or dummies for training staff, even in short sessions[5-8]. In addition, the training is able to decrease anxiety in relatives of patients with high cardiovascular risk, which can be a barrier when assistance is actually required[9-11].

Therefore, it is known that the laypeople can provide initial CPR until the arrival of an Emergency Medical Service, such as the Samu (Emergency Medical Care Service), improving the outcome of many patients. For this to occur, it is necessary to educate and train the population.

THE BANDEIRA CIENTÍFICA PROJECT AND THE SURGICAL EXPEDITION

Considering the importance of the subject and the fact that the learning of BLS by laypeople is a subject that is poorly studied, the 4th Surgical Expedition of the The Bandeira Científica Project (ECBC) decided to carry out an educational program in a small Brazilian city.

The Bandeira Científica Project of the University of São Paulo is an academic extension program that exists since the 1950s and uses the principles of care, teaching, and research in their expeditions to remote regions of Brasil, promoting activities related to health, including medical care, with interventions with impact in the short and long term[12]. The ECBC, an academic extension program of the Medical faculty of the University of São Paulo (USP), started in 2013 and annually visits a Brazilian city to offer free elective surgeries in gynecology and gastric surgery. As part of their interventions with potential long-term impact, they carry out activities with the population. In 2016, the project visited the town of Bandeirantes (PR) and offered BLS training using low-cost mannequins, giving special attention to situations that can be potentially encountered by laypeople. Recently, the ECBC went through a process of renewal and is now known as the Surgical Expedition of FMUSP[13].

OBJECTIVES

Evaluate the effectiveness of the new proposed CPR training to the lay population.

Evaluate the prior knowledge of the training participants.

METHODS

Work approved by the Research Ethics Committee of FMUSP (decision number: 1.604.841. CAAE: 57007616.4.0000.0065). Each participant signed an informed consent form to participate in the study and answered a questionnaire developed by the Nursing School of USP[14] before and after the training. Next, we detail the process.

Pre-training: training of instructors and confection of dummies

The medical students of FMUSP selected to participate in the Surgical Expedition were trained by project directors (4th-year medical students) along with the medical advisor of the study and the coordinator of the Surgical Expedition 2016. The process consisted in the study of the reference material according to the guidelines of the American Heart Association 2015[15] and in training the didactic approach to the simulation activity. In total, 16 students were trained to act as instructors in six stations on common emergencies (acute myocardial infarction with cardiac arrest - AMI with CPR; drowning; airway obstruction; seizures; amputation), including a local demand (injury by a yellow scorpion)[16].

In relation to the support to AMI victim's with CPR, important concepts of the chain of survival were reviewed with the students: identifying an emergency, calling for help, correct technique of chest compression, emphasis in compressions/no need for ventilation. In the workshop, this knowledge was passed on and evaluated with attention to self-safety before starting the support measures, good positioning of the victim and the rescuer for the compressions, not bending the arms during compression, proper depth (5 to 6 cm) and total return of the chest after each compression at a frequency of 100 to 120 per minute[15].

To facilitate the training of a large number of people, it was necessary to create a didactic model from inexpensive and widely available material. Low-cost dummies were made based on the Mass Training Project, of the Society of Cardiology of the State of São Paulo (SOCESP), a campaign for training students of 8th year of primary education[17]. We used a 2-littler bottle of polyethylene terephthalate (PET), a t-shirt, a material as filling (paper, newspaper, fabric, styrofoam), stapler, and a rope. Each pair of instructors made their own dummy: they stapled the hem, sleeves, and collar, and, through the collar,

placed a PET bottle filled with water at the center of the t-shirt. The remaining space was filled with their material of choice, and the collar was attached to the end of the bottle with the rope. In our activity, we opted to fill 70% of the bottle with water in order to increase the strength required for compression and thus give advice on the proper posture.

The Automatic External Defibrillator (AED) was not used to simplify the method, considering the profile of a small town, where there are not usually crowds that require the wide availability of the device[15].

The training

The event occurred in three periods of the same day, with the duration of 1h30min each. The event was widely publicized during the permanence of the expedition in the city. The 16 students, divided into eight pairs, staged the six clinical scenarios, encouraging the participation of the population and guided the appropriate conduct.

The questionnaire

The main outcome of the study (learning with the method described) was assessed by a questionnaire drawn up at the Nursing School of USP and validated in 2009 only to evaluate the knowledge of laypeople on BLS. It contains multiple-choice and open-ended questions on the support using CPR[14]. The questionnaire used as reference guidelines outdated today, which did not yet include the non-necessity of mouth to mouth during CPR performed by a layperson. Given that we modified the original use of the questionnaire, some adjustments were necessary to interpret the answers found. Therefore, we separated the learning process in greater concepts.

FIGURE 1. PARTICIPANTS RECEIVE INSTRUCTIONS ON THE USE OF THE DUMMY.

The simplified questionnaire is as follows (full version in reference 14). Open-ended questions are highlighted*. The others were of multiple choice.

Q1. How can you check if the victim is breathing?

Q2. How is it possible to make it easier for the victim to breathe if there is no suspicion of fracture of the spine?

Q3. How is mouth-to-mouth breathing performed?

Q4*. Would you perform mouth to mouth breathing in an unknown person, without protective equipment? Why?

Q5*. Would you perform chest compressions even if you had not performed mouth to mouth breathing? Why?

Q6*. Do you know what are chest compressions, and what are they used for?

Q7. In what position must the victim be so that you can perform chest compressions?

Q8. What is the appropriate body site to perform chest compressions?

Q9*. Do you know the number of times chest compressions must be carried out, per minute, in an adult? If so, how many?

Data Analysis

Each question of the questionnaire received a grade that could be 2, 1, or 0, depending on the participant's response. Therefore, the overall performance could vary from 0 to 18 points. For better data interpretation, the final score was calculated in the following way:. The questions on the questionnaire were divided into six clusters according to the objectives of the training: Identifying an emergency (Q1), Mouth to mouth breathing technique (Q2 and Q3), Identifying the risk of contamination in mouth to mouth breathing (Q4), Mouth to mouth breathing is not essential in cardiopulmonary resuscitation done by laypeople (Q5), The role of the chest compression (Q6), Chest compression technique (Q7, Q8 and Q9).

Three authors of the study participating in grading the questionnaires and standardized the score of the open-ended questions according to the learning objectives already mentioned, after a group discussion and consensus. In the multiple-choice questions, the score for each alternative marked ranged from 0 to 2 points. We followed the correction criteria used in the referenced study by the Nursing School of USP. According to that study, some alternatives were considered partially correct. Therefore, when chosen by the participants, they received half of the total score, i.e., 1 point.

Participants were divided into two groups in data analysis: participants in the health area (health students and professionals) and laypeople. The comparison between the performance pre- and post-intervention was performed by paired Student t-test. The significance level for all tests was 5%. The tests were entered into Microsoft Excel (2010) or interface R commander of the R software, version 3.2.5 (2016).

RESULTS

Participants

In total, 101 people participated in the activity. Five were excluded due to incomplete documents (informed consent and questionnaire), leaving 96 valid questionnaires. Of these, 78 were women (81.2%), and 18 were men (18.7%). There were 69 laypeople (71.8%), 17 health professionals (17.7%), such as nurses and nursing technicians, and ten students in the area of health (10.4%). The largest portion had at least secondary education (92%), and the average age was 34 years (ranging between 14 and 55).

Examples of open-ended answers

Below, we explain the criteria for grading answers for each open-ended question using some examples (Table 1) found in the study.

Question 4: Would you perform mouth to mouth breathing in an unknown person, without protective equipment? Why?

The purpose of this question was to assess whether the participants had some notion of the biological risks to the rescuer, not being recommended to laypeople[14]. Therefore, people who answered "no" and justified it by saying there is a "risk of transmission of diseases" and "the method is not necessary," had a maximum score (2 points). Those who would not perform the method but gave no valid justification received intermediate scores (1 point). People who answered "no" and did not present any justification and those who answered "yes," regardless of the justification, received no points. Of these, the most frequent justification was "to help/save."

Question 5: Would you perform chest compressions even if you had not performed mouth to mouth breathing? Why?

TABLE 1. SCORE FROM OPEN-ENDED ANSWERS PRE- AND POST-TRAINING

Questions	Answers	Score
Answered negatively to Q4 - Would you perform mouth to mouth breathing in an unknown person, without protective equipment? Why?	Risk of disease transmission	2
	It is not necessary	2
	For personal safety	2
	Unknown victim	2
	Inexperience	1
	I do not know how to do it	1
	I do not know why	0
Answered positively to Q5: Would you perform chest compressions even if you had not performed mouth to mouth breathing? Why?	Resume heartbeats	2
	Chest compressions are more important	2
	Chest compressions are enough to save	2
	There is an important reserve of air	2
	To stabilize the patient	1
	To save	1
	It is the right thing to do	1
	It is necessary	1
	I believe in the saving power of the compressions	1
	To resume breathing	0
	It is faster	0
	It is easier	0
Q6 - Do you know what are to chest compressions, and what are they used for?	Resuscitation/reanimation	2
	Keep heartbeats	2
	Get the heart to function again	2
	Assist in the circulation of blood to the organs	2
	Oxygenation of organs	2
	To resume breathing	0
	Force the air to exit	0
Q9 - Do you know the number of times chest compressions must be carried out, per minute, in an adult? If so, how many?	100 a 120	2
	30x2	1
	As long as necessary until help arrives	1
	Other values (10, 15, 60).	0

In this question, we evaluated whether participants knew that chest compressions are crucial, to the detriment of mouth-to-mouth breathing. Those whose answer displayed these concepts received a maximum score. Inaccurate and generic justifications scored 1, and those that did not make sense or with wrong concepts received 0 points. Those who answered "no" to the first part of the question also did not receive any points, regardless of the justification. Of these, the most common justifications were: "Because it should be associated with mouth to mouth breathing," "I can cause injury to the victim," "I do not know how" and "I do not know why."

Question 6: Do you know what are chest compressions, and what are they used for?

Participants who explained the importance of chest compressions to maintain tissue oxygenation and/or restoration of blood circulation obtained a maximum score. This question did not offer intermediate scores. Participants who related to cardiac massage to the respiratory activity received 0 points.

Question 9: Do you know the number of times chest compressions must be carried out, per minute, in an adult? If so, how many?

Answers with a heart rate of 100 to 120 received 2 points. Other values received 0 points. Those who answered "30x2" received 1 point, because, despite the obvious error of interpretation of the question, we believe that the participants acquired a correct concept (30 compressions for two breaths in the care of the CPR in adults) presented during training.

PRE- AND POST-TRAINING COMPARISON

There was global learning, especially in relation to the concepts of "mouth to mouth breathing is not necessary," "risk of contamination" (in mouth to mouth breathing), "chest compression technique" and "breathing technique." The concepts of "identifying an emergency" and "role of chest compression" showed no statistically significant difference in learning, probably because the participants already had good knowledge of it prior to the activity. This can be observed by the high average of these concepts pre-training (see table 2).

Differences between the groups

No statistically significant difference was observed between the groups of laypeople (mean pre 60.46 ±14.17; mean post 76.81 ±16.54) and health professionals and students (mean pre 68.51 ±20.05; mean post 73.25±16.9) regarding their knowledge pre- (p=0.06) or post-training (p=0.33). This contradicts the assumption that health professionals would already have prior knowledge superior to other participants. However, the groups did not have similar sizes (69 laypeople x 27 participants in the area of health), which may have interfered in the statistical power of the test.

DISCUSSION

The high incidence of cardiovascular diseases, in addition to the possibility of emergency situations in extra-hospital environments, motivated this study. It is well known that as we move away from the large Brazilian metropolitan centers, the quality of education and health services offered to the population decreases progressively. Our proposal for first-aid training was designed to meet a large number of people without the need for rooms and technological material; with the minimum cost of a PET bottle, a well-prepared team is able to teach people in places with low technology available. In our study, the participants (related or not with the area of health) have increased their knowledge of CPR.

In comparison with the results of the study that developed the original questionnaire, the prior knowledge measured in 385 respondents in Campinas (SP) was lower than that found among the participants of the training in Bandeirantes (PR): mean of 40.8% of 7 points, and mean average of 62.7% of 18 points. Detailing the percentage of correct answers by the participants in Campinas for each question of the questionnaire, we have Q1 75.8%; Q2 16.4%; Q3 9.9%; Q6 67%; Q7 14.5%; Q8 8.8%; Q9 0%. In all questions, the knowledge of untrained laypeople was lower than that found in the present study. The difference in formal education between participants of both studies may offer an explanation: while in the study by Pergola and Araujo14, 46.5% completed secondary education and 34.8% higher education, in our study these figures were 62.3% and 27.5%, respectively. In addition, there may be a selection bias, since the first study approached laypeople randomly on the street, while ours was announced by the media of the city.

Interestingly, we did not observe any difference in prior knowledge regarding BLS between laypeople and health professionals. This could indicate the lack of training on basic life support in health program in the region, as well as limitations in continuing education, essential for the subject. With regards to continuing education, Piepho et al.[18] showed that lay people who participated in BLS training over ten years before were not able to reproduce the correct sequence of CPR. We also did not observe any difference in scores after the training, comparing the two groups, showing that the understanding of BLS approaches does not require specific knowledge. This result also shows us that the way the information was presented was appropriate to the general public.

The literature shows that laypeople with knowledge in BLS had better results in the practical evaluation using the dummy in comparison with laypeople with no prior knowledge. This remained the same even after the training, showing that taking classes again brings better results[19]. Our lay population was not tested in relation to previous BLS training, and our assessment was purely theoretical; however, as stated before, continuing education is necessary for proper learning. It is also worth noting that not only health professionals, but also health students, under professional supervision and after proper training, are able to instruct even without having completed the program, as shown in this study. It has also already been demonstrated that not only medical students but even trained laypeople could teach BLS in the same way that health professionals[20,21]. That is a good thing, because it offers more options for planning an educative action for the population.

We also noted that the main gain offered by the activity was in relation to the technique of compression and mouth to mouth breathing. Participants already had sufficient previous knowledge about the other matters (except risks of mouth to mouth breathing). Therefore, training with low-cost models was an efficient strategy to teach the technique of BLS procedures. Although the results may not be fully extrapolated to the general population, data suggest that BLS training programs should focus

TABLE 2. PERCENTAGE OF CORRECT ANSWERS ACCORDING TO THE *CLUSTERS* (MAJOR CONCEPTS)

	Identifying an emergency (Q1)	Mouth to mouth breathing technique (Q2, Q3)	Risk of contamination (Q4)	Mouth to mouth breathing is not required (Q5)	Role of chest compression (Q6)	Chest compression technique (Q7, Q8, Q9)	Total
Average Pre-Train.	96.8% (±17.5)	66.7% (±30.5)	57.3% (± 48.1)	30.7% (±38.6)	81.2% (±39.2)	55.0% (±19.4)	62.7% (±16.5)
Average Post-Train.	98.9% (±10.2)	73.9% (±26.4)	73.4% (± 43.5)	54.7% (±45.3)	82.3% (±38.4)	75% (±21.1)	75.8% (±16.1)
T-Test	P= 0.16	P<0.05	P<0.01	P<0.01	P= 0.41	P<0.01	P<0.01

the technique on chest compression alone to bring new knowledge to the target audience, whose long-term retention was shown by Nishiyama et al.[22] to be superior to conventional training. A Danish study that distributed ResusciAnne dummies for training laypeople associated with the DVD lessons evaluated some concepts similar to those that we evaluated. In that study, the results were based only on the performance of CPR by participants before and after 3.5 months: there was an increase from 15% to 28% in the correct performance of the maneuvers of the opening the airways (similar to Q2 and Q3), a decrease from 24% to 13% in the correct position of the hands (similar to Q8), an increase from 4% to 23% in the correct frequency of compressions, and an increase from 55.2% to 70.8% in overall performance[5]. An overall higher score on the questionnaire that we use can be attributed to the presence of multiple-choice questions, which can induce the correct answer and allow adjustments without true knowledge. In contrast, the practical assessment of CPR would be more reliable as to the skills of the participant.

The results presented here should be interpreted in light of some limitations. Firstly, the questionnaire was validated for a cross-sectional evaluation of the knowledge of laypeople on BLS and not as a tool to assess learning in the long term. This can be observed in the fact that there were many open-ended questions that allowed freedom of answer; which make it more difficult to group answers and perform a quantitative comparison. In relation to the questionnaire, it also did not assess recognition of CPR, nor how to follow in the CPR Chain of Survival outside a hospital environment, as recommended by the AHA, as well as the learning in other conditions simulated in the same training, which can serve as a basis for future studies. Secondly, we found that the average educational level of participants was high and most were females, which does not represent the population profile of Bandeirantes[23], thus limiting the extrapolated interpretation of the data, which can involve a selection bias already discussed. Thirdly, the dummies did not provide feedback on the quality of chest compression. Some points of chest compression, therefore, may not have been adequately trained (such as the depth of compression) and make it impossible for a proper comparison with other studies in the same area. However, we found that low-cost materials can be used to demonstrate mainly the frequency of compressions, posture, and position of the hands-on practical activities, making them an interesting alternative in places with few resources.

CONCLUSION

We have demonstrated that the teaching of Cardiopulmonary Resuscitation using a low-cost model allows the retention of basic knowledge on basic support to life, at least in the short term, for a population with medium to high formal education. However, it is necessary to develop a tool more suitable for assessing the theoretical-practical learning of people and verify the effects of this method of teaching in the long term.

Since the Surgical Expedition of FMUSP annually visits a different Brazilian city, there are new opportunities for improving and adjusting our method in future studies.

RESUMO:

OBJETIVOS: *1) Avaliar a eficiência da nova proposta de ensino de ressuscitação cardiopulmonar (RCP) à população leiga. 2) Avaliar o conhecimento prévio dos participantes da oficina.*

MÉTODOS: *Instrutores foram treinados de acordo com as diretrizes de 2015 da American Heart Association com enfoque na RCP. Utilizaram-se manequins confeccionados com garrafas PET, além de aplicação de questionário aos participantes antes e depois do treinamento. A análise estatística foi realizada no programa R commander. Foram excluídos do estudo participantes com documentos incompletos.*

RESULTADOS: *Dos 101 participantes, 96 foram incluídos: 69 leigos, 17 profissionais da saúde e dez estudantes da área da saúde. Houve melhora do desempenho geral após o treinamento (média pré: 62,7%; média pós: 75,8%; p<0,01), presente também nos seguintes conceitos principais: "respiração boca a boca não é necessária" (p<0,01), "risco de contaminação" (p<0,01), "técnica de compressão" (p<0,01). Os conceitos "reconhecimento de gravidade" e "o que é massagem cardíaca" não apresentaram melhora, mas tiveram boas médias pré-teste: 96,8% e 81,2%. Não se verificou diferença estatística no conhecimento entre grupos (leigos vs profissionais e estudantes da saúde, ppre=0,06 e ppos=0,33).*

CONCLUSÃO: *As ferramentas utilizadas no treinamento se mostraram eficientes. No entanto, novos estudos são necessários para avaliar o impacto no longo prazo.*

PALAVRAS-CHAVE: *Reanimação cardiopulmonar. Parada cardíaca extra-hospitalar. Educação. Manequins.*

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REVIEW ARTICLE

Fever of unknown origin in special groups

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http://dx.doi.org/10.1590/1806-9282.65.10.1308

SUMMARY

Fever of undetermined origin (FUO) is a challenging entity with a striking presence in hospitals around the world. It is defined as temperature ≥ 37.8 ° C on several occasions, lasting ≥ three weeks, in the absence of diagnosis after three days of hospital investigation or 3 outpatient visits. The main etiologies are infectious, neoplastic, and non-infectious inflammatory diseases. The diagnosis is based on the detailed clinical history and physical examination of these patients, in order to direct the specific complementary tests to be performed in each case. The initial diagnostic approach of the FUO patient should include non-specific complementary exams. Empirical therapy is not recommended (with few exceptions) in patients with prolonged fever, as it may disguise and delay the diagnosis and conduct to treat the specific etiology. The prognosis encompasses mortality of 12-35%, varying according to the baseline etiology.

KEYWORDS: *Fever of Unknown Origin. Fever. Child. Neutropenia. Aged. HIV.*

INTRODUCTION

Fever of unknown origin (FUO) is a clinical entity that is highly prevalent worldwide and affects all age groups, with some peculiarities at extreme ages and in special groups.[1-4] Most of the times, it is associated with infectious, neoplastic, and rheumatological etiologies. A meticulous clinical examination is still the foundation for approaching patients with prolonged fever, despite a large number of diagnostic resources.[5,6] Empirical therapy is performed only in selected cases, as the diagnosis of the underlying disease may be delayed in these cases.[7,8]

The objective of this study is to review the different presentations of fever of unknown origin in special groups of patients (children, neutropenic, elderly, HIV+, and hospitalized patients).

METHODS

This is a literature review carried out on the more recent publications found in the PubMed Central® (PMC) and SciELO® databases. On PMC, the search used the descriptor "Fever of Unknown Origin" and

DATE OF SUBMISSION: 23-Jan-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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the secondary descriptors: "Analysis", "Complications", "Diagnosis", "Enzymology", "Epidemiology", "Etiology", "Immunology", "Metabolism", "Microbiology", "Mortality", "Parasitology", "Pathology", "Physiology", "Physiopathology", "Statistics and numerical data", "Therapy", "Virology". All secondary descriptors were associated with the main descriptor using the tool "OR". A total of 3,736 results were found. Then, the following filters were applied: "Review", "Clinical Trial", "Meta-Analysis", "Systematic Reviews", "Full text", "published in the last 5 years", and "Humans". After applying the filters, the results were narrowed down to 75 items. Of these, 21 articles were selected after an analysis of their *summary* and *abstract*. On Scielo, the descriptor "Febre de origem indeterminada" was used, retrieving a total of 15 matches, which were reduced to 13 after the filters "Brasil" and "Ciências da Saúde" were applied. We did not use any filter for year of publication while selecting Brazilian articles due to the scarce scientific production/update on the subject. After analyzing the papers, three were selected based on the scope of the present study, totaling 24 references.

DISCUSSION

Fever of undetermined origin was initially characterized in 1961 by Petersdorf and Beeson as a record of oral temperature >38.3°C on at least three different occasions, for a minimum of three weeks, in the absence of diagnostic hypotheses that could explain the fever after a week of investigation.[1,7-11] Since this is a condition of singular characteristics, there are still divergences among some authors regarding its exact concept. One of the most accepted concepts of classical FUO encompasses axillary temperature ≥37.8 ºC on several occasions, for a period ≥ three weeks, with no diagnosis after three days of hospital investigation or three outpatient consultations.[2,12]

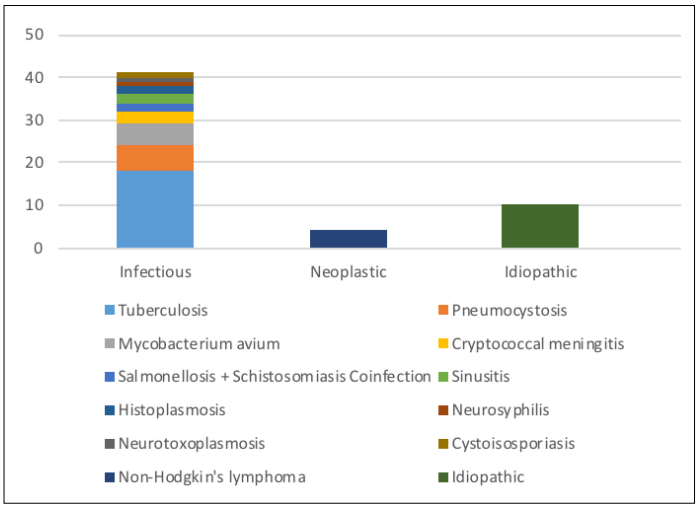
There are more than 200 possible causes for FUO; the main ones are infectious, neoplastic, and rheumatic.[1,13] Despite all the clinical, laboratory and imaging resources, 7-50% of cases can remain with no diagnosis (idiopathic).[1,14-19] In developed countries, neoplastic and rheumatic causes are usually predominant, while in developing countries infections often prevail.[1]

Some groups of patients require a special approach because they present a FUO profile with specific peculiarities in relation to the classic pattern. They are neutropenic, hospitalized (nosocomial FUO), HIV positive, elderly patients and children.[11,13,20-24]

FUO IN PEOPLE LIVING WITH HIV/AIDS (PLWHA)

The definition FUO associated to HIV requires confirmed HIV infection, fever ≥37.8 ºC in several occasions, duration ≥four weeks (outpatient) or ≥3 days in hospitalized patients, with no diagnosis after three days, despite adequate investigation (including at least 48 hours of microbiological culture).[2,14] A study conducted in Brasil between 1989 and 1997 recorded all cases of FUO in HIV positive patients at a general hospital of Minas Gerais.[3] Figure 1 shows the causes of FUO identified in the study patients. During this period, there were 55 cases of FUO associated with HIV. The specific etiology was defined in 81.8% of the cases (45 patients), of which 74.5% (41 patients) had infectious causes of FUO. Tuberculosis was the most frequent etiology (43.9%), with extrapulmonary involvement in 16 of 18 cases. Pneumocystosis, diagnosed in six patients, was the second most frequent etiology (14.6%), followed by Mycobacterium avium infection, which was found in five patients (12.5%). Cryptococcal meningitis and non-Hodgkin lymphoma were diagnosed in three patients (each) and together were the fourth most common FUO etiologies in PLWHA (7.3% each). Coinfections by salmonellosis/schistosomiasis, sinusitis and histoplasmosis were recorded in two patients (4.9% each). Neurosyphilis,

FIGURE 1. CAUSES OF FUO ASSOCIATED WITH HIV IN A STUDY CONDUCTED IN BRASIL (1989-1997), ON 55 PATIENTS[3].



Adapted from Lambertucci JR, Rayes AAM, Nunes F, Landazuri-Palacios JE, Nobre V. Fever of undetermined origin in patients with the acquired immunodeficiency syndrome in Brasil: report on 55 cases.

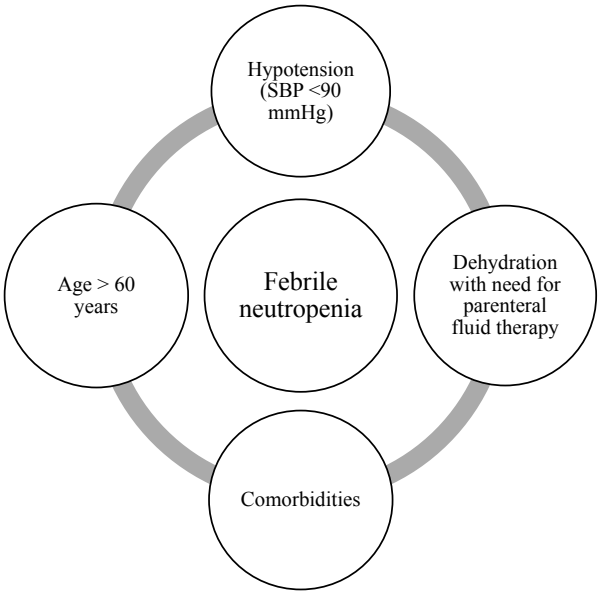
neurotoxoplasmosis, and cystoisosporiasis were diagnosed in one patient (2.4% each). Idiopathic FUO was found in 10 patients (18.2%). The more effective diagnostic procedures were biopsies (lymph node, liver, bone marrow), analysis of the cerebrospinal fluid, complete blood count, the purified protein derivative (PPD), computed tomography (CT), and parasitological stool test.[3]

The acute phase of an HIV infection may also present itself as a mononucleosis-like syndrome (rash, fever, lymphadenopathy), being a possible etiology of FUO.[13] For some authors, cytomegalovirus can be responsible for up to 5% of FUO cases in PLWHA. It is the most common viral infection associated with HIV. It has an opportunistic behavior and is reactivated when the CD4+ T serum lymphocytes are in levels <100/mm³.[13] Fever associated with the use of antiretroviral drugs should be investigated, especially when other causes of FUO have been eliminated.[13]

FUO IN NEUTROPENIC PATIENTS

The definition of FUO in neutropenic patients requires neutrophils <500/mm³, fever ≥37.8 ºC on several occasions, and no diagnosis after three days, in spite of adequate investigation (including at least 48 hours of microbiological culture).[2] Neutropenic patients present greater vulnerability to the development of infections. The peculiar approach to this group of patients is centered around the shortest interval between diagnosis and the beginning of therapy since infections can progress with high morbidity and mortality in febrile neutropenic patients when there is no appropriate antimicrobial therapy.[15] Thus, once the fever has been identified, antibiotic therapy should be initiated immediately, empirically, until the results of the microbiological cultures are available.[15] It is worth noting that the empirical treatment will remain in cases in which no specific focus or infectious agent is identified.[15]

FIGURE 2. FACTORS OF WORSE PROGNOSIS IN NEUTROPENIC PATIENTS WITH FUO



The main pathogens in these patients are *Staphylococcus aureus, Streptococcus spp., Enterococci, coagulase-negative Staphylococci,* gram-negative bacilli, and *Pseudomonas aeruginosa*.[15] A study carried out by the European Organization for Research and Treatment of Cancer (EORTC) reported that it is possible to isolate an infectious agent in febrile neutropenic patients in only 43% of the cases (22% of which are bacteremia).[14] However, 78% of the patients responded to the empirical antimicrobial treatment, reinforcing the idea that there are occult bacterial infections that can cause FUO in neutropenic patients.[14]

The risk of complications varies according to several factors such as: age, nadir and duration of the neutropenia, presence of hypotension, presence of comorbidities, and dehydration.[8] Age greater than 60 years, presence of hypotension (systolic blood pressure <90 mmHg), presence of comorbidities (eg. chronic obstructive pulmonary disease), dehydration with the need for parenteral fluid therapy (which increases the risk of hospital infection associated with the catheters) are factors that indicate a worse prognosis (Figure 2).[8] Empirical treatment with antifungal agents should be considered in some cases.[14]

FUO IN CHILDREN AND ADOLESCENTS (0-18 YEARS)

FUO in patients younger than 19 years old has the same diagnostic definition used in adults, only the age of the patients affected differs. In general, few studies are performed with a focus on children and adolescents, perhaps because there is not so much discrepancy around the natural history of the disease among pediatric and adult groups, in addition to the diagnostic approach consisting in a broad clinical, laboratory, and imaging examinations, as mentioned. However, there are some literature reviews in this context that are noteworthy.

Approximately 20% of pediatric emergencies of

children between 2 and 24 months are caused by fever, and in 20% of these patients, no initial etiological diagnosis is reached.[13,14] The patient's age is an important factor in the evaluation of FUO. In children aged <6 years, respiratory infections, urinary tract infections (UTI), and juvenile idiopathic arthritis (JIA) are more prevalent.[11] Tuberculosis, inflammatory bowel disease, and lymphomas are more common in adolescents.[11] Antipyretic therapy is recommended in the following situations: bad overall condition of the child, very high fever (> 40 ºC), presence of comorbidities that increase the metabolic demand (congenital cardiopulmonary diseases, for example), and in cases of dehydration.

The infectious etiology is also the most frequent in children.[14,20] The greatest difficulties for the correct etiological derive from the inexpressive symptomatology that is common in this age group. Urinary tract infections are the most prevalent bacterial infections in children and represent 5-7% of FUO cases in this group.[6,7,17] The likelihood of UTI as a cause of FUO depends on the presence of risk factors such as: temperature of at least 39 ºC, fever for more than one day, age <12 months, Caucasian ethnicity, in addition to the absence of another infectious focus.[14] Infectious endocarditis in the pediatric population commonly presents itself without alterations in cardiac auscultation, so the diagnosis should be confirmed by laboratory findings and imaging. Abscesses are also possible diagnoses in cases of a previous history of surgeries (mainly abdominal).[6] The prevalence of occult bacteremia (OB) went from 2.4-11.6% to 0.17-0.36%, thanks to the advent of vaccines against *Haemophilus influenzae* type b and pneumococcus, but it should still be investigated as a cause of FUO in children. Currently, its main agent is *Escherichia coli* (56%), followed by *group B Streptococcus* (21%), and *Staphylococcus aureus* (8%).[7] Rhinosinusitis, tooth infections, brucellosis, leptospirosis, systemic mycoses, visceral leishmaniasis, and osteomyelitis are described as potential etiologies of FUO.[6,11] Continuous or relapsing fever patterns with oscillations below 1 ºC can be the first sign of typhoid fever.[6] Viral infections can cause FUO in children, and its main etiologic agents are the herpes virus, adenovirus, enterovirus, and the cytomegalovirus.[6,13,18]

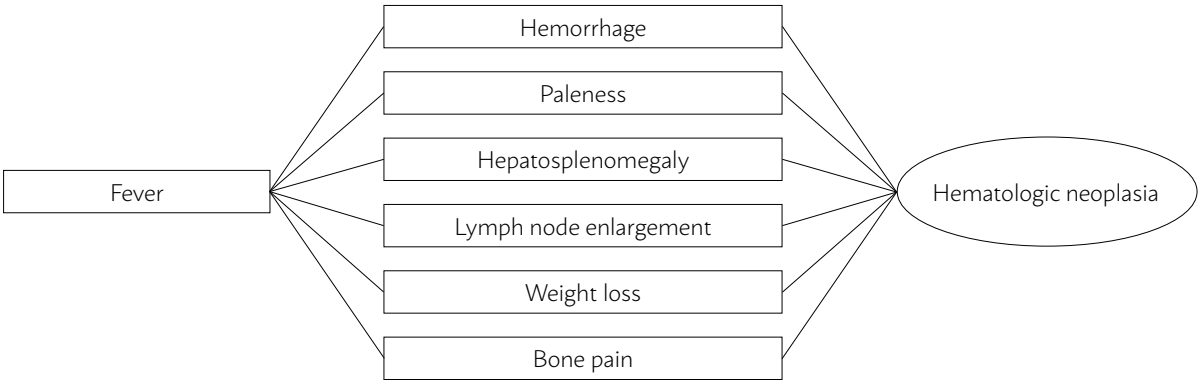
Non-infectious inflammatory diseases that cause FUO in children and adolescents are represented mainly by JIA and systemic lupus erithematosus (SLE) (together, can account for more than 90% of the cases).[11] Synovitis with high (39-40 ºC) and intermittent fever with one or two daily peaks in individuals aged <16 years may suggest JIA, especially when associated with a evanescent maculopapular rash, generalized lymphadenopathy, hepatosplenomegaly, serositis, in the absence of infectious and tumor causes. SLE is a FUO etiology, even if fever is not a diagnostic criteria of the disease, it usually accompanies the intense systemic involvement. It is more common in female children. Vasculitis are important causes of FUO in children, particularly Kawasaki disease in children younger than one year of age.[6]

The main neoplasms associated with FUO in children and adolescents are leukemias and lymphomas. Hematological neoplasms should always be suspected in cases of hemorrhages, paleness, hepatosplenomegaly, lymph node enlargement, weight loss, and bone pain associated with fever (Figure 3). The natural history of Hodgkin lymphoma may start with B symptoms, such as weight loss of >10% of body weight, night sweats, pruritus, in addition to the periodic fever, known as the Pel-Ebstein fever (peaks that exceed 40°C with a periodicity of 7-10 days). The differential diagnosis involves entities that mimic this type of neoplasia, such as Castleman disease (idiopathic and lymphoproliferative disease), and Kikuchi-Fujimoto lymphadenitis (histiocytic necrotizing lymphadenitis), both of which can cause FUO in children.[6]

Among the solid tumors that can cause FUO, the main ones are the Wilms' tumor (malignant renal tumor, more common in children), neuroblastoma (extracranial solid tumor, more common during childhood), and atrial myxomas (most common primary cardiac neoplasm).Abdominal masses, hematuria, prolonged fever, hypertension, polycythemia, besides a positive naproxen test can suggest a Wilms' tumor.Abdominal, thoracic, or cervical nodules with prolonged fever are suggestive of neuroblastoma. Murmurs intensified with dynamic auscultation maneuvers, with a history of decubitus dyspnea, and presence of a mobile mass on the echocardiography are suggestive of left atrial myxoma.[6]

Auto-inflammatory syndromes caused by genetic disorders (familial Mediterranean fever, mevalonate kinase deficiency, familial Hibernian fever) are less frequent but must be remembered, particularly when the FUO is classified as idiopathic.[6] Some classes of medications may cause FUO, and its use

FIGURE 3. WHEN TO SUSPECT OF HEMATOLOGICAL NEOPLASMS IN FUO PATIENTS.



should always be investigated when obtaining the clinical history of the patient. The main classes are antibiotics, anticonvulsants, antiarrhythmic drugs, vasodilators, antihistamines, antileukotrienes, and non-steroidal anti-inflammatory drugs.[6,11] Sickle cell disease, inflammatory bowel disease, dermatological diseases (e.g., erythema nodosum), thyroid diseases are potential causes of FUO and should also be remembered during the clinical examination.[6]

Between 10-30% of FUO cases in children remain without a diagnosis. In most of these, the fever stops spontaneously without major complications. The FUO prognosis in children depends on the underlying etiology and early diagnosis, but it is better than in adults.[6,11]

FUO IN ELDERLY PATIENTS

Few FUO studies focus on elderly patients. These patients often do not have a fever in the presence of an infection; however, when present, the fever may suggest a serious illness. The main FUO etiologies of in elderly patients are infectious (up to 35% of the cases), rheumatic (up to 30% of the cases), and neoplastic (up to 20% of the cases). In this group, it is worth mentioning the most common rheumatic diseases: temporal arteritis, polymyalgia rheumatic, granulomatosis with polyangiitis, polyarteritis nodosa, rheumatoid arthritis, and sarcoidosis. Intravascular lymphoma with uterine involvement has been described as a cause of FUO in elderly women.

NOSOCOMIAL FUO

The definition of nosocomial FUO requires that patients are hospitalized, with fever ≥37.8 ºC on several occasions, in the absence of an infection or disease incubated at admission, and with no diagnosis after three days in spite of adequate investigation (including at least 48 hours of microbiological culture).[2] Two important causes of nosocomial FUO are pseudomembranous colitis and drug-induced fever.[2]

RESUMO

Febre de origem indeterminada (FOI) é uma entidade desafiadora com presença marcante nos hospitais de todo o mundo. É definida como temperatura ≥37,8 ° C em várias ocasiões, com duração ≥3 semanas, na ausência de diagnóstico após três dias de investigação hospitalar ou três consultas ambulatoriais. As principais etiologias são de ordem infecciosa, neoplásica e doenças inflamatórias não infecciosas. O diagnóstico é baseado na história clínica e no exame físico minuciosos desses pacientes, com a finalidade de direcionar os exames complementares específicos a serem realizados em cada caso. A abordagem diagnóstica inicial do paciente com FOI deve incluir exames complementares inespecíficos. A terapia empírica não é recomendada (com poucas exceções) em pacientes com febre prolongada, uma vez que ela pode camuflar e retardar o diagnóstico e a conduta para tratar a etiologia específica. O prognóstico engloba uma mortalidade de 12-35%, variando de acordo com a etiologia de base.

PALAVRAS-CHAVE: *Febre de causa desconhecida. Febre. Criança. Neutropenia. Idoso. HIV.*

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REVIEW ARTICLE

Raynaud's phenomenon in the occupational context

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http://dx.doi.org/10.1590/1806-9282.65.10.1314

SUMMARY

OBJECTIVE: *To review articles that evaluated the prevalence of Raynaud's phenomenon of occupational origin.*

METHODS: *The search for articles was carried out in the Medline (via PubMed), Embase, Web of Science, Scientific Electronic Library Online (SciELO), and Latin America and Caribbean Health Sciences Literature (Lilacs) databases.*

RESULTS: *64 articles were obtained from the electronic search; 18 articles met the eligibility criteria. All studies discussed the exposure to vibrations in the upper limbs. In 6 of them, the thermal issue was directly or indirectly addressed. No studies have addressed exposure to vinyl chloride.*

CONCLUSION: *In general, a higher prevalence of Raynaud's phenomenon was found among vibratory tool operators compared to non-exposed workers, with an increase in the number of cases the higher the level of vibration and the time of exposure. Cold is a triggering and aggravating factor of the Raynaud phenomenon and seems to play an important role in the emergence of vascular manifestations of the hand-arm vibration syndrome.*

KEYWORDS: *Raynaud Disease. Peripheral Vascular Diseases. Vibration. Vinyl chloride. Cold Temperature.*

INTRODUCTION

Raynaud's Phenomenon: General Concepts

Raynaud's phenomenon is a condition characterized by an exaggerated vasospastic response at the level of the digital arteries and cutaneous arterioles. The episodes are evidenced by a well-marked alteration of the coloration of the fingers, which may be accompanied by paresthesias and pain. The classic triad described for Raynaud's phenomenon is the sequential alteration of white, blue, and red colors[1]. This triad may not be observed in all patients, and most authors suggest the need for at least pallor and cyanosis to characterize the episode[2].

In the primary Raynaud's phenomenon, blood vessels are structurally normal and no trophic changes, pittings, digital ulcers, and gangrene are expected. Patients who manifest vasospastic episodes due to a condition or disease that interferes with the mechanisms of vascular reactivity have secondary Raynaud's phenomenon[1]. Several conditions may be associated with this type of Raynaud's phenomenon, such as autoimmune rheumatic diseases, hematological diseases, endocrine diseases, medications (bleomycin, cisplatin, interferon), malignancies, and situations related to the occupational context[1,3].

According to the list of work-related diseases, adopt-

DATE OF SUBMISSION: 12-Mar-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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ed as a reference by the Brazilian Ministry of Health, localized vibrations, vinyl chloride, and work in low temperatures are considered etiological agents or occupational risk factors for Raynaud's phenomenon[4].

Vibrations and Raynaud's phenomenon

There are two forms of occupational exposure to vibrations: localized and full-body vibration. Localized vibration is transmitted to the hands and arms and can cause injury to the upper limbs, including Raynaud's phenomenon. On the other hand, whole-body vibration can be harmful to the spine[5].

Raynaud's phenomenon, digital neuropathy, and carpal tunnel syndrome have a well-established occupational link with exposure to localized vibrations. The injuries of the upper limbs associated with this type of exposure are called "hand-arm vibration syndrome". In this syndrome, neurosensory changes and vasospastic disease may coexist or progress independently. Vascular symptoms tend to improve at variable times after withdrawal from exposure. However, advanced cases of digital neuropathy, with loss of hand functions, are usually irreversible[5].

Occupational exposure to localized vibrations is mainly related to activities using motorized tools such as hammers, crushers, polishers, sanders, drills, lawnmowers, countersinks, and chainsaws. Exposure commonly occurs in heavy construction and civil engineering services but may be present in a variety of activities[5].

Vinyl chloride and Raynaud's phenomenon

Vinyl chloride is a volatile substance that is quickly absorbed through the lungs and metabolized by the liver. The final product of the polymerization of vinyl chloride is the polyvinyl chloride (PVC), which is widely used in the plastic industry[6].

Before the 1970s, workers were commonly exposed to high concentrations of vinyl chloride in occupational air. For this reason, the term "vinyl chloride disease" was used to describe cases of acrosteolysis, hepatopathy, neuropathy, thrombocytopenia, skin lesions, and vascular alterations (Raynaud's phenomenon) attributed to the occupational exposure to this substance. However, industries progressively reduced workers' exposure to vinyl chloride as its deleterious effects and close connection to the onset of cancer were recognized[6]. Since 1979, vinyl chloride has been considered by the *International Agency for Research on Cancer* (IARC) as a human carcinogen (Group 1)[7].

Cold environment and Raynaud's phenomenon

Concerning the work at low temperatures, it is known that cold is a triggering and aggravating factor of Raynaud's phenomenons of any etiology. Individuals with Raynaud's phenomenon are at increased risk of developing frostbite when exposed to low temperatures. Similarly, after frostbite, the affected limb may remain sensitive to cold, manifesting Raynaud's phenomenon[3,4]. Thus, avoiding exposure to cold is an essential measure for the management of Raynaud's phenomenon in all patients[1].

Rationale and objective

The determination of occupational exposures is an essential element in the investigation of all patients with Raynaud's phenomenon. Therefore, it is important to know the prevalence of Raynaud's phenomenon in workers exposed to occupational risk conditions. On the face of it, the objective of this study was to conduct a review of articles that evaluated the prevalence of Raynaud's phenomenon of occupational origin, with emphasis on exposure to localized vibrations, vinyl chloride, and work in low temperatures.

METHODS

Eligibility criteria

Observational studies investigating the prevalence of Raynaud's phenomenon in workers with exposure to localized vibration, vinyl chloride, or low temperatures were considered eligible. Articles published since 1998 in English, Spanish, or Portuguese were searched. We excluded articles about occupational risk factors for the development of autoimmune rheumatic diseases with secondary Raynaud's phenomenon.

SEARCH STRATEGY

The search for articles was carried out in the following databases: Medline (via PubMed), Embase, *Web of Science, Scientific Electronic Library Online* (SciELO), and Latin America and Caribbean Health Sciences Literature (Lilacs).

The search strategy for Medline (via PubMed) was "raynaud disease"[All Fields] AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH

Terms]) AND ("occupational exposure"[All Fields] OR "occupational diseases"[All Fields] OR "occupational injuries"[All Fields]) AND ("cold temperature"[All Fields] OR ("vibration"[MeSH Terms] OR "vibration"[All Fields]) OR "vinyl chloride"[All Fields]) AND (English[lang] OR Portuguese[lang] OR Spanish[lang]) AND ("1998/01/01"[PDAT] : "2018/01/31"[PDAT]).

This strategy was adapted to the other databases.

The searches were conducted from September 2017 to January 2018.

Selection of articles and data extraction

The studies were selected in two steps. The first step involved the screening of studies based on titles and abstracts. For the following evaluation, the full texts of the selected articles were retrieved. Information was recorded on: title, authors name, year of publication, country of origin, type of study, characteristics of subjects, occupation, type of exposure, type of evaluation and prevalence of Raynaud's phenomenon.

RESULTS

We obtained 64 articles from the electronic search. A total of 11 duplicate articles were excluded. After evaluation of the titles and abstracts, 19 articles were selected for full-text evaluation. Of these, one was excluded because it did not estimate the prevalence of Raynaud's phenomenon in the group of workers. In the end, 18 articles met the eligibility criteria and were included in the review (13 cross-sectional studies and 5 cohorts) — Figure 1.

The studies are highly heterogeneous. There are important differences in the analyzed populations, occupations, ways of estimating exposure to risk factors, definitions/evaluations of the Raynaud's phenomenon, and outcomes. All studies discussed exposure to localized vibrations. In 6 of them, the thermal issue was directly or indirectly addressed. No studies have addressed the exposure to vinyl chloride. The main features of the studies are presented in Tables 1 and 2.

DISCUSSION

The search strategy of this review contemplates three occupational risk factors for Raynaud's phenomenon according to the list of work-related diseases (Brazilian Ministry of Health): localized vibrations, cold, and vinyl chloride[4]. Despite the broad scope of the research, there is a marked predominance of the topic "localized vibration of hands and arms" among the articles included. The cold was not addressed as an isolated risk factor in any article, and vinyl chloride was not discussed in any study.

In general terms, the literature review reiterates some expected data such as a higher prevalence of Raynaud's phenomenon among vibratory tool operators compared to non-exposed workers[9,13,14], an increased prevalence of this event the longer the exposure time to vibration[8,21,23], as well as among those exposed to higher levels of hand and arm vibration[13,17,23].

The studies that addressed the thermal issue suggest that the cold environment is an important synergy factor in the emergence of vascular manifestations of vibration syndrome[10,12,13]. In the articles evaluated, temperature measurements were not performed in the workplace, but some studies considered metrological information to estimate exposure to colder environments[12,13].

In a study with construction electricians[12], among whom 95% used vibration tools at work, the

FIGURE 1.

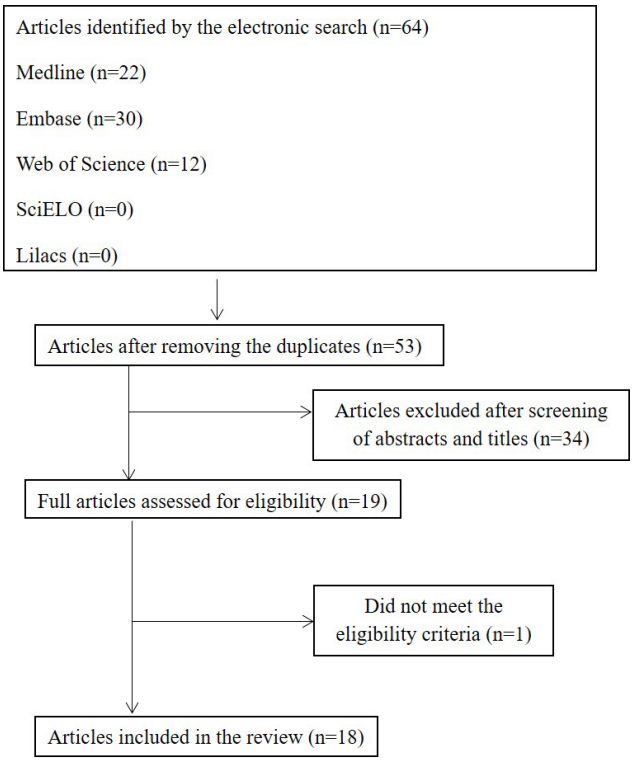

TABLE 1. RAYNAUD PHENOMENON IN WORKERS WITH EXPOSURE TO LOCALIZED VIBRATIONS, LOW TEMPERATURES, OR VINYL CHLORIDE.

First author	Year	Study design	Country	Characteristics (population)	Characteristics (occupation)	Type of exposure
Kluger[8]	2017	Transversal	Finland	1000 people invited by email; response rate: 45%, 98 women and 350 men	Tattoo artists who are members of the French Union of Tattoo Artists	Vibration: tattoo gun
Pettersson[9]	2014	Transversal	Sweden	Workers with ONIHL*; received the questionnaire: 246 men/78 women; response rate: 41%	Most common occupations: teachers, military, and welders	Vibration: questions to estimate minutes/day and years of exposure. Cold: time outdoors when working
Roquelaure[10]	2012	Transversal	France	3.710 workers, 2.161 men (58%) and 1.549 women (42%)	Almost all occupations except farmers, artisans, tenants, self-employed	Vibration tools (≥2hours/day): 460 workers. Cold temperature <15°C (≥4hours/day): 220 workers
Aiba[11]	2012	Cohort	Japan	704 workers (685 men and 19 women). Mean observation time: 10.6 ± 7.4 years	Workers using an impact wrench	Vibration: 8 vibrating tools selected to be evaluated during work. Acceleration: 4.9 - 22.6 m/s2
Inaba[12]	2010	Transversal	Japan	120 men; 74 answered a questionnaire in the winter and 83 in the summer	Electricians (construction workers)	Vibration: 95% of electricians used vibration tools. Cold: local metrological information
Burström[13]	2010	Transversal	Sweden	Cases: 19,251 men exposed to vibration of hands/arms. Controls: 3,350 office workers	Cases: construction workers with exposure to hand and arm vibration	Vibration: 0-5 scale (occupational hygienists). Cold: local metrological information
Bovenzi[14]	2010	Cohort	Italy	Cases: 249 workers with exposure to vibration. Controls: 138 workers without exposure	Forestry workers (chainsaws with anti-vibration device) and quarry workers	Vibration: ISO 5349. Estimation of daily exposure: direct observation for one week (chronometer)
Bovenzi[15]	2008	Cohort	Italy	Cohort of 128 forestry workers. At the end of the follow-up, 57 workers (44.5%) had retired	Forestry workers: chainsaw operators	Vibration: sample of 9 chainsaws during operating conditions as per ISO 5349
Bovenzi[16]	2008	Cohort	Italy	183 forestry workers and 33 quarry workers completed the follow-up	Forestry workers: chainsaws. Quarry workers: tools for processing marble	Vibration: measurements taken during tool operating conditions as per ISO 5349
Bovenzi[17]	2005	Transversal	Italy	Cases: 100 female workers using orbital sanders. Controls: 100 female office workers	G(A) orbital sanders; (B) orbital sanders/hand sanding; (C) hand sanding	Vibration: measurements performed on 9 orbital sanders. Acceleration: 6.8 m/s2
Futatsuka[18]	2005	Transversal	Japan	73 quarry drill operators; 29 controls: manual tasks in the same companies	Quarry drill operators (rock drill)	Vibration: ISO 5349. Acceleration (drills): 45-55 m/s2; 160-210 min/day. Temp: South of Vietnan >25oC
Barregard[19]	2003	Transversal	Sweden	900 car mechanics received a questionnaire; 806 replied	Mechanics of cars	Vibration: working time (average): 12 years. Exposure: 14 minutes/day. Vibration level: 3.5 m/s2
Allen[20]	2002	Transversal	Ireland	Three groups of men (79 riveters, 52 healthy controls, and 79 claimants)	Workers: riveters. Controls: no vibration. Claimants: yard/public services	Vibration: exposure time of 0.2 - 18 years among riveters and 1.5 - 48 years among claimants
Palmer[21]	2000	Transversal	United Kingdom	Questionnaires answered by 12.907 people aged 16-64 years (6.913 men/5.994 women)	Unspecified, random selection of record lists	Vibration: exposure assessed by questionnaire
Aiba[22]	1999	Cohort	Japan	383 workers (men): use of impact wrench in electric light pole factory, 1982 to 1999	Workers using an impact wrench	Vibration: ISO 5349 and JIS B 49000. Exposure: 102 to 117 minutes/day. Cold: not characterized
Palmer[23]	1998	Transversal	England	153 gas distribution agents (response rate 81%). Average of 16 years using vibrating tools	Gas distribution agents (pneumatic tools)	Vibration: ISO 5349. Vibratory tools (time of use - questionnaire): 1.2 to 5.5 hours/week (on average)
Bovenzi[24]	1998	Transversal	Italy	Cases: 822 workers exposed to vibration, Controls: 455 healthy men not exposed	Grinders, mechanics, quarry drillers, construction/forestry workers, etc.	Vibration: ISO 5349; 8.3 m/s2 (percussion); 2.8-4.7 m/s2 (percussion/rotary); <2 m/s2 (rotary hand tools)
Miyashita[25]	1998	Transversal	Japan	4652 private forestry workers (at least 1 medical examination for VS** from 1974 to 1996)	Forestry workers exposed to hand and arm vibration (chainsaws)	Vibration: estimation of career time operating vibratory tools

*ONIHL = Occupational noise-induced hearing loss; VS** = Vibration Syndrome

TABLE 2. RAYNAUD PHENOMENON IN WORKERS WITH EXPOSURE TO LOCALIZED VIBRATIONS, LOW TEMPERATURE, OR VINYL CHLORIDE: EVALUATION OF THE RAYNAUD PHENOMENON AND OUTCOME.

First author	Evaluation of the Raynaud phenomenon	Outcome
Kluger[8]	Questionnaire by e-mail. RP*: finger whitening related to cold. No evaluation was performed by a physician	448 questionnaires: 30 reported symptoms of RP*; 11 appeared after the beginning of tattooing activity. Daily work hours: association with RP*
Pettersson[9]	RP* classified by the questionnaire (with image)	RP* considered in 37% of those who reported exposure to hand and arm vibration and in 15% of those who did not report the exposure
Roquelaure[10]	Doctor asked about RP* features (last 12 months), defined as finger whitening episodes triggered by exposure to cold	87 cases of RP* diagnosed, 56 (women) and 31 (men). Female: association with psychosocial factors. Male: association with exposure to cold
Aiba[11]	Medical evaluation with questions about the signs/symptoms related to RP* and typical image to aid in reporting	RP*: 39 workers during the period. Incidence of RP*: 6.27 people per 1000 individuals-year. Prevalence: 0.6% (1982), 6.2% (1987), 4.9% (2008)
Inaba[12]	Self-administered questionnaire. "White finger in response to cold environment". No evaluation by a physician and no picture of RP*	Prevalence of RP* among construction electricians: 43.2% (winter) and 7.2% (summer)
Burström[13]	Self-administered questionnaire. Prevalence of RP* estimated by the questionnaire, without medical evaluation	Prevalence of white fingers: 13.4% (hand/arm vibration); 8.4% (controls). Higher odds ratio: intense vibration categories and workers in the North
Bovenzi[14]	Criterion 1: reliable history (images of RP*). Criterion 2 (more restrictive): history of "white fingers" and cold provocation test	Prevalence of RP*: Criterion 1: 21.7% (vibration) and 7.3% (controls). Criterion 2: 10.8% (vibration) and 0.7% (controls)
Bovenzi[15]	Physical examination; RP* related to occupation if provoked by cold and first episode after the beginning of occupational exposure	Prevalence of RP* related to vibration (beginning of the study): 26.6%; 11 new cases during the follow-up; cumulative incidence: 11.7%
Bovenzi[16]	Physical examination; RP* related to occupation if provoked by cold and first episode after the beginning of occupational exposure	Prevalence of RP* related to vibration (beginning of the study): 18.1% (forest workers:14.8%; quarry workers:36.4%). Incidence:1.7% (3 cases)
Bovenzi[17]	Physical examination; RP* related to occupation if provoked by cold and first episode after the beginning of occupational exposure	Daily vibration: higher in group A (4.7 m / s2) than in group B (3.9 m / s2); no significant difference (RP*) between furniture sander and controls
Futatsuka[18]	Subjective complaints assessed by interview. Peripheral circulation and neurosensory tests	No workers suffering from "white fingers". Hypoaesthesia, weakness, and coldness in fingers/hands: significantly higher in the drill operators
Barregard[19]	Diagnosis based on the history of well-marked pallor episodes on the fingers or parts of the fingers (induced by cold)	Estimated prevalence of RP* related to vibration: approximately 15% among car mechanics
Allen[20]	Questionnaire: medical and occupational history. Vasospasm: provocative test (cold) and systolic pressure of the finger	Riveters (6.3%) and claimants (83.5%) reported RP* symptoms. Positive test for vasospasm (finger cooling): riveters (30.4%); claimants (19%)
Palmer[21]	Questionnaire considering well-marked alterations of finger coloration caused by cold conditions	Pallor of the fingers (history): 14.2%. Cold-induced: 11.8%. Clear demarcation: 4.6%. Time of exposure (vibration): associated with symptoms
Aiba[22]	Questionnaire: medical and occupational history. Doctor asked about RP*related factors (images of RP*)	Prevalence of RP* related to vibration: 1.7% (1982), 4.86% (1986), disappearing in 1994. During the period: preventive measures introduced
Palmer[23]	Interview with doctor or nurse, questionnaire, physical examination, and hand immersion test in cold water (2-8oC for 4 minutes)	Prevalence of pallor of the fingers: 24%. Risk increased significantly with the hours of use of vibratory tools and the level of vibration
Bovenzi[24]	Diagnosis: positive history for pallor episodes involving at least 1 finger and occurring after exposure to localized upper limb vibration	Prevalence of RP*: 17.2% among workers exposed to vibration, ranging from 9.0% among grinders to 51.6% among foundry workers
Miyashita[25]	Medical evaluation records	Prevalence of workers who complained of "white fingers" induced by vibration: 25.9% (1978), 25.7% (1988) and 15.1% (1996)

RP* = Raynaud phenomenon

prevalence of subjective symptoms of Raynaud's phenomenon was found in 43.2% of them during the winter (temperature of 5.5°C on average) and only in 7.2% during the summer (temperature of 24.4°C on average). A Swedish study[13] in which the contrast of the cold environment was made by choosing a northern and a southern region of the country, suggested that the factors mainly related to the Raynaud's phenomenon were the two most intense categories of exposure to vibration in workers living farther north (colder weather) compared to the south.

Regarding the manifestations of hand-arm vibration syndrome, it is known that neurosensory alterations and vasospastic disease can coexist or progress independently[5]. A Japanese study[18] evaluating quarry workers (drill operators) from southern Vietnam did not identify cases of Raynaud's phenomenon. However, the prevalence of peripheral neurologic symptoms such as hypoaesthesia and weakness of the hands were significantly higher among the drill operators than in the controls. The hypothesis raised by the authors is that cold is an essential factor to trigger vascular manifestations of hand-arm vibration syndrome, and the workers evaluated did not develop them because they remained in environments with temperatures higher than 25°C throughout the year. In this way, the authors of this study suggest that, in a tropical environment, workers exposed to high levels of vibration could develop a dominant neurosensory form of hand-arm vibration syndrome, reinforcing the theory that circulatory and neuropathic symptoms may be independent[18].

Another issue that deserves attention when evaluating the results of the studies included in this review refers to the methodological limitations of certain forms of research. Some studies only used information obtained through questionnaires to define the presence of Raynaud's phenomenon related to vibration[8,9,12,13]. However, the self-reported symptoms alone may not be sufficiently specific to assess whether Raynaud's phenomenon is primary or secondary, and as a result, there may have been incorrect classification in some cases. Likewise, the quantification of the duration of exposure to hands and arms vibration is not an easy task and is subject to recall biases when estimated through questionnaires or even by direct interview[9].

Questionnaire responses about symptoms suggestive of Raynaud's phenomenon may be influenced by the context in which they are obtained. An Irish study[20] comparing riveters to a group of claimants for vibration-related injury showed that 6.3% of riveters and 83.5% of claimants reported symptoms of Raynaud's phenomenon. However, 30.4% of the riveters and only 19% of the claimants had a positive test for vasospasm after cooling the finger at 10°C for 5 minutes. The authors argued that only the lack of sensitivity and specificity of the cold provocation test would not explain the large discrepancy between the riveters and the claimants[20]. Thus, some contexts could underestimate, and others overestimate the symptoms.

In order to reduce the prevalence of Raynaud's phenomenon by localized upper limb vibration, measures such as limiting working hours with vibrating tools, using anti-vibration technology, and maintaining the working environment warm are performed[22]. In a Japanese study, technical improvements in tool motors with the introduction of anti-vibration mechanisms dramatically reduced the vibration transmitted to the hands of workers using impact wrenches[22]. In this study, the prevalence of Raynaud's phenomenon among workers was 4.86% in 1986 and gradually declined until disappearing in 1994. During this period, impact wrenches with anti-vibration mechanisms and measures to regulate the environment and protect workers from the cold were introduced (curtains to protect against outside cold, hand washing with warm water and impact wrench with heated handle)[22].

Articles exploring vinyl chloride as an occupational risk factor for Raynaud's phenomenon were not found in our search. This fact is probably due to two reasons. The first to be considered is that vinyl chloride disease is a rare event, and most of the studies are case reports or cases series, which were not considered in our search strategy. The second, and possibly even more important, is related to the fact that our electronic search was restricted to the last 20 years. Since 1979, vinyl chloride has been classified as carcinogenic to humans[7], and industries have made interventions to reduce the concentration of this substance in occupational air drastically. This allowed "vinyl chloride disease" to have only a historical significance today.

CONCLUSION

Localized vibrations of the upper limbs, low temperatures, and vinyl chloride are considered occupational risk factors for the development of Raynaud's phenomenon. There is a higher prevalence of Raynaud's phenomenon among vibratory tool operators compared to non-exposed workers. The higher the level of vibration and the time of exposure to it, the greater the risk of developing the disease. Cold is a triggering and aggravating factor of Raynaud's phenomenon and plays an important role in the onset of vascular manifestations of hand-arm vibration syndrome. The reduction of the time

using vibrating tools, the acquisition of equipment with anti-vibration technology, and the adoption of measures to protect workers from the cold environment should be considered to reduce the prevalence of work-related Raynaud's phenomenon.

Contributions by the authors

Author's contributions: RAC: conception, data acquisition, and manuscript writing.

RMA: conception, data acquisition, and manuscript writing.

Acknowledgements: Not applicable.

RESUMO

OBJETIVO: *Realizar um estudo de revisão dos artigos que avaliaram a prevalência do fenômeno de Raynaud de origem ocupacional.*

MÉTODOS: *A busca pelos artigos foi realizada nas bases de dados Medline (via PubMed), Embase, Web of Science, Scientific Eletronic Library Online (SciELO) e Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs).*

RESULTADOS: *Sessenta e quatro artigos foram obtidos a partir da busca eletrônica, dos quais 18 cumpriram os critérios de elegibilidade. Todos os estudos discutiram sobre a exposição a vibrações localizadas em membros superiores. Em seis deles, a questão térmica foi direta ou indiretamente abordada. Nenhum estudo abordou a exposição ao cloreto de vinila.*

CONCLUSÃO: *De maneira geral, constatou-se maior prevalência do fenômeno de Raynaud entre operadores de ferramentas vibratórias em comparação aos não expostos, com aumento do número de casos quanto maior o nível de vibração e tempo de exposição. O frio é fator desencadeante e agravante do fenômeno de Raynaud e parece exercer papel importante para o surgimento das manifestações vasculares da síndrome de vibração de mãos e braços.*

PALAVRAS-CHAVE: *Doença de Raynaud. Doenças vasculares periféricas. Vibração. Cloreto de vinil. Temperatura baixa.*

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REVIEW ARTICLE

Viability of mobile applications for remote support of radiotherapy patients

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http://dx.doi.org/10.1590/1806-9282.65.10.1321

SUMMARY

BACKGROUND: *Technological advances of the 21st century have provided greater communication, regardless of socioeconomic class and age group. Actions to promote the development of health applications are emerging around the world.*

OBJECTIVE: *To provide a perspective on the viability and usability of mobile applications dedicated to radiotherapy patients for remote support to health professionals proposing solutions to encourage Brasil in the development of these digital tools.*

METHODS: *Cross-sectional exploratory study by systematic review and literature review. We searched the PubMed, BVS, IBGE, and WHO databases, from 2014 to 2018.*

RESULTS: *6 articles were found with topics related to the use of mobile applications in the health area, two of which were published in Portuguese and four in the English, on oncology, from 2014 to 2018.*

CONCLUSIONS: *We did not find an expressive number of works on this subject in Brasil. Mobile applications have the potential to assist in the remote support of radiotherapy patients. The latest studies suggest the need for a regulation of data protection protocols to be deployed.*

KEYWORDS: *Telemedicine. Mobile Applications. Radiotherapy. Oncology.*

INTRODUCTION

Technological advancements in the 21st century have provided greater communication among all, often regardless of socioeconomic status and age. In this sense, new horizons for health through mobile technologies have been highlighted by the World Health Organization (WHO) who, in 2011, published a book with the definition of the term *mHealth*: mobile health or mobile health as medical and public health practice supported by mobile devices, such as phones, devices for monitoring patients, personal digital assistants (PDAs), and other wireless devices[1]. More recently, in 2018, the WHO published a classification of digital interventions in health in order to categorize the different ways in which digital and mobile technologies are being used to support the needs of the health system[2]. Proposals for and practical experiences with the use of smartphone or tablet applications with dedicated resources to healthcare professionals or patients have

DATE OF SUBMISSION: 15-Mar-2019
DATE OF ACCEPTANCE: 31-Mar-2019
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been described and encouraged by other health institutions worldwide. One example is the Department of Radiation Oncology of the Heidelberg University Hospital in Germany, who published, in 2018, a study on the feasibility of the use, by patients, of an application that contained the QLQ-C30 questionnaire of the European Organization for Research and Treatment of Cancer (EORTC) to evaluate health-related quality of life in oncological patients[3]. The assessment of the quality of life through the application was widely accepted by patients, and individuals were willing to use it in clinical routines, provided the privacy and security of data were guaranteed.

In a national context, the Brazilian Institute of Geography and Statistics (IBGE), through their Continuous National Household Sample Survey, found that 94% of the population 10 years of age or older, in rural and urban areas surveyed[4], have accessed the internet for sending or receiving text, or voice messages, or images using different e-mail applications. This suggests a fertile landscape for developing applications for mobile devices, such as smartphones and tablets, for the remote systematic support of oncologic patients who undergo radiotherapy treatment.

A recent review paper (2014) identified the research involving mobile technology applied to health in Brasil[5]. In this review, a total of 319 studies were found; after applying the exclusion criteria, 27 were included in the study. The topic most often discussed was professional support, and the area that benefited the most from it was multi-professional teams. The studies highlighted a gap in our country regarding the development of applications for patient support, which needs to be further explored. Finally, they have concluded that mobile applications may represent an important aid in adherence to treatment, emphasizing the importance of investing in this field of research[5]. None of the studies was targeted at radiotherapy patients.

OBJECTIVE

This work aims to offer a perspective on the feasibility and usability of smartphone and tablet applications targeted at oncologic patients for remote support of radiotherapy professionals. Through these, the radiotherapy team could acquire important data about the treatment from the patients themselves and, if possible, inform them about the possible symptoms and courses of treatment.

METHODS

This is a cross-sectional study of exploratory nature through the systematic review and analysis of the literature. We conducted searches in the PubMed, BVS, IBGE, and WHO databases using the English and Portuguese keywords: mhealth, mobile, health, oncology, radiotherapy, smartphones, *saúde, móvel, aplicativos, radioterapia, oncologia.* Six papers were selected in both languages, from 2014 to 2018, which served as the basis for the development and discussion of this study.

RESULTS

We found six articles with topics related to the use of mobile applications in the area of health; two Brazilians published in Portuguese, and four from other countries and published in English, of which the latter applied to oncology. All date from the period of 2014 to 2018. The summary of the results of these studies is presented in Table 1.

DISCUSSION

An indication of the importance and tendency of the development and evolution of digital tools applied to health can be perceived in the example by the WHO, who published, in 2018, a Digital Health Interventions Classification that categorizes the different ways in which digital and mobile technologies are being used to support the needs of the health system[2]. Actions to promote the development of applications are emerging around the world, such as the one by the United Nations Children's Fund (Unicef), who awarded the WHO in 2016 for the *OpenSRP* software.

A review article published in 2017 reported the existence of a relevant number of applications in a systematic search performed in 2015 on the Play Store (Android, Google) and App Store (iOS, Apple) platforms[7]. In general, the authors found around 195 applications, being: 19 to manage articles; 25 focused on the patient; 12 created by hospitals to organize meetings; 34 with topics not only in oncology; two for using the Aria software; 11 with learning techniques for students testing; 11 targeted at chemotherapy alone; 11 about Congress schedules; 31 tools for medical and multidisciplinary professional, and 39 others. This review article aimed to characterize and provide scientific support only to applications designed for professionals in radiology and oncology. In particular, we obtained

the following characteristics: goals, list of features, consistency in results, and usability. Lastly, those classified as dose calculators (seven applications), clinical calculators (four), titration tools (seven), polyvalent (7), and others (6). The authors found that the most recommended applications were not necessarily the most expensive, and highlighted three applications that contain wide content for radiology and oncology professionals: RadOnc Reference (in English), Easy Oncology (in German) and iOncoR (in Spanish).

Regarding applications targeted at the patient, recently, Kessel et al.[3] tested the usability by patients of an application for applying the QLQ-C30 questionnaire of the EORTC to assess health-related quality of life in oncological patients. The study involved 81 patients with a mean age of 55 years and found an average time of 4 minutes to complete the questionnaire on an iPad. 84% of patients (68/81) had a mobile device and preferred this version of the questionnaire to the traditional paper model.

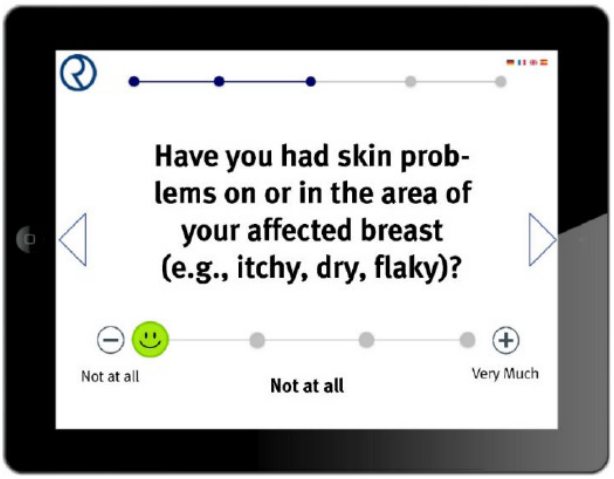
Another article also published in 2018 in the form of trial by the same institution of Kessel et al.[3] intends to prospectively evaluate the feasibility of using a mobile application to provide systematic support to oncology and radiology patients throughout the future course of their radiotherapy, with the specific objectives to monitor the patients' symptoms and facilitate the exchange of relevant information between patients and physicians. Finally, El Shafie et al.[8] intend to research the general performance, quality of life, and need to see a doctor in person of patients undergoing curative

TABLE 1. PUBLICATIONS ON THE USE OF MOBILE APPLICATIONS RELATED TO THE HEALTH SELECTED FOR ANALYSIS.

No.	Publication data		Main results
1	Title	Aplicativos móveis desenvolvidos para a área da saúde no Brasil: revisão integrativa da literatura	The final sample consisted of 27 papers. The topic most discussed was professional support. For future work, they suggest the development of apps to support the patient.
	Authors	Tibes CMS, Dias JD, Zem-Mascarenhas SH	
	Year	2014	
	Reference	5	
2	Title	Smartphone applications for cancer patients; what we know about them?	One hundred and sixty-six applications have been downloaded associated with oncologic patients: 75 for Android, 59 for iOS, and 32 on both platforms. There is limited evidence from studies that analyze the content of apps for patients with cancer.
	Authors	Collado-Borrell R, Escudero-Vilaplana V, Ribed-Sánchez A, Ibáñez-García S, Herranz-Alonso A, Sanjurjo-Sáez M	
	Year	2016	
	Reference	6	
3	Title	Apps for radiation oncology: a comprehensive review	A systematic search was performed on mobile platforms, iOS, and Android, and retrieved 157 apps. Excluding those whose purpose did not correspond to the scope of the study, 31 apps were methodically analyzed.
	Authors	Calero JJ, Oton LF, Oton CA	
	Year	2017	
	Reference	7	
4	Title	Mobile app delivery of the EORTC QLQ-C30 questionnaire to assess health-related quality of life in oncological patients: usability study	Eighty-one oncology patients with a mean age of 55 years took, on average, 4 minutes to complete the questionnaire on an iPad; 84% (68/81) of participants had a mobile device and preferred this version (mobile) of the questionnaire instead of the traditional paper template.
	Authors	Kessel KA, Vogel MM, Alles A, Dobiasch S, Fischer H, Combs SE	
	Year	2018	
	Reference	3	
5	Title	Oncologic therapy support via means of a dedicated mobile app (Optimise-1): protocol for a prospective pilot trial	The study will enroll 50 patients for a period of 12 months and will be completed after 18 months. The publication of results is expected 24 months after the beginning of the study and will serve as a basis for studies that aim to innovate in mobile apps for radiotherapy. Suggests regulation in relation to data security.
	Authors	El Shafie RA, Bougatf N, Sprave T, Weber D, Oetzel D, Machmer T, et al.	
	Year	2018	
	Reference	8	
6	Title	Aplicativos móveis para a saúde e o cuidado de idosos	They found 25 applications on three subjects: elderly health, elderly care, and information on elderly care and health. These apps aim at the practice of physical exercise, prevention or detection of falls, cognitive stimulation, search of professionals or services, and providing information on health, diseases, and treatments.
	Authors	Amorim DNP, Sampaio LVP, Carvalho GA, Vilaça KHC	
	Year	2018	
	Reference	9	

Source: Prepared by the authors (2019).

FIGURE 1. SCREEN CAPTURE OF THE OPTMIZE-1 APPLICATION FOR SUPPORT OF CANCER PATIENTS [5]



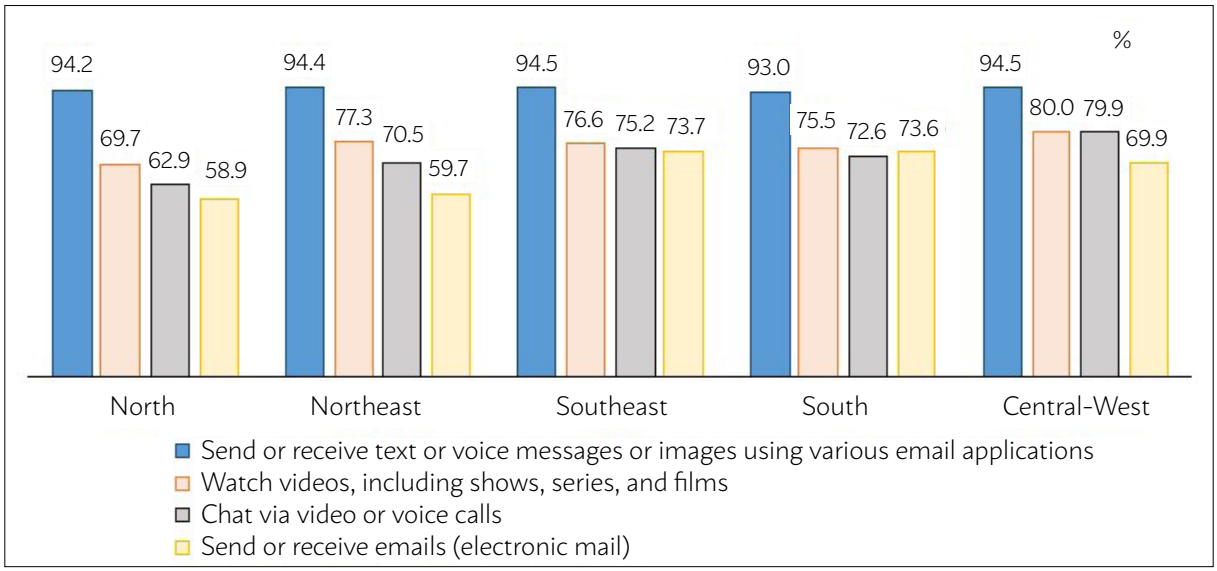
Source: Radiation and Oncology Department of the Heidelberg University Hospital in Germany (El Shafie et al, 2018) [5].

radiotherapy for thoracic or pelvic tumors, by means of a digital tool (Figure 1). The study will enroll 50 patients for a period of 12 months. The monitoring will be completed after 18 months, and the publication of results is expected 24 months after the beginning of the study. They conclude that the results will serve as a basis for future studies that aim to explore the constant innovation in mobile medical applications and integrate innovative concepts centered on the patient, in the context of radiotherapy. In addition, to prevent these applications from becoming a security issue rather than a useful tool for the patients, they suggest a regulation to be implemented[8].

It is a system that provides support to frontline health professionals to electronically register and monitor the health of patients/clients. Using mobile phones or tablets, the system frees health professionals from bureaucracy and helps ensure that each individual receives essential health interventions. Even though there is no study that demonstrates this practice in Brasil, the Continuous National Household Sample Survey (IBGE, 2016)[4] suggests potential for good acceptance, since it revealed that 94.2% of the population 10 years of age or older, in rural and urban areas surveyed, have accessed the internet for sending or receiving text, or voice messages, or images using different e-mail applications. This percentage remained above 92% even when the five regions of the country were evaluated separately (Figure 2).

In relation to the elderly population, even in Brasil, researchers reported, in 2014, what has been developed in scientific research in the country related to mobile applications for health and care of the elderly in the period from January 2006 to July 2013. After searching the databases chosen, they obtained 319 studies, of which 27 were selected for a detailed analysis. No theses were found, only articles (13), dissertations (seven) and course completion papers (seven), demonstrating a huge gap on the subject. All studies identified were classified

FIGURE 2. PERCENTAGE OF PEOPLE WHO HAVE ACCESSED THE INTERNET FOR EACH END, AMONG THE POPULATION 10 YEARS OLD OR OLDER WHO USED THE INTERNET DURING THE REFERENCE PERIOD OF THE LAST THREE MONTHS, PER GREAT REGIONS, ACCORDING TO THE PURPOSE OF THE INTERNET ACCESS - BRASIL - 4TH QUARTER OF 2016.



Source: IBGE, Research Department, Secretary of Work and Income, Continuous National Household Sample Survey.

with the evidence level 4, based on the categorization of the Agency for Healthcare Research and Quality (AHRQ), because they had a non-experimental design with descriptive, applied, or correlational research. They also found that smartphones are among the technological resources in which the elderly are interested due to the combination of computer features, internet connection, and use of applications. They consider there is a growing trend in the use of new technologies in the area of health and that the expansion of the use of smartphones among the elderly population grants mobile applications a remarkable potential for the area of aging. They also indicate that such applications can be used as a tool for monitoring, information, promotion of healthy habits, and prevention of diseases and disorders in the elderly. Finally, they highlight that, in spite of the benefits presented, these technological resources need further studies and investigations, because, in addition to technical knowledge, it is necessary to have theoretical knowledge to develop interfaces that meet the needs of the elderly, minimize barriers for technology access, and facilitate digital inclusion[5].

Thus, for the researchers in the Department of Oncology and Hematology-Oncology the University of Milan, in partnership with the European Institute of Oncology, Department of Pediatric Oncology and Hematology, Institute of Experimental Medicine (these last two in Germany), and the Computational Laboratory of Biomedicine in Heraklion, Greece, who published an article about the search for a common regulation for telemedicine and mHealth applications[10], the autonomous management in health by citizens is being made possible by innovations in information and communication technology that already affect the field of health and which also provide resources for professionals, improving the effectiveness of service delivery by hospitals. However, they indicate that the data protection law was introduced to bring uniformity among the European countries, but the guidelines shared for mHealth still need to be developed. They also noted that the development of new regulations is complex because there is a series of health-related ethical issues that must be properly addressed. They conclude that, in relation to applications, the European Commission published a document that evaluates some generic regulations for applications covered by the definition of a medical device, but the European legal framework is still not sufficiently adapted to the regulatory needs arising from mobile health[10].

In 2016, researchers from the pharmacy service of the University General Hospital Gregorio Marañón, of the city of Madrid, Spain, analyzed the characteristics of applications available on the App Store (iOS) and Google Play (Android) platforms targeted at cancer patients[6]. In this study, the objective was to evaluate the reliability of the information in terms of scientific evidence. Although the results have shown numerous benefits from the applications, they identified the lack of validity of information relating to the treatment, as well as outdated data, resulting even in therapeutic injury[6].

PROPOSALS FOR APPLICATIONS

Based on the WHO Classification of Interventions[2], we listed several solutions that could be provided by mobile applications for the remote support of radiotherapy patients. 1) Send alerts for health events targeted at specific groups of oncologic patients in treatment or already treated. 2) Provide information about the disease, diagnosis, progression, and treatment to patients based on the demographics of patients treated. 3) Send alerts and reminders of weekly consultations with physicians and multidisciplinary teams. 4) Send diagnostic results or availability of results. 5) Communication among patients via networking groups, coordinated by the institutional staff. 6) Access by patients to their own medical chart, technical characteristics, and schedule of radiotherapy treatment. 7) System of patient response to the institution. 8) Exploitation and guidance to reduce or limit the effects of radiation. Applications that can identify potential risks of a greater chance of radiation effects, compare changes between tissues irradiated or not, in addition to classifying and categorizing these changes may be of value to obtain great adherence of patients to radiotherapy treatment.

CONCLUSION

Mobile applications are important tools that can be developed, tested, and validated in our country with having great potential to support and digitally include health professionals and patients, in addition to allowing access to information, reducing bureaucracy, increasing patient safety, facilitating communication

between the parties involved (team/doctor/patient), and assisting in data acquisition for various studies. We have not found a significant number of studies in Brasil on this subject. It is necessary to recognize the needs of these users and test them in research so they can be implemented. Recent studies suggest the need for regulations of protocols that protect data transmitted to prevent these applications from becoming a security issue, rather than a useful tool for professionals and patients.

RESUMO

INTRODUÇÃO: *O avanço tecnológico no século XXI tem proporcionado maior comunicação entre todos, independentemente da classe socioeconômica e da faixa etária. Ações de fomento ao desenvolvimento de aplicativos para a área da saúde estão surgindo ao redor do mundo.*

OBJETIVO: *Oferecer uma perspectiva sobre a viabilidade e usabilidade dos aplicativos móveis dedicados aos pacientes radioterápicos para suporte remoto aos profissionais da saúde propondo soluções a fim de incentivar, no Brasil, o desenvolvimento dessas ferramentas digitais.*

MÉTODOS: *Estudo transversal de caráter exploratório por revisão sistemática e análise da literatura. Foram utilizadas buscas nas bases de dados: PubMed, BVS, IBGE, OMS, por publicações citadas de 2014 a 2018.*

RESULTADOS: *Foram encontrados cinco artigos com temas relacionados ao uso de aplicativos móveis na área da saúde, sendo dois nacionais, publicados em língua portuguesa, e três internacionais, no idioma inglês, dos quais esses últimos aplicados à oncologia no período de 2014 a 2018.*

CONCLUSÕES: *Não foi encontrado um número expressivo de trabalhos com este tema no Brasil. Aplicativos móveis têm potencial para ajudar no suporte remoto de pacientes radioterápicos. Os últimos estudos sugerem a necessidade de uma regulamentação de protocolos de proteção de dados transmitidos a ser implantada.*

PALAVRAS-CHAVE: *Telemedicina. Aplicativos móveis. Radioterapia. Oncologia médica.*

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