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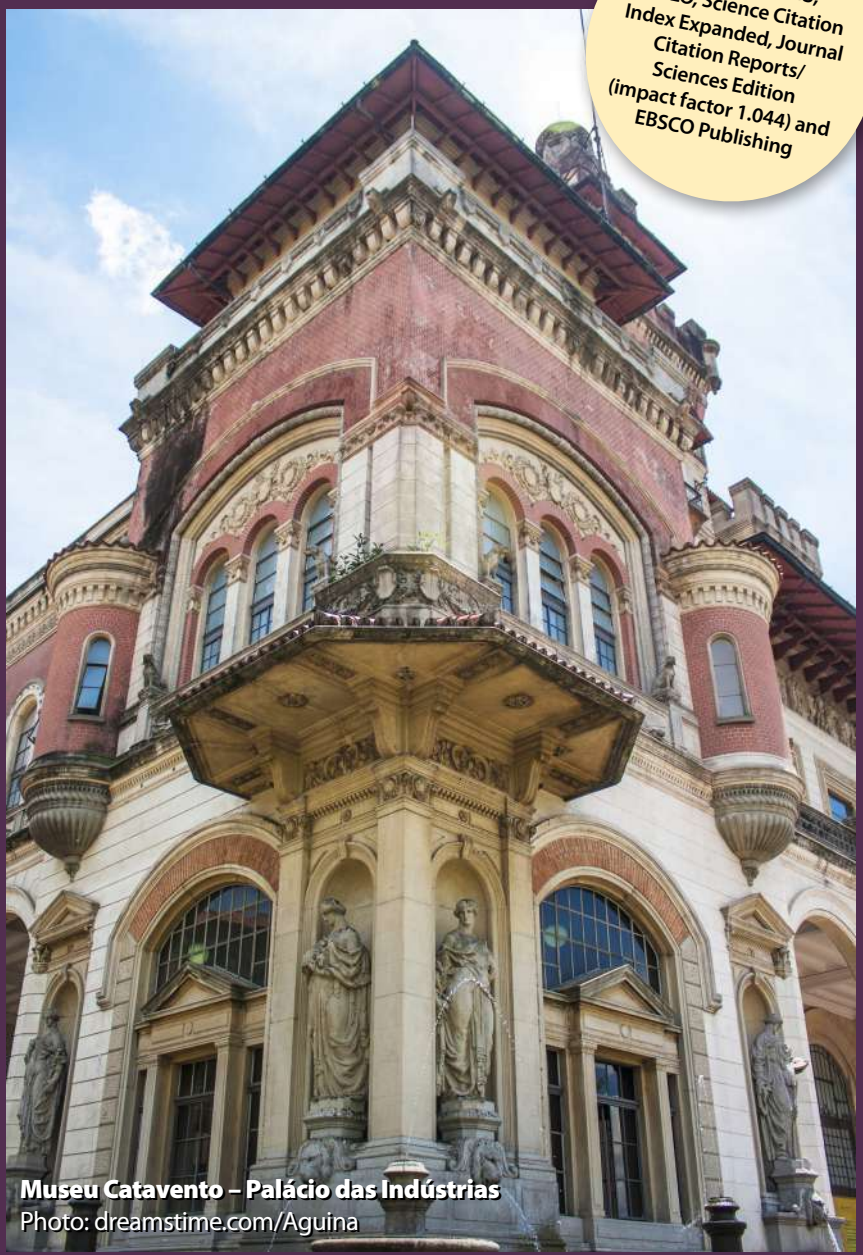

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The impact of COVID-19 on the development and consolidation of telemedicine

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The pandemic caused by coronavirus 19 (COVID-19) has given rise to a series of unprecedented challenges to various healthcare systems around the world.[1] The solutions that have been found for many of these challenges may become definitive in certain scenarios. One very significant example of this is telemedicine, which has been defined by Maldonado et al.[2] as: "use of information and communication technologies within healthcare to enable provision of healthcare-related services (expansion of attendance and coverage), especially in cases in which distance is a critical factor."

Telemedicine particularly encompasses the following concepts:

- Teleconsultation: a form of attendance in which the doctor and the patient are in different places, done by means of audio or video equipment in which exchanges of information take place in real time. The biggest challenges regarding this are the lack of physical examination and problems relating to privacy.
- Telediagnosis: this consists of remote access to a given examination and issuing of reports on this, activated by a doctor at a distance. This is much used today within radiology. The main challenge is technical, especially because of the need for a broadband connection due to the large size of the files.
- Teleinterconsultation: exchange of information between professionals, at a distance. This is much used when an opinion from a certain specialist is desired. It may take place during a consultation in which a generalist is present with the patient and the specialist is at a distance. The main challenge regarding this relates to the privacy of information.
- Telesurgery: operations conducted by robotic equipment that is commanded remotely by a surgeon. In the past, the American government took interest in this for military use. The biggest challenges relate to the cost of the robotic equipment and to guaranteeing a stable connection. Because of these technical restrictions, its use is still practically entirely experimental.
- Teletriage: this consists of brief assessment of patients' complaints through a telephone call, with referral for attendance when necessary.
- Telemonitoring: this refers to remote follow-up of patients' state of health. It takes place through analysis on data and images from equipment used by the patient.

In Brazil, telemedicine was regulated by the Federal Medical Council (Conselho Federal de Medicina, CFM) in 2002, through resolution no. 1643. However, this resolution did not bring complete definition or detailing of a variety of points relating to this topic. Consequently, a second resolution that would adapt and permit implementation of this form of medical attendance was published in 2018. However, because of a large number of controversial issues, the 2018 resolution from the CFM was revoked in 2019.[3]

The COVID-19 pandemic then brought about a major change in Brazil. On April 15, 2020, law no. 13,989 was published in the Federal Official Gazette (Diário Oficial da União). Article 1 of this law states: "This law authorizes the use of telemedicine for as long as the crisis caused by coronavirus (SARS-CoV-2) continues." From this time onwards, doctors and health-related companies started to implement a variety of aspects of telemedicine, especially with regard to teleconsultation.

The real impact of this measure, as well as its duration, remains to be defined. Nonetheless, on the basis of articles that have recently been published, the impression given is that telemedicine is here to stay, both in Brazil and worldwide.

Researchers at Duke University[4] analyzed the adoption of telemedicine by different specialties in three different periods: before the pandemic, at the peak of the pandemic and after the reduction in the number of cases. The rate of adoption of telemedicine varied greatly among specialties: 3.2% for dermatology (the lowest) to 98.3% for psychiatry (the highest). In addition, differences regarding the profile of users were seen: Afro-American and male patients were less likely to use telemedicine than were white and female patients. The analysis on the three periods showed that the phase of the pandemic with the highest number of cases was the time when telemedicine was most used.

Chu et al.[5] analyzed data on adoption of telemedicine before and during the pandemic, comparing rural and urban areas of Ontario. Before the pandemic, the use of teleconsultation was consistently low in both populations: 11 attendances per 1,000 rural patients versus 7 attendances per 1,000 urban patients (December 2019). During the pandemic (June 2020), there were increases in the use of telemedicine in both populations, but growth was higher in the urban area, to 220 visits per 1,000, versus 147 visits per 1,000 in the rural area. In relation to sex, 54.6% of the users were female, versus 45.4% who were male. These authors came to the conclusion that different strategies for promoting telemedicine might be necessary for populations living in different areas.

In relation to different specialties, a profusion of articles has been published, analyzing specific matters such as adaptation of telemedicine for use in different fields like dermatology,[6] neurosurgery,[7] cardiology[8] and allergology,[9] among others. Almost all of them come to similar conclusions: that telemedicine has become an important tool during the period of the pandemic and that its development should continue after the pandemic.

Nittari et al.[10] published a review on the ethical aspects of telemedicine. Through analysis on a diversity of articles, they concluded that the main ethical concerns were the following: data privacy; the need to guarantee that the equipment is in good working order; the ever-faster obsolescence of technology; the need for professionals to have adequate training for attending patients in a virtual environment; and the lack of legal regulation that exists in most countries. Lastly, these authors concluded that if these concerns failed to be correctly addressed, a boomerang effect might be seen: after an exponential increase in the use of telemedicine due to the current situation of the pandemic, there would then be rapid regression afterwards.

Nine years have passed by since we last wrote an editorial on this subject.[11] Since then, technology has advanced in an extraordinary manner. Nonetheless, it is certain that nothing has pushed forward the adoption of telemedicine more than the situation of the COVID-19 pandemic. We believe that this form of medical attendance is here to stay, but that it is still too early to predict what the definitive position of telemedicine will be after the COVID-19 pandemic.

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Evaluation of anti-COVID-19 measures taken by the parents of children with celiac disease: a cross-sectional study

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Prevention.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) causes negative life changes brought about through lockdowns, in addition to severe complications and death. Among these changes, asplenism or hyposplenism has been reported in patients with celiac disease. It has been reported that the risk of pneumococcal sepsis is higher in celiac patients with hyposplenism. Moreover, celiac patients present high risk of admission to hospital due to influenza.

OBJECTIVE: To determine the degree of awareness of COVID-19 among parents of children with celiac disease and examine the measures that they take.

DESIGN AND SETTING: Cross-sectional study at a university hospital in the Middle Anatolian region of Turkey.

METHODS: The diagnosis of celiac disease was confirmed through a survey conducted online among 73 parents between May and July 2020.

RESULTS: The mean age was 37.57 ± 6.56 years for the mothers, 41.15 ± 5.56 years for the fathers and 11.36 ± 4.36 years for the children. 90.4% of the parents reported that COVID-19 was transmitted through "speaking, coughing, sneezing and infection of the face after contact with virus-infected surfaces". Moreover, 78.1% indicated that they did not have any difficulty in finding gluten-free foods.

CONCLUSION: These parents of children with celiac disease believed that their children's risk of developing COVID-19 did not differ from that of healthy children. It was also observed that appetite and states of nervousness were higher among these children with celiac disease during lockdowns and that their sleep patterns were affected.

INTRODUCTION

Coronavirus disease (COVID-19) first emerged in the city of Wuhan, China, in December 2019 and has spread all over the world. Its causative factor is a ribonucleic acid (RNA) virus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which is similar to SARS-CoV.[1,2]

Although the mortality rate for COVID-19 ranges between 1.4 and 7.2%, the rates have been found to be higher among individuals who have underlying comorbid diseases.[1,2]While COVID-19 has primarily been characterized by the respiratory impact of viral pneumonia, it affects multiple organ systems with significant morbidity and mortality among critically ill patients.[3]

Coronavirus disease 2019 (COVID-19) is seen in all age groups. Its clinical course and prognosis are relatively mild in children, compared with adults. It may result in mortality among adults, especially those who have underlying comorbid disease such as diabetes and cancer.[4,5] All countries have taken serious measures in line with the recommendations of the World Health Organization (WHO), including lockdowns,social distancing, hand hygiene, mask use and limitations of hospital visits in order to prevent the spread of this disease. There is no clear evidence regarding how lockdowns affect quality of life, especially among children and individuals with chronic diseases.[1,6]

The World Health Organization has reported that the coronavirus causing COVID-19 is transmitted through droplets and by touching one's mouth, nose or conjunctiva after touching virus-contaminated surfaces. Moreover, it can be transmitted on objects that have been used by an infected person.[1,7] For working individuals, it is important to regularly clean the working environment and the keyboards, tables and telephones that are used in the workplace.[1]

Celiac disease is an autoimmune enteropathy caused by the immune reaction that is developed through gluten intake among individuals who have a genetic predisposition to this. The treatment for celiac disease consists of a lifelong gluten-free diet.[8,9] Since celiac patients may have difficulty in finding gluten-free foods during lockdownperiods, asking for support from self-care agencies is recommended.[10]

The Celiac Disease Foundation has proposed that, in the present pandemic situation, individuals with celiac disease should maintain stocks of gluten-free foods and should make gluten-free meal plans and train themselves to use new gluten-free recipes. Moreover, this foundation has underlined the need for celiac patients to stay away from crowds and to stay at home, in order to minimize their exposure to the virus.[11] Defective spleen function is frequently seen in autoimmune gastrointestinal diseases such as celiac disease. As it is well known that celiac patients are at high risk of developing sepsis with encapsulated bacteria, pneumococcal vaccination is recommended.[9,12]Asplenism or hyposplenism has been also reported in celiac patients, along with gastrointestinal symptoms. It has also been reported that the risk of pneumococcal sepsis is higher in celiac patients with hyposplenism.[13]Mårild et al. reported that celiac patients were at higher risk of hospital admissions due to influenza. Celiac patients experience anxiety and depression due to the increased risk of infection.[14] Moreover, lockdown conditions and limitations during the pandemic, along with fear of the difficulties that may be experienced in trying to find gluten-free foods, increase anxiety.

Celiac disease is a chronic disease that has leads to the risk of sepsis and hospitalizations due to influenza, and the risk of pneumococcal sepsis due to hyposplenism that patients may experience. For this reason, patients with celiac disease need to be more careful in terms of the precautions to be taken in preventing COVID-19, which is known to cause severe complications. Since the daily life requirements of children with celiac disease will be controlled by their parents, the measures taken by parents for their children were evaluated in this study.

OBJECTIVE

This study was carried out to determine the degree of awareness of COVID-19 among the parents of children with celiac disease and the measures that they take.

METHODS

This was a cross-sectional study that was conducted among the parents of patients aged 4-18 years who had been diagnosed with celiac disease in the pediatric gastroenterology outpatient clinic of a health sciences university in Afyonkarahisar, Turkey. The diagnosis of celiac disease was made based on serological tests to detect immunoglobulin A (IgA)-tissue transglutaminase IgA (tTGA) and/or immunoglobulin G (IgG)-tissue transglutaminase IgG (tTGG); and on and histological examination of small-intestine mucosal biopsies. Data for this study were collected by means of a questionnaire, which was generated online and could be completed within 10 minutes, between May 2020 and July 2020.

We arbitrarily decided to include the parents of patients with celiac disease who were undergoing regular follow-up at the study hospital. We included the mothers or fathers of children in the 0-18 age group with celiac disease. We collected data using a semi-structured questionnaire (this questionnaire is presented in the **Appendix**). The questionnaire was created based on up-to-date information from the literature. The parents who agreed to participate in the study were asked to fill out a demographic information form consisting of 17 questions and an information form relating to COVID-19 infection that included 34 questions. Although our aim was to reach a total of 150 parents, only 73 parents who agreed to participate and who were contacted through the internet were included in the study.

The data obtained were assessed by means of descriptive statistics (arithmetic mean, median, standard deviation and percentage distribution). Means were compared between groups and the compliance of the data with normal distribution was analyzed using the Shapiro-Wilk test. An independent-sample t test was used for parametric data and the Mann-Whitney U test was used for nonparametric data. The chi-square test was used to compare percentage distributions of categorical variables between groups. The analyses on the data were conducted using the IBM SPSS Statistics™ software, version 20.0 (IBM Corporation, Armonk, NY). The results were analyzed within a 95% confidence interval and $P < 0.05$ was considered to be statistically significant.

Approval for this study was obtained from the clinical research ethics committee of the local medical school (5.5.20/ 2011-KAEK-2/2020/186). All the participants in this study gave written consent for their inclusion.

RESULTS

Among the parents included in the study, 42 (57.5%) were mothers and 31 (42.4%) were fathers. Out of the children with celiac disease, 45 (61.6%) were females and 28 (38.4%) were males and their mean age was 11.36 ± 4.36 years. In terms of age group, 22 (30.1%) were 4-8 years, 21 (28.8%) were 9-12 years and 30 (41.1%) were 13-18 years. The children's ages at diagnosis were found to be 1-4 years in 48 cases (65.8%), 5-8 years in 23 cases (31.5%) and 9-11 years in two cases (2.7%). The patients' mean height was 139.97 centimeters (range, 100-168 centimeters) and their mean weight was 35.7 kilograms (range, 13-70 kilograms). Within the last month, 15 patients (20.5%) had had a weight gain of less than one kilogram, 17 patients (23.3%) had not had any weight change, 39 patients (53.4%) had had a weight gain of more than one kilogram and two patients (2.7%) had had a weight loss of more than one kilogram.

Among the families, 24 (32.9%) were living in a village, 14 (19.2%) were living in a town and 35 (47.9%) were living in a city center. Sixty-seven families (91.8%) were nuclear families and 6 (8.2%) were extended families. Among all the families participating in this study, four (5.5%) had one child, 28 (38.4%) had two

children, 30 (41.1%) had three children and 11 (15.1%) had four or more children. Fifty-two families (71.2%) had health insurance and 21 (28.8%) did not. Thirty-four families (46.6%) indicated that they had experienced a loss of income during this pandemic period. The parents' education levels and employment statuses are shown in **Table 1**.

In response to the question "Do you think that your child has a greater risk of developing coronavirus disease (COVID-19) compared with other children?", 53.4% of the parents answered "yes" and 46.6% answered "no". No statistically significant difference was found between the mothers and fathers (P = 0.46).

The parents' answers to the question "How is COVID-19 transmitted?" were "coughing" (2; 2.7%), "transmission after contact with virus-contaminated surfaces" (5; 6.8%) and "speaking, coughing, sneezing and contamination of the face after contact with virus-contaminated surfaces" (66; 90.4%).

"How should your child behave while coughing or sneezing?" was answered as "use the area inside the elbow while sneezing" by 75.3%, "use a napkin or handkerchief if available" by 23.3% and "use the back of the hand" by 1.4% of the parents.

19.2% of the individuals participating in the survey were found to have pets in their homes. They answered the question "Is coronavirus disease (COVID-19) transmitted from pets?" as "yes" by 37% and "no" by 63%.

The question "Which of the following precautions is effective in preventing transmission of coronavirus disease (COVID-19)?" was responded as "washing hands frequently with soap and water" by 17.8%, "staying away from people showing flu-like symptoms" by 1.4% and "washing hands frequently with soap and water, cleaning hands with alcohol-based disinfectants, avoiding face-to-face contact and staying away from people showing flu-like symptoms" by 80.8%.

The question "Which age groups are affected by coronavirus disease (COVID-19)?" was answered as "over 65 years old" by 23.3%, "20-65 years old" by 6.8% and "all age groups" by 69.9%. "Is the spread of coronavirus disease (COVID-19) affected by air temperature change?" was answered as "yes" by 93.4% and as "no" by 6.6% of the participants.

Table 1. Sociodemographic characteristics of the parents

Education level	Mother (n = 42)	Father (n = 31)
Literate/elementary school	22 (52.3%)	5 (16.1%)
Secondary school/high school	14 (33.3%)	21 (67.7%)
University/higher	6 (14.2%)	5 (16.1%)
Employment status of parents		
Office employee	9 (21.4%)	10 (32.2%)
Other employees	14 (33.3%)	11 (35.4%)
Self-employed	10 (23.8%)	1 (3.2%)
Retired	1 (2.3%)	3 (9.6%)
Unemployed	7 (16.6%)	6 (19.2%)

"What is the minimum alcohol content (%) that disinfectants need to have in order to kill the viral factor that causes coronavirus disease (COVID-19)?" was answered as "disinfectants containing at least 70% alcohol" by 72.6%.

"Is there a specific medication to treat coronavirus disease (COVID-19)?" was answered as "no" by 89% of the participants.

The question "For at least how long should hands be washed in order to kill the viral factor that causes coronavirus disease (COVID-19)?" was answered as "20 seconds" by 94.5%.

"What do you use to clean common areas in your home (tables, stairs, door handles, light switches, counters, toilets, taps and sinks) in order to prevent transmission of coronavirus disease (COVID-19)?" was answered as "bleach" by 57.5%, "disinfectants containing 70% alcohol" by 19.2% and "vinegar" by 23.3%.

"What have you been using to clean electronic devices in your home during the coronavirus disease (COVID-19) pandemic?" was answered as "1/100 diluted bleach" by 24.7%, disinfectants containing 70% alcohol" by 23.3%, "spray containing alcohol" by 13.7% and "vinegar" by 38.4%.

The question "What have you been using to clean places such as the toilet and bathroom in your home during the coronavirus disease (COVID-19) pandemic?" was answered as "1/100 diluted bleach" by 97.3% and "disinfectant containing 70% alcohol" by 2.7%.

The question "Have you been going out from your home for any reasons other than your urgent needs or for work during the coronavirus disease (COVID-19) pandemic?" was answered as "no" by 50.7% of the participants.

"Have you been allowing your child to go out from your home during the coronavirus disease (COVID-19) pandemic?" was answered as "no" by 78.1% of the parents included in the study.

"From where do you mostly get news about the coronavirus disease (COVID-19) pandemic?" was answered as "television" by 68.5, "internet" by 30.1% and "I do not follow the news" by 1.1%.

The question "Do you clean materials bought or brought from outside before using them, because of the coronavirus disease (COVID-19) pandemic?" was answered as "yes" by 95.9%.

"Have you been paying attention to social distancing rules during interactions with individuals outside your home during the coronavirus disease (COVID-19) pandemic?" was answered as "yes" by 98.6%.

"Have you been using a mask while going out during the coronavirus disease (COVID-19) pandemic?" was answered as "yes" by 98.6% of the parents. No relationship could be found between the education levels of the parents and their responses (P > 0.46).

"What should be the social distance in order to prevent transmission of coronavirus disease (COVID-19)?" was answered as "1-2 meters" by 97.3%.

"Have you been having any problems in finding foods for your child (gluten-free foods) during the coronavirus disease

(COVID-19) pandemic?" was answered as "no" by 78.1% of the parents and "yes" by 29.9%.

"Do you believe that it is important to pay attention to your children's diet in order to strengthen their immune systems and protect them from coronavirus disease (COVID-19)?" was answered as "yes" by all of the parents.

In relation to the question "Have you been giving vitamin-mineral supplementation to your children during the coronavirus disease (COVID-19) pandemic?", 26 individuals (35.6%) said that they were not giving any vitamin-mineral supplementation to their children. Administration of propolis was reported by 16 participants (21%), vitamin C by 20 (27.3%), fish oil by 2 (2.7%) and iron by two (2.7%). Moreover, five (6.8%) reported giving their children both propolis and fish oil, one (1.3%) reported giving both carob extract and vitamin C and one (1.3%) reported giving propolis, vitamin C and vitamin D.

In the question "Which foods do you consider to be good for the immune system?", the responses were the following: garlic (stated by 79.4% of the parents), kefir (a fermented milk drink) (60.2%), oranges/kiwi fruit (57.5%), spinach (56.16%), oily fish (52%), broccoli (49.3%), pickles (47.9%), ginger (45.2%), turmeric(34.2%), red peppers(26%), green tea (17.8%), blueberries(15.1%), potatoes(10.9%) and bitter chocolate (6.8%).

"Which of the following symptoms increased in your child with the closure of schools due to coronavirus disease (COVID-19)?" was answered as "no complaint" by 42 (57.5%), "state of nervousness" by 24.6%, "increase in appetite" by 13.6%, "lack of appetite" by 8.21%, "headache" by 6.84%, "stomach ache" by 4.1%, "increase in hair loss" by 2.73%, "allergic skin rash" by 2.73%, "having nightmares and scary dreams" by 1.36%, "nausea" by 1.36% and "constipation" by 1.36%. There were no mentions of abdominal distension, diarrhea or vomiting complaints in the answers.

"Has your child had any sickness requiring medication (like antibiotics), such as flu, cold or urinary tract infection, in the past month?" was answered as "no" by 94.5%.

"Has your child's sleep pattern and quality changed in the past month?" was answered as "increase in sleep duration" by 8.2% of the parents, "decrease in sleep duration" by 6.8%, "change in sleep pattern" by 43.8% and "no effect on sleep pattern" by 41.1%.

Among the answers given by the parents to the questions regarding COVID-19, a statistically significant difference was found only in relation to their preference for mask use, and this is shown in **Table 2**. The parents stated that they had not had their children vaccinated against the flu or pneumococcus in the last year.

The details of the survey questionnaire and survey responses are shown in the **Appendix**.

DISCUSSION

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and it has become a global health crisis through spreading all over the world very quickly. Pediatric patients have constituted 1-5% of the patients diagnosed with COVID-19. All countries have taken serious measures, most notably consisting of lockdowns, in order to prevent the spread of this disease.[15,16]

This study is the first in the literature to evaluate the measures taken by the parents of children with celiac disease with regard to COVID-19 infection. 90.4% of the parents stated that COVID-19 disease was transmitted through "speaking, coughing, sneezing and face contamination after contact with virus-contaminated surfaces". Pal et al. reported that 83% of the young adults with type 1 diabetes mellitus who they surveyed thought that COVID-19 disease was transmitted through droplets.[17]

Fifty-nine parents (80.8%) indicated that "washing hands frequently with soap and water, cleaning the hands with alcohol-based disinfectants, avoiding face contact and staying away from people with flu-like symptoms" were important for prevention of transmission of COVID-19. Moreover, washing hands "for 20 seconds" was reported to be important by 94.5% of them. In the study by Pal et al., 53% of the participants stated that staying at home, ensuring that they paid attention to social distancing and doing regular hand washing were important for prevention of transmission of COVID-19.[17]72.6% of the parents in the present study stated that "disinfectants containing at least 70% alcohol" should be used in order to kill coronavirus, and 57.5% indicated that they cleaned common areas at home (tables, chairs, door handles, light switches, counters, toilets, taps and sinks) with bleach in order to

Table 2. Comparison of the answers given by the parents to the questions regarding COVID-19 disease

	Mother		Father		P*
	Yes	No	Yes	No	
Do you think that your child is at greater risk of developing coronavirus disease (COVID-19), compared with other children?[1]	24 57.1%	18 42.9%	15 48.4%	16 51.6%	0.459
Have you been allowing your child to go out during the coronavirus disease (COVID-19) pandemic?[18]	8 19.0%	34 81.0%	8 25.8%	23 74.2%	0.490
Have you been making your child wear a mask when you have needed to take your child out during the coronavirus disease (COVID-19) pandemic?[25]	35 83.3%	7 16.7%	31 100%	0 0.0%	**0.017**

*Chi-square test.

prevent transmission of the pandemic. These parents of children with celiac disease also reported that their children's anxiety about coronavirus contamination was not so different from the concerns of healthy children.

They also reported that they had not had their children vaccinated against flu or pneumococcus over the last year. Siniscalchi et al. reported in their study conducted in Italy that only one child with celiac disease got vaccinated against flu.[18]

In our study, we found that 78.1% of the parents of celiac patients did not experience any problems in finding gluten-free foods for their children during the lockdown, and they did not have any difficulties in complying with their children's gluten-free dietary needs. Since routine daily activities such as going to school were interrupted during the lockdown, the children became bored. With boredom, they found solace through foods rich in fat, carbohydrates and proteins, which supplied them with large amounts of calories. Furthermore, hearing or reading news about the pandemic created distress and increased their likelihood of consuming certain foods.[19] Excessive intake of macronutrients during a lockdown situation causes lack of micronutrients and development of obesity.

We also found that 53.4% of the children with celiac disease had had a weight gain of more than one kilogram in the last month. Pietrobelli et al. reported that there was a tendency towards weight gain among 41 children who had stayed at home and had experienced lifestyle changes for three weeks due to a lockdown during COVID-19 pandemic.[20]

Most of the parents indicated that they continued to give propolis and vitamin C supplementation to their children during this period. Furthermore, carob extract, vitamin D, fish oil and iron were among the supplements preferred by the families. Most of the parents reported that they were giving food supplements to their children in accordance with their doctors' advice.

Supplementation of individuals' general nutritional status through vitamins and minerals may affect the functioning of their immune system either positively or negatively. Supplementing diet with nutrients such as vitamin D and zinc may alter immune functions.[21] It has become known that antioxidants increase T cell subgroups, empower lymphocyte responses against mitogens and enhance interleukin 2 (IL-2) production, the number of natural killer cells and the response to influenza vaccines.

Vitamin D decreases the possibility of occurrence of a cytokine storm through protecting tight junctions in the respiratory system, increases virus death through induction of cathelicidin and defensin and decreases the production of proinflammatory cytokines. Thus, it is recommended that patients with celiac disease should take vitamin D supplementation and should consume foods containing vitamin D. The parents surveyed in the present study indicated that they preferred mainly garlic, kefir, oranges, kiwi fruit, spinach, fish, broccoli and pickles for strengthening their children's immune systems.

Taking immune-boosting foods and balanced planning of meals and portions have been also recommended for patients with celiac disease. Especially cellular immunity, phagocyte function, cytokine production, antibody response, antibody affinity and disturbance in complement system make patients with celiac disease more susceptible to viral infections. During a pandemic situation, consumption of foods containing high amounts of antioxidants, vitamins and minerals strengthens the immune system.[19]

In this study, 58.9% of the parents surveyed here stated that their children's sleep patterns changed. It has been reported that social isolation during lockdowns causes sleep disorders through increasing anxiety and stress and that this also increases food intake.[19,22]

In this study, we evaluated the parents' levels of knowledge about COVID-19 and the measures that they took in relation to their children. In addition, we evaluated these children's access to a gluten-free diet within their daily lives and their sleep and nutrition patterns during this period. The questions were multiple-choice and open-ended, so as not to affect the answers given by the parents.

The limitations of this study were the small sample size, the lack of a control group and the fact that it was conducted in a single center. We were aware that parents' feelings about their children's behaviors would possibly be heightened and that, therefore, their answers might be unintentionally biased. Therefore, we avoided asking directional questions.

CONCLUSION

This study is important with regard to determining the awareness of COVID-19 among parents who have children with celiac disease and examining the precautions that they take. The results from this study showed that these parents thought that their children with celiac disease did not present a risk of getting COVID-19 that differed from the risk among healthy children. This finding revealed that the parents of children with celiac disease should be informed more about the COVID-19 pandemic.

It was seen that the children's state of nervousness and associated state of weight gain were found to be affected by the lockdown that was applied to prevent the spread of COVID-19. This lockdown situation had a negative effect on the conditions required to maintain a healthy lifestyle.

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Appendix. Survey Questionnaire and Survey Responses

1. Do you think that your child is at greater risk of developing coronavirus disease (COVID-19), compared with other children?		
Yes	39	53.4%
No	34	46.6%
2. How is COVID-19 disease transmitted?		
Coughing	2	2.7%
Transmission after contact with virus-contaminated surfaces	5	6.8%
Speaking, coughing, sneezing and contamination of the face after contact with virus-contaminated surfaces	66	90.4%
3. How should your child behave while coughing or sneezing?		
Use the area inside the elbow while sneezing	55	75.3%
Use a napkin or handkerchief if available	17	23.3%
Use the back of the hand	1	1.4%
Use palm	0	0%
4. Do you keep pets at home?		
Yes	14	19.2%
No	59	80.8%
5. Is coronavirus disease (COVID-19) transmitted from pets?		
Yes	27	37%
No	46	63%
6. Which of the following precautions is effective in preventing transmission of coronavirus disease (COVID-19)?		
Washing hands frequently with soap and water	13	17.8%
Cleaning hands with alcohol-based disinfectants	0	0%
Avoiding contact with face	0	0%
Staying away from people showing flu-like symptoms	1	1.4%
Washing hands frequently with soap and water, cleaning hands with alcohol-based disinfectants, avoiding face-to-face contact and staying away from people showing flu-like symptoms	59	80.8%
7. Which age groups are affected by coronavirus disease (COVID-19)?		
Over 65 years old	17	23.3%
20-65 years old	5	6.8%
Under 20 years old	0	0%
All age groups	51	69.9%
8. Is any member of your family over 65 years old?		
Yes	68	93.2%
No	5	6.8%
9. Is the spread of coronavirus disease (COVID-19) affectedby air temperature change?		
Yes	34	46.6%
No	39	53.4%
10. What is the minimum alcohol content (%) that disinfectants need to have in order to kill the viral factor that causes coronavirus disease (COVID-19)?		
50%	14	19.2%
60%	6	8.2%
70%	53	72.6%
11. Is there a specific medication to treat coronavirus disease (COVID-19)?		
Yes	8	11%
No	65	89%
12. For at least how long should hands be washed in order to kill the viral factor that causes coronavirus disease (COVID-19)?		
5 seconds	1	1.4%
10 seconds	1	1.4%
15 seconds	2	2.7%
20 seconds	69	94.5%
13. What do you use to clean common areas in your home (tables, stairs, doorhandles, light switches, counters, toilets, taps and sinks) in order to prevent transmission of coronavirus disease (COVID-19)?		
Bleach	42	57.5%
Disinfectants containing 70% alcohol	14	19.2%
Vinegar	17	23.3%

Continue...

Appendix. Continuation.

14. What have you been using to clean electronic devices in your home during the coronavirus disease (COVID-19) pandemic?		
1/100 diluted bleach	18	24.7%
Disinfectants containing 70% alcohol	17	23.3%
Spray containing alcohol	10	13.7%
Vinegar	28	38.4%
15. What have you been using to clean places such as the toilet and bathroom in your home during the coronavirus disease (COVID-19) pandemic?		
1/100 diluted bleach	71	97.3%
Disinfectants containing 70% alcohol	2	2.7%
Alcohol containing spray	0	0%
Vinegar	0	0%
16. Should the bleach used for surfaces and toilets be diluted at the same rate as used for disinfection, when used for prevention of transmission of coronavirus disease (COVID-19) disease?		
Yes	31	42.5%
No	42	57.5%
17. Have you been going out from your home for any reasons other than your urgent needs or for work during the coronavirus disease (COVID-19) pandemic?		
Yes	36	49.3%
No	37	50.7%
18. Have you been allowing your child to go out from your home during the coronavirus disease (COVID-19) pandemic?		
Yes	16	21.9%
No	57	78.1%
19. From where do you mostly get news about the coronavirus disease (COVID-19) pandemic?		
Television	50	68.5%
Internet	22	30.1%
Friends	0	0%
Newspaper	0	0%
I do not follow the news	1	1.4%
20. Do you clean materials bought or brought from outside before using them, because of the coronavirus disease (COVID-19) pandemic?		
Yes	70	95.9%
No	3	4.1%
21. How do you clean the materials purchased from outside? (If you answered yes to question 20, please answer this)		
By wiping the packaging boxes with diluted bleach	20	27.4%
By only bringing them inside after they have been kept outside for a day	25	34.2%
By changing the bags from outside	20	27.4%
By wiping with soapy water	2	2.7%
By wiping the surface with disinfectant	3	4.1%
By washing with plenty of water	2	2.7%
By cleansing with vinegar	1	1.4%
22. Have you been paying attention to social distancing rules during interactions with individuals outside your home during the coronavirus disease (COVID-19) pandemic?		
Yes	72	98.6%
No	1	1.4%
23. Have you been using a mask while going out during the coronavirus disease (COVID-19) pandemic?		
Yes	72	98.6%
No	1	1.4%
24. What should be the social distance in order to prevent transmission of coronavirus disease (COVID-19)?		
1-2 meters	71	97.3%
50 cm	2	2.7%
25. Have you been making your child wear a mask when you have needed to take your child out during the coronavirus disease (COVID-19) pandemic?		
Yes	66	90.4%
No	7	9.6%
26. Have you been having any problems in finding foods for your child (gluten-free foods) during the coronavirus disease (COVID-19) pandemic?		
Yes	41	56.2%
No	32	43.8%

Continue...

Appendix. Continuation.

27. Do you believe that it is important to pay attention to your children's diet in order to strengthen their immune systems and to protect them from coronavirus disease (COVID-19)?		
Yes	73	100%
No	0	0%
28. Have you been giving vitamin-mineral supplementation to your children during the coronavirus disease (COVID-19) pandemic?		
Yes	46	63%
No	26	35.6%
29. If your answer to question 28 was yes, what have you been giving and how much?		
Propolis	16	21%
Vitamin C	20	27.3%
Fish oil	2	2.7%
Iron	2	2.7%
Fish oil and propolis	5	6,8%
Carob extract and vitamin C	1	1.3%
Propolis and vitamin C and vitamin D	1	1.3%
30. Which of the following foods do you think are good for the immune system?		
Blueberries	11/73	15.1%
Bitter chocolate	5/73	6.8%
Turmeric	25/73	34.2%
Oily fish	38/73	52%
Broccoli	36/73	49.3%
Spinach	41/73	56.16%
Green tea	13/73	17.8%
Garlic	58/73	79.4%
Kefir (a fermented milk drink)	44/73	60.2%
Oranges or kiwi fruit	42/73	57.5%
Ginger	33/73	45.2%
Red peppers	19/73	26%
Pickles	35/73	47.9%
Potatoes	8/73	10.9%
31. Which of the following symptoms increased in your child with the closure of schools due to coronavirus disease (COVID-19)?		
No complaint	42/73	57.5%
State of nervousness	18/73	24.6%
Increase in appetite	10/73	13.6%
Lack of appetite	6/73	8,21%
Headache	5/73	6.84%
Stomach ache	3/73	4.1%
Increase in hair loss	2/73	2.73%
Allergic skin rash	2/73	2.73%
Having nightmares and scary dreams	1/73	1.36%
Nausea	1/73	1.36%
Constipation	1/73	1.36%
Distension	0/73	0%
Diarrhea	0/73	0%
Vomiting	0/73	0%
32. Has your child had any sickness requiring medication (like antibiotics), such as flu, cold or urinary tract infection, in the past month		
Yes	4	5.5%
No	69	94.5%
33. Which of the following vaccines has your child had in the last year?		
Influenza vaccine	0	0%
Pneumococcal vaccine	0	0%
Neither of these	73	100%
34. Has your child's sleep pattern and quality changed in the past month?		
Increase in sleep duration	6	8.2%
Decrease in sleep duration	5	6.8%
Change in sleep pattern	32	43.8%
No effect on sleep pattern	30	41.1%

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Development of language and arithmetic skills: risk and protective factors. Comparative cross-sectional study

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ABSTRACT

BACKGROUND: In a literate society, linguistic/arithmetic performance is highly valued. Based on defined risk factors, strategies for promotion of better performance can be developed.

OBJECTIVE: To ascertain the risk and protective factors relating to development of language and arithmetic.

DESIGN AND SETTING: Observational comparative cross-sectional study at a public elementary school in Ribeirão Preto (SP), Brazil.

METHODS: A total of 66 children (41% females) attending first to fifth grades participated in this study. They were divided into two groups: G1, children classified as presenting language or arithmetic deficits; G2, average performance. Language (oral and written) and arithmetic skills were assessed through standardized tests. Variables relating to social skills, home environment resources and behavioral problems were assessed through standardized scales. Data on other variables (pre, peri and postnatal complications, maternal variables and others) were collected through interviews. The logistic regression technique with LASSO was used ($\alpha = 0.05$).

RESULTS: Teenage pregnancy and consumption of psychoactive substances during pregnancy or complications during pregnancy were risk factors for performance regarding arithmetic and language. Higher schooling level for the mother was a protective factor in the development of arithmetic and language. Being female and having a history of otitis were risk factors for language. Altered social skills (responsibility and civility) and complaints of inattention were risk factor for arithmetic. Adequate linguistic development was a protective factor for the development of arithmetic.

CONCLUSION: The risk/protective factors included variables relating to the gestational period, mother's age when pregnant, mother's schooling, social skills, behavior and development issues.

INTRODUCTION

Language is a complex cognitive function, characterized by a system of principles and rules that enable people to code their meaning in a symbol, and vice-versa.[1] It has both expressive and receptive components.[1] Under a natural course, oral language skills are developed first (pragmatic, phonological, morphosyntactic and semantic aspects), and then metalinguistic and written language skills are acquired.

Arithmetic skills, in turn, are related to numerical properties and operations.[1] To develop arithmetic skills, three different systems are recruited, depending on the task: a nonverbal system (responsible for presenting the relationship between numbers); a verbal system (the numbers are expressed as a type of word); and a visual system (numbers can be decoded as Arabic numerals).[2]

Development of the abovementioned cognitive skills is of utmost importance to the life of every human being within literate society.[3] For these skills to be adequately developed, children need to be integrated into various environments, and to acquire other levels of development.

Recent reports have shown prevalences of alterations in written language and/or arithmetic performance of approximately 22% among Indian schoolchildren[4] and 54% among Brazilian schoolchildren.[5] Regarding the prevalence of specific learning disorders (dyslexia and/or dyscalculia), the same studies stated that the percentage was 3% in Brazil,[5] 9% in Turkish-born children[6] and 7.5% in India[4]. They also showed that high rates of comorbidities were present in children with

complaints of reading, writing and/or arithmetic difficulty: the conditions most present were attention-deficit/hyperactivity disorder and mood disorders.[5,6]

Despite variability from country to country regarding the prevalence rates of low school performance, researchers share the unanimous opinion that early intervention should be implemented among these children in order to promote adequate social and cognitive development.[5,6] To this end, the risk and protective factors concerning language and arithmetic development need to be identified.

By definition, risk factors encompass negative events that take place in one's life; when these are present, the likelihood of having physical, social or emotional problems increase.[7] Protective factors, on the other hand, are those that are capable of protecting people who are at risk (thereby reducing the impact of risks and the negative chain reactions that follow the person's exposure to a situation of risk); these can be both individual and environmental factors.[8]

The studies in the literature regarding risk factors for language and/or arithmetic skills have mostly analyzed one variable at a time, e.g. studies on prematurity,[9,10] severe malnutrition in the first years of life[11] or resources present at home,[12,13] among others. However, few studies have analyzed which variables out of these many factors are the most likely to impair linguistic and mathematical development.

OBJECTIVE

The aim of study was to assess several variables – maternal and environmental variables, pre, peri and postnatal conditions and social skills/behavioral problems – and ascertain which of these are the risk and protective factors for development of language and arithmetic skills.

METHODS

This was an observational comparative cross-sectional study. It was approved by our institution's human research ethics committee (evaluation report: 3.774.559; certificate CAAE: 26465219.8.0000.5440; date: December 16, 2019).

Sample characterization and selection

All the children studying in the first to fifth grades in one public elementary school were eligible to participate in this study. For this, prior authorization from the adults responsible for them was required. Firstly, the parents/guardians (approximately 170 in number) were invited to participate in a meeting at which the project was explained; then, they were sent a consent form to authorize the minors' participation in this study. Out of the 170 invitations, 77 parents/guardians authorized their children to participate; however, based on the inclusion and exclusion criteria, the final sample comprised 66 children.

The inclusion criteria were that the children needed to be 6.5 years to 11 years old, attending that elementary school at first to fifth-grade level, and did not present any syndrome or pathological condition that impaired their cognitive capacity, e.g. fetal alcohol syndrome, Down syndrome or others. The exclusion criteria encompassed situations in which the parents/guardians did not fill out the questionnaires used in this study and the assessments on linguistic and arithmetic skills were incomplete.

Among the 66 children participating in this study, 27 (41%) were female. The children's mean age was 8.3 years (standard deviation 1.3). Regarding their school year, 8 (12%) were attending the first year; 12 (18%), the second year; 24 (36%), the third year; 13 (20%), the fourth year; and 9 (14%), the fifth year.

Based on these children's classification concerning linguistic and arithmetic skill performance for their age, they were divided into two groups, namely:

- Group 1 (G1): children classified as borderline or deficient (any degree) in the language test (oral and written) or arithmetic test (depending on the variable studied in the statistical model);
- Group 2 (G2): children whose performance was classified as average or superior for their age in the language test (oral and written) or arithmetic test (depending on the variable studied in the statistical model).

Data collection instruments and procedures

The data collection was divided into two parallel phases. The first one involved oral and written language and arithmetic skills assessments, and used a standardized, validated instrument for the Brazilian population (see description below), individually administered at the school.

The second phase investigated occurrences of several variables that might interfere with linguistic and arithmetic development. These variables are described in **Table 1**. A brief interview was conducted with the parents/guardians to collect this information; they were then asked to fill out certain questionnaires. These instruments are described below.

The instruments administered for data collection (variables listed in **Table 1**) are described in sequence, along with the linguistic and arithmetic performance assessment tests.

- Child Neupsilin test:[1] This is a brief neuropsychological instrument that, through 26 subtests, assesses components of eight neuropsychological functions: orientation; attention; visual perception; working, episodic, and semantic memory; arithmetic skills; oral and written language; visuoconstructive abilities; and executive functions. It can be administered to children from 6 to 12 years old, and only by professional psychologists or speech-language-hearing therapists.

The items administered in this study were language (oral and written) and arithmetic skills, which are composed of the following subitems:

(a1) Oral language (pragmatic, lexical-semantic and phonological aspects, and metalinguistic skills): picture-naming task; phonological awareness, i.e. rhyming and phoneme deletion; and oral comprehension and inferential processing.

(a2) Written language: tasks involving reading syllables, words and pseudowords aloud; writing words and pseudowords; understanding written sentences; spontaneously writing a sentence; and copying a written sentence.

(b) Arithmetic skills: counting sticks and doing arithmetic calculations.

In each item, the child's performance is classified according to their age, by calculating the Z score (number of standard deviations above or below the population's mean value). This classification was used to form the groups. Children whose performance was classified as "borderline" (Z score between −1 and −1.49) or "deficient" (Z score below −1.5) were classified as having altered performance. On the other hand, those with a Z score between −0.99 and +1 were classified as average and thus were placed in group 2.

- Printed interview: A brief questionnaire structured by the researchers was directed to the parents/guardians in order to gather information relating to the child's medical history, gestational complications, cognitive, motor and linguistic development, history of recurrent otitis, hearing complaints, food-related complaints, school complaints, sleep alterations and other matters. Before each adult answered it, the researchers personally explained the questionnaire and clarified any questions that they might have.
- **Home Environment Resources Scale (HERS):**[14] This instrument evaluates the resources at home that might contribute to academic learning during elementary school. It encompasses three domains:
  (a) resources that promote proximal processes;
  (b) activities that indicate stability in family life;
  (c) parental practices that help to connect family and school.

This instrument was administered as a semi-structured interview, in which each topic was presented orally to the interviewee. The interviewer was free to paraphrase the question if there was any difficulty in being understood.

It has ten questions: seven that are open-ended (with items for the parent/guardian to mark) and three on a three-point scale represented by 0 (never), 1 (sometimes) and 2 (always).

For this study, the crude score was used, i.e. each item marked in the first seven questions received one point. This score was added to that of the last three questions, which used the scale. The higher the score was, the more resources that there were in that home.

- **Social Skills Rating System (SSRS):**[15] This is a validated precise instrument for mapping social skills and behavioral alterations, and for monitoring the effectiveness of interventions aimed at the socioemotional development of children and adolescents.

This instrument enables information from three different sources – the child, the parents and the teachers – to be collected and compared. However, for this study, only the questionnaire approaching the parents was used.

The parents' questionnaire is composed of 38 questions: 23 relating to social skills (measured in terms of frequency, considering affectivity/cooperation, responsibility, self-control, civility and social interaction); and 15 relating to behavioral problems (assessed in terms of how frequently they occurred, considering both externalizing and internalizing behaviors).

The parent/guardian was asked to answer the questions on these two frequency-related scales as follows: 0 (never), 1 (sometimes) or 2 (very frequently). Afterwards, the score was calculated and compared with the percentile indicated for the test, to verify whether the child had a behavioral and/or social skill alteration. In this study, a social skill was considered altered when the child was classified below the 25th percentile and behavior was considered altered when the child was classified over the 75th percentile, as recommended in the instructions for this test.

Table 1. Variables selected for this study

Identification data	Date of birth Current age Gender
Maternal and social variables	Mother's age during pregnancy (≤ 18 years = teenage pregnancy) Consumption of psychoactive substances during pregnancy (alcoholic beverages, tobacco and other drugs) Complications during pregnancy (e.g. physical trauma, surgery, bleeding and others) Mother's schooling level Home environment resources[14]
Birth and postnatal conditions	Gestational age (preterm, full-term or post-term) Size for gestational age (weight and length) Birth complications Delay in neuropsychomotor development Delay in speech and language development Epilepsy and other conditions in early childhood (malnutrition, anemia, etc.) Current complaints of sleep alterations History of recurrent otitis or serous otitis in early childhood
Social behavior/skills	Alterations in social skills[15] Alterations in behavior (SSRS and SNAP)[15,16]

- **SNAP-IV questionnaire:**[16] This is an assessment instrument that is used to track and assess the frequency of inattention, hyperactivity and impulsivity symptoms, based on the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), of the American Psychiatric Association. The Portuguese-language version of SNAP-IV was validated for use in Brazil by Mattos et al.[16] Even though this translation refers to the diagnostic criteria of the fourth version of the DSM, it is still used in research because in the updated manual (DSM-5) the symptoms and cutoff score for diagnosing this disorder remain unchanged. Hence, to state that the child's score indicates inattention or hyperactivity/impulsivity, the parent/guardian needs to have marked six or more symptoms in each category as "very much" or "too much". In this study, children were considered to present scores indicating inattention and/or impulsivity/hyperactivity, or not to present this, in accordance with the responses given by their parent/guardian.

Statistical analysis of the data

The data analysis employed the following statistical procedures. Descriptive statistics were used to characterize the results. In making statistical inferences, a machine-learning technique (logistic regression with LASSO) was used to evaluate which variables were risk or protective factors for the development of language and/or arithmetic skills. The significance level used for the logistic regression models was $\alpha = 0.05$.

A logistic regression is defined as where is the probability of a certain class or event such as pass/fail, alive/dead or healthy/sick existing for the *i*-th individual, is the value of the *j*-th variable for the *i*-th individual and s are the regression coefficients. The variables can be quantitative (continuous or discrete) or binary, taking values of 1 if the *i*-th individual has a specific feature or 0 otherwise. A categorical variable with *d* classes is usually represented by *d-1* binary variables in this model. The regression coefficients are estimated based on the observed sample through maximum likelihood or least-squares methods.

In general, only the variables that are significant (risk factors) are kept in the model to explain the probability . In this study, we selected the significant variables using LASSO, a machine-learning method, estimated their regression coefficients using the maximum likelihood method and verified whether they were really significant at the significance level 0.05. The LASSO method consists of estimating the regression coefficients through the least-squares method, including the restriction , where *t* is a prespecified positive value. This restriction forces the regression coefficient of non-significant variables to be zero, and they can then be removed from the model.

RESULTS

Among the 66 participating children, 17 (26%) were classified as "average" for language and arithmetic skills, whereas 28 (42%) had alterations in both. The other 21 children (32%) had an alteration in either language or arithmetic. **Table 2** provides a description (age, sex and school year) of the children who formed groups 1 and 2 in each statistical inference model (model for language ability and model for arithmetic skill).

The two logistic regression models are presented below. The first (**Table 3**) shows the results regarding language skills: group 1 = 41 children (62%) with language alterations and group 2 = 25 (38%) without language alterations. The second (**Table 4**) shows the results regarding arithmetic skills: group 1 = 36 children (55%) with arithmetic alterations and group 2 = 30 (45%) without arithmetic alterations.

The results from the statistical model investigating the relationship between the development of language (oral and written)

Table 2. Description (age, sex and school year) of the children who formed groups 1 and 2, according to performance in language and arithmetic

	Language (oral and written language)		Arithmetic skills	
	Group 1 (n = 41)	Group 2 (n = 25)	Group 1 (n = 36)	Group 2 (n = 30)
Female	20	7	16	14
Male	21	18	20	16
6 years old	3	3	5	1
7 years old	6	3	6	3
8 years old	10	9	9	10
9 years old	15	8	11	12
10 years old	4	1	2	3
11 years old	3	1	3	1
First year	6	2	7	1
Second year	7	6	9	4
Third year	16	7	12	11
Fourth year	7	6	4	9
Fifth year	5	4	4	5

Table 3. Logistic regression model with LASSO, analyzing which variables were risk or protective factors for linguistic development (oral and written language)

	Estimated coefficient	P-value
Adequate arithmetic performance	2.7	0.004*
Gender – female	-1.7	0.02*
Hyperactivity/impulsivity	-1.6	0.07
Mother's schooling level – higher education	1.9	0.04*
Age when pregnant ≤ 18	-2.1	0.02*
Consumption of psychoactive substances during pregnancy	-3.1	0.01*
History of otitis in early childhood	-2.3	0.02*

Logistic regression test with LASSO (α = 0.5); *Statistically significant variables. A positive coefficient is a protective factor, i.e. the presence of this variable increases the possibility of adequate linguistic development. A negative coefficient is a risk factor, i.e. the presence of this variable is a risk for language alterations. Note: The test results are presented only as the P-value and the estimated coefficient of the significant variables with α = 0.1. Variables selected for this study: mother's age during pregnancy (≤ 18 years = teenage pregnancy); consumption of psychoactive substances during pregnancy (alcoholic beverages, tobacco and other drugs); complications during pregnancy (e.g. physical trauma, surgery, bleeding and others); mother's schooling level; home environment resources; gestational age (preterm, full-term or post-term); size for gestational age (weight and length); birth complications; delay in neuropsychomotor development; delay in speech and language development; epilepsy and other conditions in early childhood (malnutrition, anemia, etc.); current complaints of sleep alterations; history of recurrent otitis or serous otitis in early childhood; alterations in social skills; and alterations in behavior.

Table 4. Logistic regression model with LASSO, analyzing which variables are risk or protective factors for arithmetic skills

	Estimated coefficient	P-value
Adequate language performance	2.4	0.01*
Alteration in responsibility skill	-7.5	0.01*
Alteration in civility skill	-3.7	0.01*
Inattention	-3.1	0.03*
Mother's schooling level – higher education	4.5	0.02*
Age when pregnant ≤ 18	-2.6	0.03*
Complications during pregnancy	-2.6	0.05*
Absence of delay in speech and language development	3.3	0.03*

Logistic regression test with LASSO (α = 0.5); *Statistically significant variables. A positive coefficient is a protective factor, i.e. the presence of this variable increases the possibility of adequate mathematical performance. A negative coefficient is a risk factor, i.e. the presence of this variable is a risk for alterations in arithmetical skills. Note: The test results are presented only as the P-value and the estimated coefficient of the significant variables with α = 0.1. Variables selected for this study: mother's age during pregnancy (≤ 18 years = teenage pregnancy); consumption of psychoactive substances during pregnancy (alcoholic beverages, tobacco and other drugs); complications during pregnancy (e.g. physical trauma, surgery, bleeding and others); mother's schooling level; home environment resources; gestational age (preterm, full-term or post-term); size for gestational age (weight and length); birth complications; delay in neuropsychomotor development; delay in speech and language development; epilepsy and other conditions in early childhood (malnutrition, anemia, etc.); current complaints of sleep alterations; history of recurrent otitis or serous otitis in early childhood; alterations in social skills; and alterations in behavior.

and several variables (**Table 3**) showed that the mother's age when pregnant, mother's schooling level and events during pregnancy were important variables. The mothers of children with good language development had completed higher education. However, young maternal age at pregnancy (teenage pregnancy), gestational complications and consumption of psychoactive substances during pregnancy are variables that compromise adequate language development. Being female and having a history of ear infections were also variables negatively related to language development.

Adequate development of arithmetic skills was positively influenced (protective factors) by the variables of higher mother's schooling (higher education) and adequate linguistic development, along with not having any history of delay in the child's first words. Young maternal age during pregnancy and complications/substance use during pregnancy were also risk factors (negative association) for development of arithmetic skills, but in addition, we found that the variables of altered social skills (civility or responsibility) and symptoms of inattention were risk factors. These variables were not significant in the model for linguistic ability (**Table 4**).

DISCUSSION

The results from this study indicated what the risk and protective factors for the development of language and arithmetic skills are. It was observed that adolescent pregnancy (mother 18 years old or younger during pregnancy), consumption of psychoactive substances and complications during pregnancy were risk factors for the development of both skills studied here. The mother's schooling level (higher education), on the other hand, was a protective factor.

Regarding language development alone, being female and having a positive history of recurrent otitis in early childhood were risk factors. However, having adequate performance in arithmetic was a protective factor.

Arithmetic skill, in turn, was negatively influenced by complaints of inattention, and alterations in the social skills of responsibility and civility. In contrast, adequate language development (no history of speech delay and average current linguistic performance) was a protective factor.

The first datum to be discussed is the prevalence of low school performance. In this study, only 26% of the children had adequate linguistic and arithmetic performance. The others had some degree of impairment, either mildly (dysorthography) or severely (illiterate children). These data are similar to those from other studies conducted in Brazil and are also in agreement with data published by federal government agencies, through the Primary Education Assessment System (SAEB).[5,17] According to data from the SAEB, the number of children with adequate reading and arithmetic performance by the end of fifth grade is lower than 20%.

Regarding protective factors, there is a positive relationship between language and arithmetic development. Analysis has been conducted on cognitive differences between children with alterations only in reading/writing, those with alterations only in arithmetic and those with alterations in both skills.[18] It was observed that children with more complex cognitive alterations (as in working memory, phonological awareness, numerical sense and others) are the ones that have difficulties in both domains (language and arithmetic). However, children with difficulties only in arithmetic also presented some alterations in linguistic skills, such as narrative memory. Other studies have shown that to develop arithmetic skills it is necessary to develop certain linguistic skills.[2,19]

Regarding environmental variables (mother's schooling, home environment resources and mother's age during pregnancy), this study showed that these can be risk or protective factors. Teenage pregnancy is considered to be a public health issue in Brazil, where it is estimated that one out of every five children is born of a teenage mother.[20] In some regions of Brazil, this rate can reach 50%.[21] In this study, this variable was considered to be a risk factor for language and arithmetic development.

Teenage pregnancy is also related to lower socioeconomic level and to difficulties that teenage mothers face in trying to study further and even to reach higher education, which is considered to be a protective factor.[20,21] This is a high-risk scenario, in which teenage mothers are less likely to finish their education, thus resulting in low schooling levels.

Furthermore, there are home environment resources, which were not a significant variable in this study. However, it has been demonstrated in the literature that there is a positive relationship between environmental resources and linguistic/cognitive development.[13,22] In an environment where adults have low schooling, it is common not to find many resources/opportunities for their children's development.[13,22]

Consumption of psychoactive substances such as alcoholic beverages, tobacco or other types of drugs while pregnant, and its negative relationship with development has been widely addressed in the literature. Review studies have concluded unanimously that consuming psychoactive substances during pregnancy causes functional and/or organic alterations in the central nervous system, which lead to alterations in the auditory pathway, and in motor and cognitive development.[23-25]

Complaints of inattention, which were considered in this study to be a risk factor for arithmetic skills, may be signs of alterations in the central nervous system. These could be caused through consumption of substances during pregnancy, genetic issues or other factors.[26] Attentional complaints may point to a diagnosis of attention-deficit/hyperactivity disorder or mood alterations,[26] which have high rates of comorbidities relating to learning difficulty.[5,6] Whenever attentional complaints and/or externalizing behaviors are present, it is essential to make a differential diagnosis and institute adequate treatment.

Prematurity, which has been pointed out as a risk factor for linguistic and cognitive development, was not a significant variable in this study. One possible explanation for this is that prematurity would not be a risk factor in itself: instead, the risk would be due to other factors related to this.[9] Premature children whose language development was at risk were found in a previous study to be those who had peri-intraventricular hemorrhage or bronchopulmonary dysplasia, birth weight lower than 1,000 grams and long hospitalization.[9] On the other hand, low-risk premature children, i.e. those without a history of the abovementioned variables, usually have adequate language and writing development.[10]

Regarding gender, the literature indicates that primary language disorders (language development disorder, specific learning disorder, childhood apraxia of speech and others) are more prevalent in males.[26] However, in the present study, being female was a risk factor for language development.

One possible explanation for this finding is that the children sampled in this study had alterations mostly in written language. However, the purpose of the present study was not to verify the differential diagnoses of the causes underlying language alteration, but to ascertain the risks in a sample with language alterations, regardless of their degree and cause. Therefore, and also based on the literature regarding the percentage of children with primary language alterations,[5,6,26] it can be suggested that the risk factor for language that relates to being female depends on other factors not investigated here, such as mood alterations, which females more often present, along with other factors.[26]

A history of otitis in early childhood is related to difficulties in phonological development,[27] which in turn is related to the metalinguistic skill of phonological awareness. This essential skill for written language development was assessed in the present paper.[1,18]

Lastly, there are social skills. In this study, difficulties regarding responsibility and civility skills were observed in relation to arithmetic alterations. Alterations in social skills may be present in 20% to 42% of the children with school difficulties.[28] Deficits in the skills needed to make and maintain friends, end a conversation, play together with other children and interact with classmates are characteristic of children with learning difficulties. Moreover, these deficits tend to affect friendships, as well as important behaviors related to school learning, e.g. asking questions, having questions answered and asking a classmate or teacher's help.[28,29]

A piece of research demonstrated that the ability to write to dictation is positively correlated with civility and altruism skills; assertiveness, in turn, was correlated with arithmetic skills.[29] An intervention study demonstrated that children who had received an intervention to train their social skills improved in this area and in academic skills as well. In contrast, children who had received reading and writing interventions only improved in that educational area.[30]

CONCLUSION

Only 26% of the children enrolled in this elementary school (first to fifth grades) had adequate language and arithmetic development. The others had some type of alteration that ranged from mild to severe deficits. These data confirm the sad reality of Brazilian public education.

Among the variables analyzed, i.e. social skills and maternal/environmental variables (mother's age during pregnancy, mother's schooling, environmental resources and others; behavioral problems/inattention and hyperactivity complaints; pre, peri and postnatal complications; and neuropsychomotor development), the risk factors for both skills (language and arithmetic) were those relating to gestation (consumption of psychoactive substances or complications during that period) and teenage pregnancy. The protective factor, on the other hand, was the mother's schooling level (higher education).

For the linguistic model, being female and having a history of otitis were also risk factors. For arithmetic, alterations in the social skills of responsibility and civility, as well as inattention complaints, were risk factors. The protective factor in the arithmetic model was adequate linguistic development.

Regarding impairment of social skills and inattentive behavior, it was not possible to establish a clear link of cause and effect, since we did not investigate whether these changes preceded the arithmetic trouble or vice versa. Hence, we can only conclude that they are related. Thus, children with difficulties in arithmetic have more attentional complaints and deficiencies in specific social skills.

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The risk of post-polypectomy bleeding among patients receiving antithrombotic agents: A prospective observational study

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ABSTRACT

BACKGROUND: In July 2012, the Japan Gastroenterological Endoscopy Society updated their guidelines for gastroenterological endoscopy in patients receiving antithrombotic therapy. Colonoscopic polypectomy procedures are associated with a high risk of bleeding.

OBJECTIVES: The present study evaluated the safety of colonoscopic polypectomy procedures in terms of bleeding, among patients receiving antithrombotic therapy.

DESIGN AND SETTING: Prospective observational study conducted in a tertiary-level public cardiovascular hospital in Istanbul, Turkey.

METHODS: Colonoscopic polypectomies carried out in a single endoscopy unit between July 2018 and July 2019 were evaluated prospectively. The patients' data, including age, gender, comorbidities, whether antithrombotic drug use was ceased or whether patients were switched to bridging therapy, polyp size, polyp type, polyp location, histopathology, resection methods (hot snare, cold snare or forceps) and complications relating to the procedures were recorded.

RESULTS: The study was completed with 94 patients who underwent a total of 167 polypectomy procedures. As per the advice of the physicians who prescribed antithrombotic medications, 108 polypectomy procedures were performed on 60 patients without discontinuing medication and 59 polypectomy procedures were performed on 34 patients after discontinuing medication. The age, gender distribution and rate of bleeding did not differ significantly between the patients whose medication was discontinued and those whose medication was continued ($P > 0.05$).

CONCLUSION: This study found that the colonoscopic polypectomy procedure without discontinuation of antithrombotic medication did not increase the risk of bleeding. This procedure can be safely performed by experienced endoscopists in patients with an international normalized ratio (INR) below 2.5.

INTRODUCTION

Colonoscopic polypectomy is an effective treatment method that reduces the mortality associated with colorectal cancer,[1] which is the second highest cause of cancer-related deaths. Colonoscopy as a screening test and colonoscopic polypectomy as an effective means of therapy reduce the risk of development of colon cancer by preventing progression of adenoma to carcinoma.[2] As is the case with other interventional procedures, this procedure has been associated with some significant complications,[3,4] among which postpolypectomy bleeding is the most common. The incidence of postpolypectomy bleeding ranges from 0.3% to 3.6% per patient.[5,6] The use of antithrombotic medications is increasing worldwide, having been shown to be effective in preventing thrombosis. In conjunction with their increasing use by the general population, their use has also increased among patients undergoing endoscopic procedures.[7]

Colonoscopic diagnostic and therapeutic procedures need to be carried out with full awareness of the risk of hemorrhage.[8] Discontinuation of antithrombotic medications prior to colonoscopic examination is believed to reduce the risk of gastrointestinal hemorrhage.[9] However, the potential for thrombosis following discontinuation of antithrombotic medication is closely associated with major complications, including a high mortality rate.[10] In 2012, the Japan Gastroenterological Endoscopy Society (JGES) published new guidelines regarding the use of anticoagulant and antiplatelet agents in endoscopic procedures.[11] Colonoscopic polypectomy, among other endoscopic procedures, was described as a procedure presenting high risk of hemorrhage.

OBJECTIVE

There are only a limited number of studies in the literature detailing polypectomy and its complications among patients receiving antithrombotic medication. The aim of the present study was to evaluate the safety of the colonoscopic polypectomy procedure among patients receiving antithrombotic medication.

METHODS

In this observational study, colonoscopic polypectomies performed in a single center between July 2018 and July 2019 were evaluated prospectively. The study included patients aged 18 years and over who were on antithrombotic medication to treat cardiovascular complaints. The study primarily included patients undergoing diagnostic and therapeutic colonoscopic polypectomy due to suspected malignancy, to screen for malignancy, and investigations of the etiology of occurrences of anemia. Those undergoing hemostatic emergency procedures performed due to gastrointestinal hemorrhage, and those undergoing diagnostic endoscopic mucosal biopsies, were excluded. Colonoscopy procedures that were not completed due to inadequate bowel preparation and looping were also excluded. Lastly, only patients providing consent to participate in the study were included in the study.

Cessations of antithrombotic medication prior to endoscopic procedures, switches to bridging therapy and the continuation of these therapies during the procedure were decided upon by the cardiology physicians who prescribed the medication initially.

The data gathered on the patients included age, gender, comorbidities (hypertension, antihypertensive drug use, diabetes mellitus and antihyperglycemic drug use), whether use of antithrombotic drugs were ceased or whether the patient was switched to bridging therapy, proton pump inhibitor (PPI) use, polyp size, polyp type, polyp location, histopathology, characteristics of the surgical margin, resection methods (hot snare, cold snare or forceps) and complications relating to the procedures. In the present study, the anticoagulant medications included warfarin (5 mg) and rivaroxaban (15 mg), and the antiplatelet medications included aspirin (100 mg) and clopidogrel (75 mg). Because of the single-center study design, no other anticoagulant or antiplatelet medications were included due to the limited number of cases.

No interventions were made if the prothrombin time (PT-INR) level was above 2.5 in patients undergoing warfarin therapy, given that the risk of hemorrhage was significantly higher in such patients. If the international normalized ratio (INR) was above 2.5, the prescribing physician was consulted, and either warfarin therapy was discontinued or the patient was switched to bridging therapy to reduce their INR to below 2.5 prior to the procedure.

The polyp size was recorded as the actual size in millimeters, measured histopathologically. Polyp type was classified as sessile, pedunculated or flat, in accordance with the Paris classification guidelines.[12] Polyp location was defined as either in the proximal colon (cecum, ascending colon and transverse colon) or in the distal colon (descending colon, sigmoid colon and rectum). The histopathological classification included carcinoma, high-grade dysplasia, moderate dysplasia, low-grade dysplasia, tubular adenoma, serrated adenoma, hyperplastic polyp, inflammatory polyp or missing.

The colonoscopies were performed by endoscopists in a single center. Polypectomies were performed using cold or hot snares (Micro-Tech, Nanjing, China) or forceps (Micro-Tech, Nanjing, China; 2.3 mm). The method to be used was decided upon by the operating endoscopist during the procedure. Coagulation catheters were used in the event of bleeding. All procedures were performed using the same endoscopy system.

The patients were advised to return to the clinic if they experienced hematemesis or melena after the polypectomy and were invited to attend a control visit four weeks after the polypectomy. Postpolypectomy bleeding (PPB) was defined as bleeding occurring within four weeks of the polypectomy. A diagnosis of PPB was established by means of emergency colonoscopy in patients presenting with hematochezia, based on the presence of active bleeding, a newly formed blood clot or visible vessels at the polypectomy site, and on the presence of intraluminal blood. PPB was ruled out if the hematochezia was mild and self-limiting without requiring emergency colonoscopy.[13]

This study was approved by the ethics committee of our hospital (approval no. 2018.4/1-98; approval date: May 25, 2018).

Statistical analysis

Descriptive statistics were presented as numbers and percentages for categorical variables, while quantitative variables were presented as mean, standard deviation, minimum, maximum and median values. The normality of the distribution of the data was ascertained using the Kolmogorov-Smirnov test. A Mann-Whitney U-test was used for the analysis on quantitative independent variables. A chi-square test was used in the analysis on qualitative variables and Fisher's exact test was used if the conditions were not met for a chi-square test. The SPSS 22.0 for software package (IBM Corp, Armonk, NY, United States) was used for the statistical analysis.

RESULTS

The study was completed with 94 patients who underwent colonoscopic polypectomy. A total of 167 polypectomy procedures were performed on these 94 patients (**Figure 1**). The general characteristics and demographic data of the patients is presented in **Table 1**.

As per the advice of the physicians who prescribed the antithrombotic medications, 108 polypectomy procedures were

performed on 60 patients whose medication was continued, and 59 polypectomy procedures were performed on 34 patients whose medication was discontinued. Among the 34 patients whose medication was discontinued, 26 were switched to bridging therapy with low-molecular-weight heparin (LMWH).

The age, gender distribution and rate of bleeding did not differ significantly between those whose medication was discontinued and those whose medication was continued ($P > 0.05$). The rate of use of bridging therapy was significantly higher among the patients whose medication was discontinued than among those whose medication was continued ($P < 0.05$). The INR and platelet count were significantly higher in those whose medication was discontinued than in those whose medication was continued ($P < 0.05$) (**Table 2**).

The distribution of localization did not differ significantly between the forceps and snare groups ($P > 0.05$). Polyp size was significantly greater in the snare group than in the forceps group ($P < 0.05$) (**Table 3**). The distribution of polyp type did not differ significantly between the cold snare and hot snare groups ($P > 0.05$). The distribution of localization did not differ significantly between the cold snare and hot snare groups ($P > 0.05$). Polyp size was significantly greater in the hot snare group than in the cold snare group ($P < 0.05$) (**Table 4**).

Postpolypectomy bleeding occurred in two patients: one among the patients who used aspirin and whose medication was not discontinued; and one among the patients who used clopidogrel and whose medication was discontinued (**Table 5**). No thromboembolic events occurred in any of the participating patients.

DISCUSSION

The present single-center, prospective and observational study investigated the risk of bleeding following colonoscopic polypectomy procedures performed with or without cessation of medication, among patients who had been receiving antithrombotic medication. The results from the study suggest that colonoscopic polypectomy procedures without discontinuation of drugs among patients who had been receiving antithrombotic medication did not increase the risk of bleeding within 30 days of the procedure.

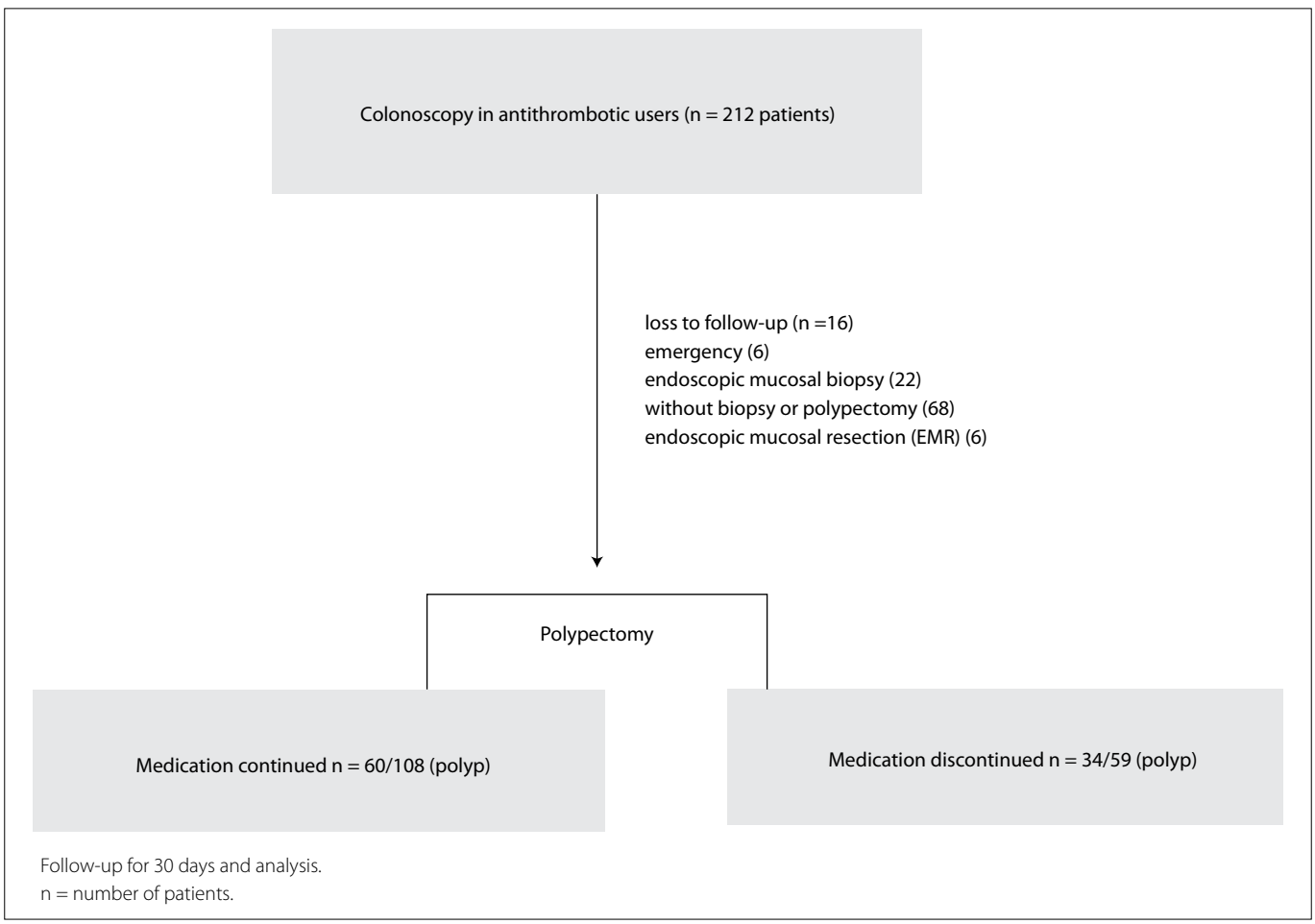

Figure 1. Flow chart of the present study: antithrombotic users.

Table 1. Demographic data

		Min-Max	Median	Median ± SD or n (%)
Age		44.0-83.0	65.0	65.3 ± 8.4
Sex	Female			29 (30.9%)
	Male			65 (69.1%)
Indication	Malignancy screening			45 (47.9%)
	Anemia			49 (52.1%)
Disease	Atrial fibrillation			9 (9.6%)
	Coronary bypass			6 (6.4%)
	CAD			31 (33.0%)
	Mitral valve replacement			8 (8.5%)
	Cardiac stents			36 (38.3%)
	Cardiac insufficiency			4 (4.3%)
Antithrombotic	Aspirin (100 mg)			42 (44.7%)
	Warfarin			16 (17.0%)
	Clopidogrel			24 (25.5%)
	Clopidogrel+ aspirin			2 (2.1%)
	Rivaroxaban			10 (10.6%)
LMWH bridging	No			68 (72.3%)
	Yes			26 (27.7%)
Diabetes mellitus	No			69 (73.4%)
	Yes			25 (26.6%)
Hypertension	No			45 (47.9%)
	Yes			49 (52.1%)
CAD	No			63 (67.0%)
	Yes			31 (33.0%)
Bleeding	No			92 (97.8%)
	Yes			2 (2.2%)
Platelets		126.00-495.00	231.50	241.26 ± 72.07
INR		0.88-2.10	1.04	1.13 ± 0.25
Continued medication	Yes			60 (63.8%)
	No			34 (36.2%)
PPI	Yes			48 (51.1%)
	No			46 (48.9%)
Polyp type	Flat			5 (3.0%)
	Pedunculated			17 (10.2%)
	Sessile			145 (86.8%)
Location	Distal colon			100 (59.9%)
	Proximal colon			67 (40.1%)
Polyp size (mm)		4.0-20.0	7.0	7.9 ± 3.3
Pathology				
Inflammatory polyp				2 (1.2%)
High-grade dysplasia				4 (2.4%)
Hyperplastic polyp				41 (24.6%)
Intramucosal adenocarcinoma				1 (0.6%)
Lost pathology				2 (1.2%)
Low-grade dysplasia				50 (29.9%)
Moderate dysplasia				6 (3.6%)
Serrated polyp				5 (3.0%)
Tubular adenoma				56 (33.5%)

Min-Max = minimum-maximum; SD = standard deviation; CAD = coronary artery disease; LMWH = low molecular weight heparin; INR = international normalized ratio; PPI = proton pump inhibitor.

Table 2. Groups that discontinued and continued the drug during polypectomy

		Medication continued		Medication discontinued		P
		Median ± SD or n (%)	Median	Median ± SD or n (%)	Median	
Age		64.2 ± 9.0	62.5	64.5 ± 5.8	64.5	0.741[m]
Sex	Female	20 (33.3%)		9 (26.5%)		0.489[χ²]
	Male	40 (66.7%)		25 (73.5%)		
Indication	Malignancy screening	31 (51.7%)		14 (41.2%)		0.328[χ²]
	Anemia	29 (48.3%)		20 (58.8%)		
Disease	Atrial fibrillation	2 (3.3%)		7 (20.6%)		**0.006**[χ²]
	Coronary bypass	4 (6.7%)		2 (5.9%)		0.881[χ²]
	CAD	26 (43.3%)		5 (14.7%)		**0.005**[χ²]
	Mitral valve replacement	3 (5.0%)		5 (14.7%)		0.105[χ²]
	Cardiac stents	23 (38.3%)		13 (38.2%)		0.993[χ²]
	Cardiac insufficiency	2 (3.3%)		2 (5.9%)		0.618[χ²]
Antithrombotic	Aspirin (100 mg)	33 (55.0%)		9 (26.5%)		**0.008**[χ²]
	Warfarin	4 (6.7%)		12 (35.3%)		**0.000**[χ²]
	Clopidogrel	13 (21.7%)		11 (32.4%)		0.254[χ²]
	Clopidogrel + aspirin	2 (3.3%)		0 (0.0%)		0.533[χ²]
	Rivaroxaban	8 (13.3%)		2 (5.9%)		0.260[χ²]
LMWH bridging	No	60 (100.0%)		8 (23.5%)		**0.000**[χ²]
	Yes	0 (0.0%)		26 (76.5%)		
Diabetes mellitus	No	46 (76.7%)		23 (67.6%)		0.342[χ²]
	Yes	14 (23.3%)		11 (32.4%)		
Hypertension	No	32 (53.3%)		13 (38.2%)		0.159[χ²]
	Yes	28 (46.7%)		21 (61.8%)		
Bleeding	No	58 (96.7%)		33 (97.1%)		1.000[χ²]
	Yes	1 (1.7%)		1 (2.9%)		
Platelets		231.8 ± 64.1	225.0	249.2 ± 54.5	250.0	**0.040**[m]
INR		1.1 ± 0.2	1.0	1.2 ± 0.3	1.1	**0.009**[m]

[m]Mann-Whitney U test; [χ²]chi-square test. SD = standard deviation; CAD = coronary artery disease; LMWH = low molecular weight heparin; INR = international normalized ratio.

Table 3. Types of polypectomy

		Forceps		Snare		P
		Median ± SD or n (%)	Median	Median ± SD or n (%)	Median	
Polyp type	Flat	0 (0.0%)		5 (5.5%)		**0.004**[χ²]
	Pedunculated	3 (3.9%)		14 (15.4%)		
	Sessile	73 (96.1%)		72 (79.1%)		
Location	Distal colon	40 (52.6%)		60 (65.9%)		0.081[χ²]
	Proximal colon	36 (47.4%)		31 (34.1%)		
Polyp size (mm)		4.8 ± 1.0	5.0	7.8 ± 3.2	7.0	**0.000**[m]

[m]Mann-Whitney U test; [χ²]chi-square test. SD = standard deviation.

Table 4. Types of snare polypectomy

		Cold			Hot			P
		Median ± SD or n %		Median	Median ± SD or n %		Median	
Polyp type	Flat	1	2.1%		4	10.3%		0.054[χ²]
	Pedunculated	5	10.4%		9	23.1%		
	Sessile	42	87.5%		26	66.7%		
Location	Distal colon	32	66.7%		26	66.7%		1.000[χ²]
	Proximal colon	16	33.3%		13	33.3%		
Polyp size (mm)		7.0 ±	2.1	6.0	9.0 ±	4.0	8.0	**0.011**[m]

[m]Mann-Whitney U test; [χ²]chi-square test. SD = standard deviation.

Aspirin is in common use for secondary prophylaxis against cardiovascular events and increases the bleeding time following endoscopic biopsy and polypectomy.[14] In a retrospective cohort study on 450 polypectomy procedures performed on 145 patients, comparing those who received aspirin with those who did not receive aspirin, Pan et al.[15] detected postpolypectomy bleeding in eight of the 145 patients, with a significantly higher risk of bleeding, compared with those who did not use aspirin.

According to the 2009 guidelines published by the American Society for Gastrointestinal Endoscopy (ASGE), cessation of aspirin usage is recommended in gastroenterological endoscopic procedures in which there is a high risk of bleeding.[16] Similarly, the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) recommend that aspirin therapy should be continued but then ceased five days prior to the procedure, among patients at low risk of thromboembolic events.[17] In the 2012 guidelines of the Japan Gastroenterological Endoscopy Society (JGES), cessation of aspirin therapy prior to a colonoscopic polypectomy procedure was not recommended.[11]

In a retrospective study, Yousfi et al.[18] showed that aspirin use did not increase the risk of bleeding; and a similar study by Manocha et al.[19] showed that aspirin use does not increase the risk of bleeding (3% versus 3.2%). In the present study, 73 polypectomy procedures were performed on 42 patients who were on aspirin therapy, and bleeding occurred in one patient. This bleeding rate was considered acceptable and comparable to the rates reported in the literature. We consider that the procedure may be performed safely in experienced clinics without cessation of this drug, considering the possibility that serious thromboembolic events could occur in cases of discontinuation of aspirin use.

Clopidogrel is a strong inhibitor of platelet adhesion and aggregation, and its use has increased significantly worldwide. The number of colonoscopic procedures performed while receiving this drug has also increased in parallel with the overall increase in the frequency and duration of clopidogrel use. In a meta-analysis on five studies, Gandhi et al.[20] reported that bleeding occurred following colonoscopic polypectomy in 37 (6.45%) out of 574 patients who used clopidogrel and that the risk of bleeding was significantly higher than in the control group. In contrast to this study, Chan et al.[21] reported that there was no significant difference in postpolypectomy bleeding in a randomized controlled study on 449 polypectomy procedures performed on 216 patients. Likewise, Singh et al.[22] showed in a retrospective study that clopidogrel use alone did not increase the risk of bleeding. In the present study, 39 polypectomy procedures were performed on 24 patients who were on clopidogrel therapy. The procedure was performed without cessation of the drug in 13 patients and with cessation of the drug in 11 patients. Bleeding occurred following the procedure in one patient whose medication was discontinued. Although no bleeding occurred in any patient in the group that continued to use the medication, these patients required close monitoring after the procedure, due to the higher risk of bleeding than with other antiplatelet medications.

The main guidelines recommend cessation of anticoagulants and bridging heparin therapy prior to polypectomy among patients at high risk of thrombosis.[11,23,24] In a retrospective study by Kubo et al.,[25] anticoagulant use was shown to be an independent risk factor, even if the anticoagulant medication was discontinued and the patient was switched to bridging therapy before the procedure. There have been many studies showing that a relationship exists between anticoagulant use and postpolypectomy bleeding.[26,27] Similarly, Sakai et al.[28] compared the bridging treatment group and the control group that did not use anticoagulants and found that there was higher risk of bleeding in the group treated with bridging. In the present study, 34 polypectomy procedures were performed on 16 patients who were on warfarin therapy. The polypectomy was performed without cessation of warfarin in four patients, whereas 12 patients were switched to bridging therapy prior to the procedure. No bleeding occurred during these procedures. Anticoagulant use and polypectomy procedures are still classified as high-risk procedures in the current guidelines. We suggest that utmost attention should be paid to the risk of bleeding, even if the international normalized ratio has returned to normal ranges.

In comparison with bleeding complications, thromboembolic events may have more serious consequences in patients whose antithrombotic medication is discontinued prior to an endoscopic biopsy.[9] Over recent years, systematic reviews and meta-analyses have been conducted to determine the risk of postpolypectomy bleeding in patients receiving antithrombotic therapy.[29] In one meta-analysis, Pigò et al.[30] showed that aspirin use increased the risk of bleeding from colorectal polyps. Similarly, Chan et al.,[21] in a randomized controlled study, found that clopidogrel use did not increase the risk of bleeding during or after the procedure. In a study involving 210 patients, Kubo et al.[25] found that there was no significant increase in the risk of bleeding other than with anticoagulant use and with bridging therapy in patients receiving antithrombotic medications.

Table 5. Bleeding patients

	Patient 1	Patient 2
Age	58	71
Sex	Female	Male
Drug	Aspirin (100 mg)	Clopidogrel
Disease	Coronary bypass	Cardiac stents
Location	Distal colon	Distal colon
Polyp size	8 mm	11 mm
Indication	Malignancy screening	Malignancy screening
Resection type	Forceps	Hot snare
With cessation	No	Yes
INR	0.96	1.04

INR = international normalized ratio.

In a similar study on 906 patients, Ishigami et al.[13] showed that anticoagulant use and bridging heparin therapy did not increase the risk of bleeding. In the present study, polypectomies were performed without cessation of antithrombotic medication in 60 out of 94 patients. Bleeding occurred following the procedure in one patient. In line with the current guidelines, we believe that polypectomies can be performed without discontinuing antiplatelet drugs such as aspirin and clopidogrel. Nonetheless, we recommend that patients on warfarin therapy should undergo the procedure with careful monitoring in well-established clinics, even if the international normalized ratio values are found to be within normal ranges.

The limitations of this study include its single-center design, the lack of sufficient randomization between the groups due to the observational nature of the study and the lack of power analysis, since the patients were using a wide variety of drugs. In addition, this study did not include patients with a high risk of bleeding, since the procedure was not performed on patients with an international normalized ratio level above 2.5. This was an important limitation of the study.

CONCLUSION

The present study showed that colonoscopic polypectomy procedures without discontinuation of antithrombotic medications do not increase the risk of bleeding. High-risk procedures such as colonoscopic polypectomies can be safely performed by experienced endoscopists in patients with an international normalized ratio below 2.5. However, these procedures are not necessarily mandatory in any patient undergoing anticoagulation.

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Association between frailty syndrome and sedentary behavior among community-dwelling older adults in the Amazon region: a cross-sectional study

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ABSTRACT

BACKGROUND: Existence of an association between sedentary behavior and frailty among older adults has been suggested. However, there is a lack of studies conducted in Brazil, especially in areas of the Amazon region.

OBJECTIVE: To analyze the association between frailty syndrome and sedentary behavior among community-dwelling older adults.

DESIGN AND SETTING: Cross-sectional study carried out in Macapá, state of Amapá, Brazil.

METHODS: Frailty status was assessed using Fried's frailty phenotype, and sedentary behavior was evaluated using two questions concerning time spent in a seated position, from the International Physical Activity Questionnaire (IPAQ). A multinomial logistic regression model was used to verify the association between frailty syndrome and sedentary behavior.

RESULTS: The final study sample was made up of 411 older adults with a mean age of 70.14 ± 7.25 years and an average daily duration of sedentary behavior of 2.86 ± 2.53 hours. The prevalence of non-frailty was 28.7%, prevalence of pre-frailty was 58.4% and prevalence of frailty was 12.9%. The adjusted analysis showed that there were independent associations between sedentary behavior and pre-frailty (odds ratio, OR = 1.18; 95% confidence interval, CI: 1.03-1.34) and between sedentary behavior and frailty (OR = 1.20; 95% CI: 1.02-1.40).

CONCLUSION: Frailty and pre-frailty status were associated with sedentary behavior among community-dwelling older adults.

INTRODUCTION

Over recent decades, the older adult population has dramatically increased worldwide.[1] This global phenomenon provides a challenge for healthcare systems,[2] and the World Health Organization has emphasized that achieving successful aging is currently a major concern.[3] Therefore, reducing the risks of sarcopenia, frailty and non-communicable diseases (NCDs) is a key goal for both individuals and policymakers.[3]

Diminution of sarcopenia (i.e. age-related loss of muscle mass and strength) could play a central role in reducing these risks, given that presence of sarcopenia can lead to reduced physical performance and impaired ability to perform activities of daily living, therefore increasing the risk of being frail.[4] Frailty (i.e. a state of vulnerability to stressors due to cumulative decline of physiological systems over the course of an individual's life) is associated with increased risk of falls, fractures, hospitalizations, iatrogenic complications and death.[5-7] In parallel with research on sarcopenia and frailty, sedentary behavior has gained prominence in the literature as a risk factor for NCDs.[8]

NCDs are the leading causes of death worldwide, with a disproportionate burden in low and middle-income countries.[9] Furthermore, a previous systematic review demonstrated that there was a clear dose-response relationship between physical activity and all-cause mortality among middle-aged and older adults.[10] Importantly, sedentary behavior has also been associated with sarcopenia[11] and frailty[12] among older adults.

Several studies have provided robust evidence on the relationship between sedentary behavior, physical activity and sarcopenia.[11,13-18] However, the association between sedentary behavior, physical activity and frailty has been less investigated. A recent systematic review investigated the association of sedentary behavior and frailty and highlighted the heterogeneity of samples included across studies, which may limit the generalizability of the results.[12]

It is noteworthy that there is a lack of studies conducted in the Amazon region, a place with great ethnocultural diversity and different socioeconomic characteristics. The diversity of this region may influence behaviors and health outcomes.[19]

Investigating this relationship can provide evidence for future healthcare policy strategies for elderly populations and for clinical decision-making processes.

OBJECTIVE

The aim of this study was to analyze the association between frailty syndrome and sedentary behavior among community-dwelling older adults. The hypothesis of this study was that sedentary behavior would be positively associated with frailty syndrome among older adults.

METHODS

Design and sample

This cross-sectional study was conducted in the urban area of Macapá, state of Amapá, Brazil. The study was approved (protocol no. 1.738.671; dated September 21, 2016) by the local human research ethics committee, and all participants signed an informed consent statement before commencing their study participation. Some results from this study have been previously reported.[20-22]

The urban population of Macapá was defined using multistage sampling with random selection of conglomerates. For the sample size calculation, the health problem was assumed to have a prevalence of 50% among the urban population of 19,955 older adults. With an accuracy of 5% and a confidence interval of 95%, a minimum sample of 377 individuals was found to be needed, to reach a representative sample of this population.

Adults aged 60 years or over who were able to walk, with or without walking assistance devices, were included. The exclusion criteria included: being lost to follow-up after three attempts, being institutionalized or hospitalized, having neurological diseases that made it impossible to do evaluations or presenting cognitive decline. The validated Brazilian version of the Mini-Mental State Examination was used to screen participants for cognitive decline.[23] A total of 443 older adults were recruited and assessed, of whom 27 were excluded because they showed cognitive decline, and another 5 were excluded for other reasons (such as incomplete data). After considering the eligibility and loss criteria, 411 community-dwelling older adults were finally included in this study.[22]

Data collection

Frailty syndrome (dependent variable)

Frailty was assessed using the frailty phenotype proposed by Fried et al.,[24] which is divided into five criteria.

The first criterion, (i) *Loss of muscle strength*, was assessed by means of a handgrip strength test, using a manual hydraulic dynamometer, and this was done in line with the recommendations of the American Society of Hand Therapists.[25] The mean of three measurements was used for the analysis, segmented with the cut-off values proposed by Fried et al.[24]

The second criterion, (ii) *Self-reported fatigue*, was evaluated using two items (7th and 20th) of the Brazilian version of the Center for Epidemiological Studies (CES-D) scale.[26] Participants who answered "2" or "3" to either of these items fulfilled the self-reported fatigue criterion.

The third criterion, (iii) *Low level of physical activity* was evaluated using the elderly-adapted long version of the International Physical Activity Questionnaire (IPAQ).[27] Participants who spent zero to 149 minutes per week on physical activities were classified as insufficiently active, as suggested by the American Heart Association and the College of Sports Medicine.[28] Those who spent 150 minutes or more on physical activities were considered sufficiently active.

The fourth criterion, (iv) *Slowed walking speed*, was defined as the time taken for the participant to walk the middle 4.6 meters of an 8.6-meter course, at his or her usual pace. The first two meters (acceleration) and the last two meters (deceleration) were excluded. The mean of three measurements was recorded for the analysis.

Lastly, (v) *Unintentional weight loss* was assessed through the question: "In the last year, have you lost more than 4.5 kg unintentionally (i.e. not due to dieting or exercise)?"

Individuals fulfilling three or more of these five components were classified as frail. Those who fulfilled one or two components were considered pre-frail, and those who fulfilled none of these criteria were classified as non-frail.[24]

Sedentary behavior (independent variable)

Sedentary behavior was the independent variable. The length of time exposed to sedentary behavior was evaluated through questions on the amount of time spent in a seated position on a usual weekday and on a usual weekend day (minutes/day). This was assessed using questions from IPAQ,[29] as validated for the elderly Brazilian population.[30,31] A weighted average, calculated as [(weekday x 5) + (weekend day x 2)]/7, was considered for the analysis.

Adjustment variables

The exploratory and adjustment variables were the following: (i) socioeconomic: age, gender, education, living arrangement and marital status; (ii) physical health: health perception, smoking and hospitalization in the last year (yes/no); and (iii) functional capacity. Functional capacity was measured using the Katz

index[32] and the Lawton and Brody scale,[33] which assess functional impairment with regard to basic and instrumental activities of daily living, respectively.

Data analysis

The descriptive statistics calculated included means, standard deviations, absolute numbers and percentages. To verify associations between the categorical variables, the chi-square test was applied; and, between numerical variables, one-way analysis of variance (ANOVA) with post-hoc Dunnett T3, for multiple comparisons among groups ($P < 0.05$). A multinomial logistic regression model, adjusted for socioeconomic, clinical and health characteristics, was run to examine the association between frailty syndrome and sedentary behavior. Odds ratios (OR) with 95% confidence interval (CI) and a significance level of 5% ($P < 0.05$) were used. All the data were analyzed using version 25.0 of the Statistical Package for the Social Sciences (SPSS) software (New Orchard Road, Armonk, New York, United States).

RESULTS

Four hundred and eleven older adults with a mean age of 70.14 ± 7.25 years were evaluated. Women comprised 66.4% of the sample. The length of time spent on sedentary behavior was 2.86 ± 2.53 hours. Only 12.9% (n = 53) of the participants were classified as frail, while 58.4% (n = 240) were classified as pre-frail and 28.7% (n = 118) as non-frail. Frailty syndrome was associated with age, education, marital status, health perception, hospitalization in the last year and functional dependence regarding basic and instrumental activities of daily living ($P < 0.05$) (**Table 1**)

The adjusted analysis showed that there were independent positive associations between sedentary behavior and frailty (OR = 1.20; 95% CI: 1.02-1.40) and between sedentary behavior and pre-frailty (OR = 1.18: 95% CI: 1.03-1.34) (**Table 2**).

DISCUSSION

The findings from this study conducted using a representative sample of older adults differ from those in previous studies conducted in Brazil and elsewhere around the world, in community-dwelling

Table 1. Socioeconomic, clinical and health characteristics of community-dwelling older adults. Macapá, Amapá, Brazil, 2017 (n = 411)

Variables	Frailty syndrome			P	Total sample (n = 411)
	Frail 53 (12.9%)	Pre-frail 240 (58.4%)	Non-frail 118 (28.7%)		
Age (years)	74 ± 8.49	70.64 ± 7.26	67.41 ± 5.44	< 0.001*	70.14 ± 7.25
Sex					
Male	13 (24.5%)	77 (32.1%)	48 (40.7%)	0.088	138 (33.6%)
Female	40 (75.5%)	163 (67.9%)	70 (59.3%)		273 (66.4%)
Education (years)	4.43 ± 4.37	5.61 ± 5.21	6.78 ± 5.55	0.010**	5.79 ± 5.25
Marital status					
With partner	49 (41.5%)	140 (58.3%)	31 (58.5%)	0.008	220 (53.5%)
Without partner	69 (58.5%)	100 (41.7%)	22 (41.5%)		191 (46.5%)
Living arrangement					
Alone	2 (3.8%)	15 (6.2%)	11 (9.3%)	0.357	28 (6.8%)
Accompanied	51 (96.2%)	225 (93.8%)	107 (90.7%)		383 (93.2%)
Health perception					
Positive	53 (44.9%)	63 (26.3%)	8 (15.4%)	< 0.001	124 (30.2%)
Negative	65 (55.1%)	177 (73.8%)	44 (84.6%)		286 (69.6%)
Smoking habit					
Yes	10 (8.5%)	25 (11.7%)	1 (1.9%)	0.081	39 (9.5%)
No	118 (91.5%)	212 (88.3%)	52 (98.1%)		372 (90.5%)
Hospitalization in the last year					
Yes	10 (8.5%)	35 (14.6%)	13 (24.5%)	0.019	58 (14.1%)
No	108 (91.5%)	205 (85.4%)	40 (75.5%)		353 (85.9%)
BADL					
Dependent	8 (15.1%)	18 (7.5%)	4 (3.4%)	0.024	30 (7.3%)
Independent	45 (84.9%)	222 (92.5%)	114 (96.6%)		381 (92.7%)
IADL					
Dependent	43 (81.1%)	175 (72.9%)	68 (57.6%)	0.002	286 (69.6%)
Independent	10 (18.9%)	65 (27.1%)	50 (42.4%)		125 (30.4%)
Sedentary behavior (hours)	3.28 ± 2.77	3.01 ± 2.77	2.40 ± 1.74	0.038***	2.86 ± 2.53

Data are reported as n = number of subjects; mean ± standard deviation; $P < 0.05$; BADL = basic activities of daily living; IADL = instrumental activities of daily living; Multiple comparisons between groups: significant differences ($P < 0.05$) were observed between the three groups. *Non-frail ≠ Pre-frail ≠ Frail; **Non-frail ≠ Frail; ***Non-frail ≠ Pre-frail.

and hospitalized elderly populations.[34-38] We found shorter exposure to sedentary behavior than in previous studies and independent associations between sedentary behavior and both frailty and pre-frailty. While we found that community-dwelling older adults were spending nearly 2.88 hours engaged in sedentary behavior, previous studies have found that older adults engage in sedentary behavior for an average of 6.1[37] to 8.5 hours[34] per day. The exposure to sedentary behavior in the present study was also shorter than the exposure reported in other Brazilian studies. Da Silva et al. analyzed 285 women and 172 men between 60 and 97 years old, and identified that the an average length of time that they were spending on sedentary behavior was nearly 7 hours a day.[37]

It should be noted that previous studies have demonstrated that respondents may overestimate their physical activity levels when using self-reported instruments.[39,40] Nevertheless, previous Brazilian studies that used self-reported instruments also found higher values for exposure to sedentary behavior than we found in our present study.[37]

Our hypothesis for the difference regarding the time spent on sedentary behavior is that the population of this study has specific sociocultural conditions. It is known that older women are usually more physically active than older men,[41,42] as older women tend to spend more time on physical activities, such as doing housework and taking care of their grandchildren.[43] Moreover, domestic physical activity accounts for a significant proportion of self-reported daily physical activity, particularly among females.[43] Since most of our sample was composed of women, and women in the north of Brazil often do most of the housework,[19] this may explain why we found lower values for exposure to sedentary behavior than in previous studies.

Another important factor relates to the place of residence. A previous study conducted among older adults in the Amazon region found that these individuals engaged in higher levels of physical activity than what had been found in previous studies.[19] These results suggest that the physical activity level of older adults and, consequently, the aging process, is influenced by where they have resided

Table 2. Association between frailty syndrome and sedentary behavior, controlled for socioeconomic, clinical and health characteristics. Macapá, Amapá, Brazil, 2017 (n = 411)

Variables	Frailty syndrome*					
	Pre-frail			Frail		
	OR	95% CI	P	OR	95% CI	P
Age (years)	1.06	1.02-1.10	0.003	1.11	1.05-1.17	< 0.001
Sex						
Male	1.95	1.17-3.26	0.755	1.66	0.70-3.88	0.243
Female		1			1	
Education (years)	0.98	0.94-1.03	0.556	0.96	0.88-1.03	0.317
Marital status						
With partner		1			1	
Without partner	0.50	0.29-0.85	0.011	0.62	0.28-1.37	0.243
Living arrangement						
Alone	1.72	0.67-4.41	0.255	1.54	0.27-8.56	0.619
Accompanied		1			1	
Health perception						
Positive		1			1	
Negative	1.95	1.17-3.26	0.010	3.24	1.31-8.02	0.011
Smoking habit						
Yes	2.19	0.94-5.07	0.067	0.41	0.04-3.52	0.418
No		1			1	
Hospitalization in the last year						
Yes	2.02	0.90-4.51	0.085	3.42	1.23-9.47	0.011
No		1			1	
BADL						
Dependent	2.02	0.61-6.67	0.249	3.01	0.73-12.46	0.127
Independent		1			1	
IADL						
Dependent	1.46	0.87-2.47	0.149	1.55	0.65-3.72	0.321
Independent		1			1	
Sedentary behavior (hours)	1.18	1.03-1.34	0.013	1.20	1.02-1.40	0.023

Data are reported as n = number of subjects; mean ± standard deviation; OR = odds ratio; 95% CI = 95% confidence interval; P < 0.05; BADL = basic activities of daily living: IADL = instrumental activities of daily living; 1 = reference category; *Non-frail = reference category; Adjusted for age, gender, education, living arrangement, marital status, health perception, smoking, hospitalization in the last year and functional impairment regarding basic and instrumental activities of daily living.

over their lives.[19] Further studies may clarify the influence of housing conditions on the exposure to sedentary behavior and physical activity levels among older adults in the Amazon region.

The prevalence of frailty (12.9%) in the present study was also lower than what was reported through a systematic review with meta-analysis on studies conducted in countries in Latin America and the Caribbean, in which it was found that 19.6% of the older adults were frail.[44] One likely explanation for divergences in the prevalence of frailty may lie in the conceptual and operational definitions used for identification of frailty, along with the locoregional specificities of the study sample.[45] Importantly, a previous study also found lower prevalence of frailty (9.4%) among older adults in the Amazon region than among those in other Brazilian cities. The authors of that study highlighted that the influence that Amazonian culture and environment have on lifestyle over the course of life may have a protective effect on health outcomes in later life.[46]

In line with our hypothesis, sedentary behavior was associated with both pre-frailty and frailty. In agreement with our findings, Silva Coqueiro et al.,[47] Da Silva et al.[37] and Da Silva et al.[48] found associations between frailty and sedentary behavior among older adults. However, our study was the first Brazilian study to also identify an association between pre-frailty and sedentary behavior, even after adjusting for other variables. This result is especially important, since it indicates that as the exposure to sedentary behavior rises, the level of frailty increases. In line with this hypothesis, a previous study found that the effect of sedentary behavior on mortality varied according to the level of frailty, such that participants with the highest frailty level experienced the greatest adverse impact on mortality rates.[49]

The fact that most of our sample was found to be pre-frail (58.4%) deserves special attention, considering that this group is more likely to progress to frailty, a potentially severe condition. Sedentary behavior is a potentially modifiable factor and, therefore, the fact that over half of our population showed pre-frailty underscores the need for wider early identification and intervention efforts among older adults. Although pre-frail older adults will not necessarily become frail, they face the possibility that their condition may worsen. Indeed, around one-quarter[50] to one-third[51] of pre-frail adults can expect to transition to frailty within a year's time. This possibility of a worsening condition implies the need for timely management aimed at delaying or possibly preventing additional deterioration in pre-frail individuals and, hence, future functional losses. It is not clear whether specific interventions could prevent frailty in already-at-risk individuals, but studies seem to suggest that pre-frail older adults respond better to health interventions than do frail older adults.[52-54]

Importantly, previous studies demonstrated that more prolonged exposure to sedentary behavior is detrimentally associated not only with frailty, but also with higher levels of inflammatory markers[55] and higher risk of cardiovascular diseases, cancer and all-cause mortality among older adults.[56,57] There is still much to be understood about physiological maladaptation to sedentary behavior. However, finding interventions to reduce sedentary behavior effectively should be a key research priority for healthcare providers and policymakers. This is because sedentary individuals may experience a vicious cycle, in which loss of muscle mass and strength may lead to disability[4] and disability boosts sedentariness.[58] This, in turn, may perpetuate an elevated inflammatory load[55] and promote subsequent additional loss of muscle mass.[18] Despite the devastating consequences that loss of muscle mass, chronic inflammation and impaired physical function have on older adults, society and the economy, few interventions have been proven to be effective in counteracting age-related loss of muscle mass. While physical activity is known to be beneficial to the functioning of different systems in individuals with NCDs,[59] and to be helpful in preventing functional declines, more intense and better targeted efforts are needed in order to disrupt the cycle of loss of muscle mass.

Due to the cross-sectional nature of the present study, our results should be interpreted with caution. However, this study was conducted on a representative sample of well-described community-dwelling older adults, and it underscores the notion that sedentary behavior can potentialize functional decline among both frail and pre-frail older adults. Therefore, future randomized controlled trials will be crucial in helping to find effective interventions, not only to improve adherence to regular physical activity, but also to help mitigate exposure to sedentary behavior and prevent further functional declines and adverse health outcomes.

CONCLUSION

Frailty and pre-frailty were associated with sedentary behavior among these community-dwelling older adults. This study provides critical data upon which to base future strategies that would target diminution of sedentary behavior, so as to aid in prevention of pre-frailty and frailty among community-dwelling older adults.

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Association between tracking of extracurricular sports practice and weight status during childhood: a prospective cohort study

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ABSTRACT

BACKGROUND: Overweight and obesity have reached epidemic prevalences. Obesity control involves many factors and needs to begin early in childhood.

OBJECTIVES: To ascertain the association between tracked extracurricular sports practice and weight status; and to analyze tracking of overweight and obesity among school-aged children.

DESIGN AND SETTING: Prospective cohort study conducted in 13 public schools in Cianorte, Paraná, in 2012-2016.

METHODS: The sample comprised 2459 schoolchildren in Cianorte, of mean age 6.3 years at baseline and 9.4 years at follow-up. Body mass index was calculated from body mass and height measurements. The children were grouped as normal weight, overweight or obese. Information on extracurricular sports practice was collected through the dichotomous question "Do you participate in any extracurricular sports?" ("yes" or "no").

RESULTS: Tracking of weight status showed that 75.5% maintained this, with kappa of 0.530. Tracking of extracurricular sports practice showed that 80.9% maintained this, with low concordance (kappa of 0.054). Weight status correlation between baseline and follow-up showed that overweight or obese individuals were 4.65 times (CI: 4.05-5.34) more likely to maintain the same classification or move from overweight to obese at follow-up. Correlation of extracurricular sports practice with overweight or obesity at follow-up was not significant.

CONCLUSIONS: These results demonstrated that overweight or obese children were at higher risk of gaining weight than were normal-weight children. In addition, the proportion of these children who maintained extracurricular sports practices over the years was low. Maintenance of this variable was not associated with weight status.

INTRODUCTION

Elevation of body mass index (BMI) levels has reached an alarming status within public health, both in developed and in developing countries. This has been seen as a gradual rise in the prevalence of overweight and obesity in different age groups.[1-5] In a systematic review performed by Ng et al.,[6] the prevalence of overweight or obesity was reported to be approximately 47% among children worldwide. Among the different factors that have contributed to this increase is a decline in physical activity levels.

In Brazil, it has been estimated that 269.6 million dollars are spent annually on combating obesity and related complications.[7] A survey conducted in state capitals in 2014 showed that the prevalence of overweight in the Brazilian adult population was more than 51%.[8] Among children and adolescents, the prevalence of overweight was 22% and 24%, respectively.[9] More than 70% of subjects who presented higher adiposity in childhood remained under the same condition during adolescence.[10] This is worrying, as the adolescent population presents a higher risk of maintaining this indicator in adulthood.[11,12]

The Bogalusa Heart Study, conducted between the 1970s and 1990s, indicated that obesity in children and adolescents is linked, respectively, to 2.4 and 7.1 times higher risk of presenting high cholesterol and triglycerides, in comparison with the population with normal body mass index.[12] This increase in body mass index is associated with different risk factors for cardiovascular diseases, for example: high blood pressure, dyslipidemias, fasting insulin and risk score.[13,14]

Sports practice, predominantly performed in schools, has been considered to be one of the main forms of elevating daily energy expenditure among school-age children, and this is associated with weight control.[15] However, little is known about the longitudinal impacts of sports practice on prevention of overweight in childhood, since the majority of studies have attempted to observe this occurrence using cross-sectional designs.[15-17] Such studies do not longitudinally evaluate changes in or maintenance of weight status, or sports practice, in this population.

OBJECTIVE

The aim of this study was to ascertain the association between tracked extracurricular sports practice and weight status; and to analyze the tracking of overweight and obesity among schoolchildren during childhood.

METHODS

Study design and sample selection

The data used in this study formed part of a database named: "Relationship of high blood pressure with body composition indicators among students in Cianorte, Paraná". This project was carried out between 2012 and 2016 and was approved by a local university ethics committee for human research (no. 1,362,937). All the parents were informed of the procedures and only the children whose parents had signed a consent statement participated in the research. Data were collected by a previously trained researcher with understanding about protocols.

Cianorte is a municipality in the state of Paraná, Brazil, with 69,958 inhabitants, a literacy rate of 94.4%, human development index of 0.755 and *per capita* gross domestic product of 29,321 reais in 2015.

The sample was composed of all students enrolled in the municipality's 13 public schools, aged 5-8 years. All students were invited to participate in the research, and only those who were absent on the day of the test were not included in the sample. For the present study, only the data from the students who underwent both baseline and follow-up measurements (follow-up three years later) were used in the analysis, totaling 2,459 subjects in the sample. The total number of children who dropped out from the research was 981 individuals. A comparison between the children who dropped out and those who completed the follow-up is presented in **Table 1**.

Weight status classification

Body mass was assessed using a platform digital scale (model CA8000; G-life, São Paulo, Brazil), with precision of 0.1 kg. Height was measured using a portable stadiometer (Alturexata, Belo Horizonte, Brazil), with accuracy of 0.1 cm. The protocols followed the procedures described by Gordon et al.[18] Body mass index (BMI) was determined from the body mass/height^2 quotient, in which body mass was expressed in kilograms (kg) and height in meters (m).

The BMI cutoff points used followed the recommendations of the World Health Organization,[19] in agreement with age and sex. Body mass index values were classified as underweight, normal weight, overweight or obese. For the purposes of this analysis, subjects classified as underweight and normal weight were grouped as normal weight (NW), while overweight (OW) and obesity (OB) were maintained as separate categories.

Sports practice

Extracurricular sports practice was observed during data collection every year throughout the study, using the following dichotomous question "Do you participate in any extracurricular sports?" with answer options of "yes" or "no". In the analysis in which extracurricular sports practice was tracked, the subjects were grouped into the following categories: practice to practice (P-P); practice to no practice (P-NP); no practice to practice (NP-P); or no practice to no practice (NP-NP).

Table 1. Dropout analysis

	5 years old		6 years old		7 years old		8 years old	
	Dropped out (n = 115)	Followed (n = 525)	Dropped out (n = 172)	Followed (n = 881)	Dropped out (n = 170)	Followed (n = 764)	Dropped out (n = 524)	Followed (n = 289)
Age (years)	5.1 (4.9-5.3)	5.2 (5.0-5.3)	6.0 (5.8-6.2)	6.0 (5.7-6.3)	7.0 (6.8-7.3)	7.0 (6.7-7.2)	**8.1 (7.8-8.2)***	**7.7 (7.6-8.0)***
Body mass (kilograms)	19.4 (18.0-21.7)	19.7 (17.6-21.8)	21.6 (19.5-24.0)	21.7 (19.6-24.8)	24.8 (22.1-27.6)	24.2 (21.6-28.2)	**27.7 (24.6-32.9)***	**26.0 (23.3-30.4)***
Height (centimeters)	110.7 (108.5-114.2)	111.1 (107.5-114.4)	116.9 (114.0-120.6)	116.8 (113.1-120.5)	122.1 (118.4-126.8)	122.4 (118.6-126.5)	**129.0 (124.8-132.7)***	**126.4 (123.2-130.9)***
Body mass index (kg/m^2)	15.9 (15.0-17.2)	15.9 (14.9-17.1)	15.6 (14.8-17.2)	16.0 (15.0-17.4)	16.4 (15.4-18.1)	16.2 (15.0-18.0)	**16.9 (15.4-19.1)***	**16.3 (15.3-18.1)***

*Significant differences ($P < 0.05$) between children who dropped out and those who continued to be followed up in the study. Values are expressed in medians and interquartile ranges. Groups were compared by means of the Mann-Whitney U test.

Statistical analysis

The sample were characterized in terms of medians and interquartile ranges. Data normality was tested using the Kolmogorov-Smirnov test, and comparisons were then made using the Wilcoxon test. BMI was tracked in relation to extracurricular sports practice and was evaluated through the percentage of subjects who remained in the same classification over the years. The agreement between baseline and follow-up was calculated by means of the kappa index, which takes into account the proportion of observed (Po) and expected (Pe) agreement (kappa: Po - Pe / 1 - Pe); analyses were performed stratified according to sex and group. Associations were analyzed using hazard ratios (HR) and assessed using the Cox multivariate regression model. All analyses were adjusted for sex, age, extracurricular sports practice and BMI at baseline. The software used was SPSS 25.0 (IBM, New York, United States) and values were considered significant at $P < 0.05$.

RESULTS

Table 1 presents sample characterization values at both analysis times (baseline and follow-up). The sample consisted of 1,247 boys and 1,212 girls and all sample characterization values presented significant differences ($P < 0.05$) between the analysis times. Body mass and height values presented increases of approximately 30% and 15%, respectively, for both sexes by the end of the analysis period. These disproportionate increases resulted in higher body mass index values for this population at the time of the follow-up.

The tracked weight status values are presented in **Table 2**. It can be seen that 74.4% of the boys presented maintenance of weight status classification over the three years, with kappa classified as moderate ($K = 0.523$; $P < 0.01$), while 76.8% of the girls maintained this, with moderate kappa index ($K = 0.537$; $P > 0.01$). In contrast, approximately 25% of the subjects changed their weight status classification. This occurred mostly among individuals in the normal weight group, who increased their BMI. Only a small proportion of the overweight or obese children at the baseline changed their weight status to normal weight.

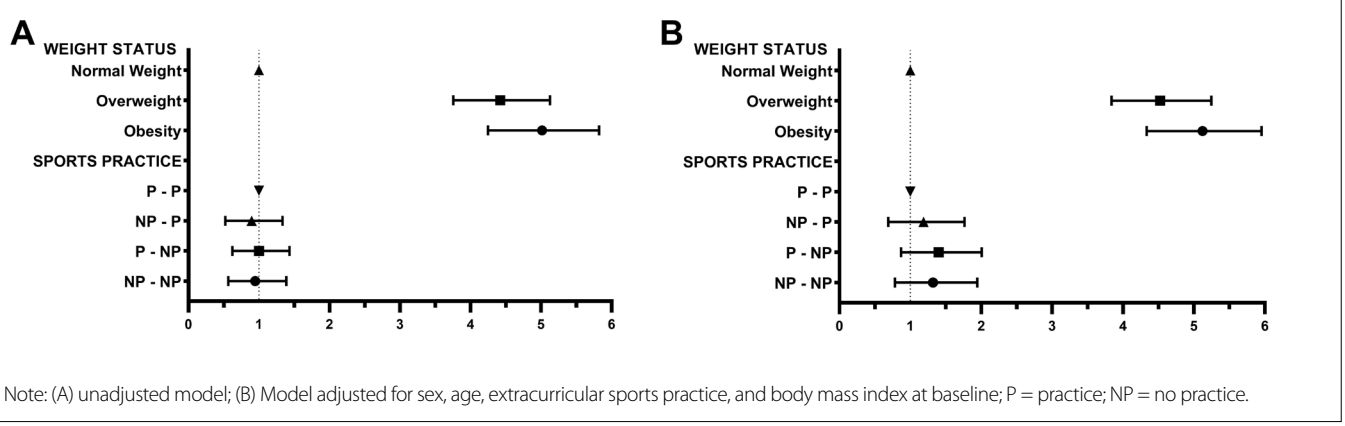
Table 3 shows that the children tended to remain within the same sports practice classification, since tracking values of 76.5% and 84.2% were reported for the boys and girls, respectively. The incidence of extracurricular sports practice was extremely low (12.3%), and only 1.8% of the individuals maintained this practice over the three years. The kappa values for the boys did not show significant agreement, and the girls presented a poor kappa index ($K = 0.108$).

Figure 1 presented the hazard ratio analysis (HR). This showed that overweight in childhood resulted in a 4.48 times higher risk of remaining in the same category or being classified as obese at the follow-up (odds ratio, OR: 4.48; confidence interval, CI: 3.83-5.24),

Table 2. Characteristics of the sample, separated according to sex, between the baseline and the follow-up

	Boys (n = 1,247)			Girls (n = 1,212)		
	Baseline	Follow-up	P	Baseline	Follow-up	P
Age (years)	6.4 (5.6-7.1)	9.7 (8.7-10.2)	< 0.01	6.2 (5.5-7.0)	9.5 (8.6-10.0)	< 0.01
Body mass (kilograms)	22.9 (20.3-26.4)	32.7 (28.4-40.2)	< 0.01	22.0 (19.6-25.7)	32.2 (27.2-39.3)	< 0.01
Height (centimeters)	119.3 (114.0-124.5)	137.1 (131.6-142.3)	< 0.01	117.5 (112.5-123.0)	136.0 (130.3-142.2)	< 0.01
Body mass index (kg/m²)	16.1 (15.1-17.5)	17.4 (15.8-20.4)	< 0.01	16.0 (14.9-17.6)	17.3 (15.6-20.0)	< 0.01

Values are presented as medians and interquartile ranges. The baseline and follow-up values were compared and differences were considered significant if $P < 0.05$.



Note: (A) unadjusted model; (B) Model adjusted for sex, age, extracurricular sports practice, and body mass index at baseline; P = practice; NP = no practice.

Figure 1. Cox regression model: hazard ratio of overweight or obesity in follow-up, with weight status at baseline and tracking of extracurricular sports practice.

compared with individuals of normal weight. Children classified as obese presented the same tendency, with a 5.08 times greater risk (OR: 5.08; CI: 4.33-5.95).

The tracking of extracurricular sports practice in relation to excess weight at the follow-up did not present significant results. The reference category was the group that practiced sports at both analysis times. For the group that practiced sports only at the time of the follow-up (NP – P), the OR was 1.10 (CI: 0.69-1.76). For the group that did not practice sports at the time of the follow-up (P – NP) or at either time (NP – NP), the ORs were 1.32 (CI: 0.87-2.00) and 1.23 (CI: 0.78-1.99), respectively.

DISCUSSION

The aim of the present study was to ascertain the association between tracked extracurricular sports practice and weight status, and to track overweight and obesity among schoolchildren during three years of follow-up. The main finding was that children with excess weight maintained their classification after three years of evaluation. In addition, no association was found between tracked extracurricular sports practice and weight status. Only a low number of children participated in sports outside school.

Although no direct association was found between extracurricular sports practice and the prevalence of obesity at the time of the follow-up, it was observed that a large number of children did not practice sports frequently: approximately 85%. This is worrying, since sports practice may be directly associated with levels of physical activity and cardiorespiratory fitness during adolescence. Werneck et al.[20] showed that sports practice was indirectly associated with metabolic risks and demonstrated that there was an association between sports practice during childhood and physical activity during adolescence.

In a systematic review, Hallal et al.[21] confirmed the hypothesis that sports practice during childhood was directly linked to physical activity levels during adolescence. In addition, a study in Finland on 7,794 individuals found that sports practice during childhood led to greater likelihood that these children would become physically active adults.[22] Moreover, maintenance of sports practice during adolescence is an essential indicator of weight status in adulthood; maintenance of sports practice during adolescence plays an important role in controlling BMI in adulthood.[23]

One possible explanation for the present results, in which no association was found between extracurricular sports practice and weight status, is that the sports practice tracked tended to be significant only for late adolescence and adulthood. Tracking of sports practice from early adolescence to adulthood shows that this practice seems to be not significant,[24] thus suggesting that there is a specific point within adolescence (late adolescence) that influences individuals' involvement in sports practice.

Moreover, sports practice has been correlated with daily calorie expenditure,[25] which seems to be influenced by the intensity, duration, and frequency of sports. This is another possible factor affecting the association between sports practice and weight status,

Table 3. Tracking of weight status and sports practice between the baseline and follow-up

Weight status		Boys (n = 1,245)	Girls (n = 1,211)	Total (n = 2,456)
Baseline	**Follow-up**	**% (n)**	**% (n)**	**% (n)**
NW	**NW**	53.8 (667)	59.1 (716)	56.3 (1383)
NW	**OW**	10.2 (127)	9.2 (112)	9.7 (239)
NW	**OB**	3.1 (38)	1.5 (18)	2.3 (56)
OW	**NW**	4.1 (51)	3.8 (46)	3.9 (97)
OW	**OW**	7.7 (96)	8.4 (102)	8.1 (198)
OW	**OB**	5.8 (72)	6.0 (73)	5.9 (145)
OB	**NW**	0.5 (6)	0.7 (9)	0.6 (15)
OB	**OW**	2.2 (28)	1.8 (22)	2.0 (50)
OB	**OB**	12.9 (160)	9.3 (113)	11.1 (273)
% Tracking		74.4	76.8	75.5
Kappa		0.523*	0.537*	0.530*
Extracurricular sports		**Boys (n = 1,241)**	**Girls (n = 1,203)**	**Total (n = 2,444)**
Baseline	**Follow-up**	**% (n)**	**% (n)**	**% (n)**
P	**P**	1.7 (21)	1.8 (22)	1.8 (43)
P	**NP**	8.3 (103)	5.3 (64)	6.8 (167)
NP	**NP**	75.8 (941)	82.5 (992)	79.1 (1993)
NP	**P**	14.2 (176)	10.4 (125)	12.3 (301)
% Tracking		76.5	84.2	80.9
Kappa		0.009	0.108*	0.054#

*Values with P < 0.001; #Values with P < 0.05.

NW = normal weight; EW = excess weight; P = practice; NP = no practice.

although the intensity, duration, and frequency of sports practiced were not evaluated in the present study.

Median body mass index values of 16.1 and 16.0 kg/m² at the baseline and 17.4 and 17.3 km/m² at the follow up were shown for boys and girls respectively in the present study. Over this three-year period, there was an increase in body mass index of 1.3 kg/m² for the boys and girls. The results from the present study are in accordance with findings from the NCD Risk Factor Collaboration, in which data on 128.9 million children and adolescents aged 5-19 years were analyzed. It was found that body mass index values were increasing by approximately 0.40 kg/m² every decade. These changes in body mass index had resulted in increased health risks relating to weight status.[26]

In a longitudinal analysis covering 22 years, Freedman et al.[27] reported that high body mass index values in childhood were strongly associated with obesity in adulthood (BMI ≥ 40). Their results demonstrated that weight status had strong tendency to remain in the same classification from childhood to adolescence,[28,29] and that the trend became stronger with increasing body mass index among children with severe obesity, in comparison with their peers.[27] This can be explained, at least in part, by the fact that children who tend to maintain the same excess weight classification may have inadequate dietary habits and sedentary behavior. In other words, they consume larger amounts of sugary foods and spend more time watching television.[30] However, these hypotheses could not be verified in the present study.

Likewise, a study in which body adiposity was tracked among children, based on skinfold measurements (subscapular and triceps) and controlled in relation to baseline body mass index, showed that 70% of the subjects remained in the highest tercile. It was also found that approximately 29% of the subjects classified in the low and medium terciles presented increased adiposity and were reclassified into the highest tercile over the three-year period.[10] The results from that study were similar to those of the present study, in which 12.0% of the subjects changed from normal weight to overweight or obesity.

The results from the hazard ratio analysis on the children and adolescents at the three-year follow-up demonstrated that overweight or obese children at the baseline were 4.65 times (CI: 4.05-5.34) more likely to remain in the same classification or to move from the overweight group to the obese group. This was very similar to what was found in an American population that was followed up for 22 years, in which obese children were 2.7 times more likely to present class 3 obesity in adulthood.[27]

Obesity control is important, given that obese children are up to 1.5 times more likely to develop type 2 diabetes in adulthood than their peers with adequate weight status. A population that continually presented obesity from childhood to adulthood was three times more likely to develop type 2 diabetes.[31] Children in the highest body mass index tercile were 4.8 and 1.9 times more likely to present altered fasting insulin and triglyceride values, respectively, than were their peers in the lowest tercile.[12]

Regarding limitations of the present study, some information relating to extracurricular sports practice was not obtained, including intensity, volume and type of sport practiced. Also, no information about sociodemographic variables was assessed. On the other hand, the strong points of the present study were that it provided a longitudinal analysis over a three-year period, with a large sample size in relation to the total population.

CONCLUSION

The results from the present study demonstrated that there was a tendency for these children and pre-adolescents to present increases in body mass index values over time. Moreover, the risk that overweight children would gain weight (thus becoming obese) was higher than the risk that normal-weight children would gain weight. The analysis on extracurricular sports practice did not demonstrate any association with weight status among these schoolchildren. Further longitudinal studies should explore the characteristics of sports practice (intensity, volume, frequency and type), analyzed in relation to tracking of excess weight.

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The effect of proliferative hypertrophic scars on determining treatment options for preventing recurrence of vesicourethral anastomotic stenosis after radical prostatectomy: a single-center cross-sectional study

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Vesicourethral anastomotic stenosis.

ABSTRACT

BACKGROUND: Vesicourethral anastomotic stenosis (VUAS) following retropubic radical prostatectomy (RRP) significantly worsens quality of life.

OBJECTIVES: To investigate the relationship between proliferative hypertrophic scar formation and VUAS, and predict more appropriate surgical intervention for preventing recurrent VUAS.

DESIGN AND SETTING: Retrospective cross-sectional single-center study on data covering January 2009 to December 2019.

METHODS: Among 573 male patients who underwent RRP due to prostate cancer, 80 with VUAS were included. They were divided into two groups according to VUAS treatment method: dilatation using Amplatz renal dilators (39 patients); or endoscopic bladder neck incision/resection (41 patients). The Vancouver scar scale (VSS) was used to evaluate the characteristics of scars that occurred for any reason before development of VUAS.

RESULTS: Over a median follow-up of 72 months (range 12-105) after RRP, 17 patients (21.3%) had recurrence of VUAS. Although the treatment success rates were similar (79.5% versus 78.0%; P = 0.875), receiver operating characteristic (ROC) curve analysis indicated that dilatation using Amplatz dilators rather than endoscopic bladder neck incision/resection in patients with VSS scores 4, 5 and 6 may significantly reduce VUAS recurrence. A strong positive relationship was observed between VSS and total number of VUAS occurrences (r: 0.689; P < 0.001). VSS score (odds ratio, OR: 5.380; P < 0.001) and time until occurrence of VUAS (OR: 1.628; P = 0.008) were the most significant predictors for VUAS recurrence.

CONCLUSIONS: VSS score can be used as a prediction tool for choosing more appropriate surgical intervention, for preventing recurrent VUAS.

INTRODUCTION

The common feature of urethral stricture, bladder neck stenosis and surgical incision scars is that they develop due to poor wound healing.[1,2] In the pathogenesis of these disorders, many mediators and molecules such as transforming growth factor-β1, basic fibroblast growth factor and platelet-derived growth factor play a role. These conditions develop as a result of chronic inflammation.[3]

The rate of hypertrophic scar development in the whole population has been reported to be 1.5-4.5%.[4] Although the anterior chest wall and posterior ear are the most common sites for hypertrophic scar formation among anatomical regions, these scars may also be commonly seen elsewhere in the upper body. Individual predisposition, various genetic and hereditary factors and various systemic diseases may also facilitate development of proliferative hypertrophic scars.[4]

Although some studies have shown that the presence of hypertrophic scars may be an independent factor for predicting the development of urethral stenosis, we could not find any study that had directly investigated the relationship between proliferative hypertrophic scar formation and vesicourethral anastomotic stenosis (VUAS) after retropubic radical prostatectomy (RRP).

OBJECTIVES

Our aim was to evaluate the existence of this relationship. In addition, we aimed to predict which surgical intervention for VUAS might be more appropriate for preventing recurrent stenosis, depending on the degree of proliferative hypertrophic scar formation.

METHODS

Patients and study design

Our study was designed as a cross-sectional study after obtaining approval from the local ethics committee (protocol number: 77192459-050.99-E.12077 - 7/35; date of approval: November 12, 2019) and written informed patient consent. A total of 573 male patients aged 56-74 years who underwent open RRP due to prostate cancer, operated by the same surgical team between January 2009 and December 2019, were retrospectively evaluated. Our study was conducted 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. We also used a checklist in accordance with the STROBE recommendations (STrengthening the Reporting of OBservational studies in Epidemiology).

Patient demographic data, comorbidities, medical treatments, previous surgeries and clinical data relating to prostate cancer were recorded. Intraoperative and postoperative complications following radical prostatectomy, the history of VUAS, the time when VUAS developed and the surgical method that was used to treat VUAS were recorded. Data relating to scar status were obtained during routine three-month postoperative follow-up examinations. Among the patients with complete data, those who had previously developed incision scar formation for any reason before surgical intervention to treat VUAS were included in the study. The exclusion criteria are listed below:

- Patients with missing data relating to incision scar formation and postprostatectomy follow-up period
- Patients who underwent any bladder, prostate or urethral operation prior to radical prostatectomy or development of VUAS
- Patients who received radiotherapy in the pelvic region for any reason prior to radical prostatectomy
- Patients without incision scar formation on the body for any reason before VUAS
- Patients with a history of urethral stricture or bladder neck stenosis prior to radical prostatectomy or those with urethral stricture concomitant with VUAS

A flowchart of the study population is shown in **Figure 1**.

Vancouver scar scale

This scale evaluates the characteristics of scars in terms of vascularity, height/thickness, pliability and pigmentation. It was first described by Sullivan in 1990, for burn scar assessment.[5] The patient's subjective perception of the scars is not included in the general score. The scoring on this scale is as follows:

Vascularity: normal (0), pink (1), red (2), purple (3)

Pigmentation: normal (0), hypopigmentation (1), hyperpigmentation (2)

Pliability: normal (0), supple (1), yielding (2), firm (3), ropes (4), contracture (5)

Height: flat (0), ≤ 2 mm (1), 2-5 mm (2), ≥ 5 mm (3)

The total score can range from 0 to 13.

The patients were divided into two groups according to the treatment method for VUAS. The first group consisted of 39 patients who underwent dilatation using Amplatz renal dilators. The second group consisted of 41 patients who underwent endoscopic bladder neck incision and/or resection. Any presence of recurrent stenosis during the follow-up was recorded in both groups.

Surgical procedure for vesicourethral anastomosis in retropubic radical prostatectomy

A non-bladder neck sparing approach was used to remove the prostate. A 2/0 absorbable multifilament suture in a 'tennis racquet' fashion, to a size of 22 French (Fr), was used for bladder neck reconstruction. After the mucosa had been everted over the bladder neck with 4/0 absorbable sutures, vesicourethral anastomosis was performed using six 1/0 absorbable multifilament sutures at the 2, 4, 6, 8, 10 and 12 o'clock positions, over a 20 Fr Foley catheter. The urethral catheter was left in place for three weeks.

Dilatation technique using Amplatz renal dilators

Under regional or local anesthesia and in the lithotomy position, a 0.038-inch stiff hydrophilic guidewire was manipulated beyond the stenosis, through cystoscopy, and was advanced into the bladder. Sequential dilatation was performed using Amplatz renal dilators from 10F to 26F with an 8F stylet. During the dilatation, the Amplatz dilators were advanced by means of rotation towards the bladder with use of a lubricant. After dilatation, an 18 Fr urethral catheter was inserted with guidance through a guidewire and was maintained there for 5 days. A three-month self-catheterization protocol was recommended after removal of the catheter.

Technique for endoscopic bladder neck incision and/or resection

Under regional anesthesia and in the lithotomy position, the narrow-sclerosis part of the bladder neck was incised with diathermic incisions at the 4, 8 and 12 o'clock positions with 2-4 radial incisions. The incisions were made as far as the perivesical area of the bladder neck. If necessary, sclerotic areas of the bladder neck were resected with a 26 F resectoscope. These resections were performed deeply at the 3 and 9 o'clock positions. After both procedures, an 18 Fr urethral catheter was inserted and maintained there for 5 days. A three-month self-catheterization protocol was recommended after removal of the catheter.

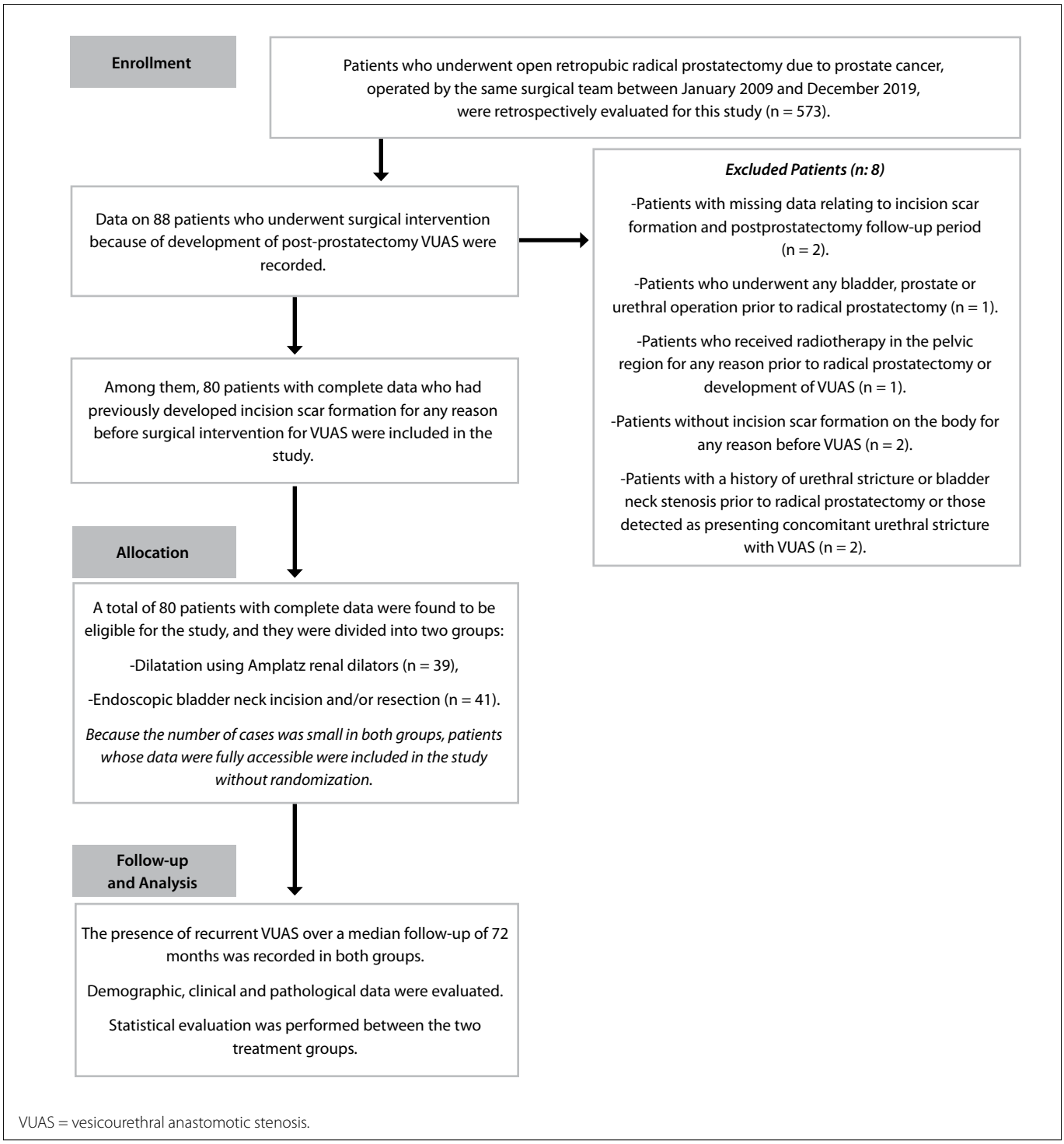
Diagnosis of postoperative vesicourethral anastomotic stenosis

The patients presented with complaints such as weak urinary flow rate, dripping after urination, incontinence, residual urinary sensation and inability to completely drain the bladder after radical prostatectomy.

Occurrences of weak urinary flow (Qmax < 10 ml/sec) were determined through uroflowmetry and post-micturition residual urine through ultrasonography. Retrograde urethrography was used to make the differential diagnosis between VUAS and concomitant urethral stricture and to identify the location and length of stenosis.

Because contrast did not adequately pass the proximal urethra or bladder neck in cases of very tight stenosis, voiding cystourethrography was performed if necessary, by passing a small feeding tube into the bladder. Alternatively, anterograde urethrography was performed by placing a suprapubic tube. Urodynamic testing was performed to evaluate bladder capacity, compliance and detrusor contractility whenever there was suspicion of bladder dysfunction.

The definitive diagnosis was made by means of cystourethroscopy, using a 17 Fr cystoscope. Although urethral dilatation to 22



VUAS = vesicourethral anastomotic stenosis.

Figure 1. Flowchart of the study population.

Fr via a catheter was tried as the initial management, endoscopic intervention was required in resistant cases. Incision scar and cystoscopy images from a single patient are shown in **Figure 2**.

Surgical success in both groups was defined as having no evidence of recurrence (Qmax more than 15 ml/sec; post-micturition residual urine < 50 ml) at the 1st, 3rd, 6th and 12th postoperative months and every three-month follow-up. Obstructive symptoms, Qmax smaller than 10 ml/sec and any need for repeated surgical urethral interventions were defined as recurrence.

Statistical analyses

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate normality of distribution. An independent-sample t test was used to detect differences between two groups of normally distributed variables, and the Mann-Whitney U test was performed for non-normal distribution. The chi-square test was used for categorical variables. The relationship between variables was assessed by means of the Spearman correlation test. Receiver operating characteristic (ROC) curve analysis was performed to determine cutoff values for Vancouver scar scale (VSS) scores in order to predict recurrent VUAS. Binary logistic regression analysis was used to determine the predictive factors for recurrence of VUAS. P-values of < 0.05 were considered statistically significant. All the statistical analyses were performed using IBM SPSS Statistics v23 (IBM, Armonk, NY, United States).

RESULTS

Among all the 573 patients who underwent RRP, VUAS developed in 88 patients (15.3%). For 80 patients with a median age of 66 years (range 56-74), complete data were available, and these patients were included in our study. Demographic, clinical and pathological data on these patients are shown in **Table 1**. During the median follow-up of 72 months (range 12-105) after RRP, 17 patients (21.3%) had recurrence of VUAS. None of these patients complained of severe urinary incontinence. Pelvic floor exercises were enough to relieve the symptoms in most patients.

There was no significant difference between the two treatment groups in terms of demographic data, clinical data or oncological outcomes (**Table 1**). Dilatation using Amplatz renal dilators and endoscopic bladder neck incision and/or resection were found to have similar success rates for preventing recurrence of VUAS (79.5% versus 78.0%; P = 0.875, respectively). There was also no significant difference between the groups in terms of the time until the occurrence of VUAS (9 versus 10 months; P = 0.433, respectively) and the time until the recurrence of VUAS (7 versus 9 months; P = 0.373, respectively).

The cutoff values of VSS scores for predicting recurrence of VUAS in the two groups are shown in **Table 2**. According to these results, patients with a VSS score > 3.5 were more likely to have recurrence of VUAS if endoscopic bladder neck incision and/or resection was performed. Conversely, patients with a VSS score > 6.5 were more likely to have recurrence of VUAS if dilatation using Amplatz renal dilators was performed. Although there was no significant difference between the groups in terms of median VSS scores, we observed a strong positive relationship between VSS and total number of occurrences of VUAS (rho: 0.689; P < 0.001). A moderate negative correlation was also observed between VSS and the time until the occurrence of VUAS (rho: -0.530, P < 0.001), but no relationship was found between VSS and time until recurrence of VUAS (rho: -0.310; P = 0.115).

In multivariate analysis, VSS score (OR: 5.380; P < 0.001) and time until occurrence of VUAS (OR: 1.628; P = 0.008) were found to be the most significant determinants for predicting recurrence of VUAS (**Table 3**).

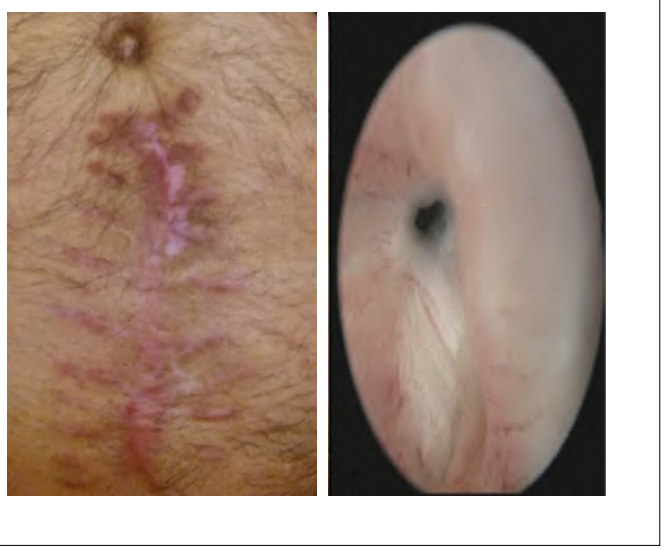


Figure 2. Incision scar (Vancouver scar scale = 8) and cystoscopy images from a single patient.

DISCUSSION

The incidence of VUAS after open RRP has been found to range from 0.4% to 32% in different series.[6,7] The incidence has been decreasing through the help of surgical techniques and new technological developments over recent years.[8] The rate of VUAS was found to be 1.1% after robotic assisted laparoscopic radical prostatectomy (RALP), whereas it was reported as 4.7% in a series that underwent laparoscopic radical prostatectomy.[9] Most studies have only reported on the patients who underwent treatment for VUAS, so the rates in the literature are considered to be lower than the true incidence.[10] Although there are studies reporting that the development of VUAS is significantly reduced by means of bladder neck protection methods during RALP,[11] there are also contradictory findings suggesting that preservation of the bladder neck reduces VUAS rates.[10,12] Symptomatic

Table 1. Demographic, clinical and pathological data and oncological outcomes of the patients

Parameters	Group I (n = 39)	Group II (n = 41)	Total (n = 80)	P-value
Median age	68.00	66.00	66.00	0.367§
(25th 75th percentile)	(64.00-69.00)	(63.00-69.50)	(63.00-69.00)	
minimum-maximum	56-74	57-74	56-74	
Median BMI	25.20	24.50	24.65	0.174§
(25th 75th percentile)	(23.10-27.80)	(21.95-27.10)	(22.35-27.57)	
Median preoperative PSA level	7.44	8.95	8.00	0.115§
(25th 75th percentile)	(5.19-9.60)	(6.38-11.00)	(6.03-10.34)	
Biopsy Gleason grade (n, %)				
-6	30 (76.9)	26 (63.5)	56 (70.0)	0.504‡
-7	5 (12.9)	6 (14.6)	11 (13.7)	
-8	2 (5.1)	6 (14.6)	8 (10.0)	
-9	2 (5.1)	2 (4.9)	4 (5.0)	
-10	0 (0.0)	1 (2.4)	1 (1.3)	
Preoperative clinical T stage (n, %)				
-T1c	24 (61.5)	31 (75.6)	55 (68.7)	0.324‡
-T2a	7 (17.9)	4 (9.8)	11 (13.8)	
-T2b	1 (2.6)	3 (7.3)	4 (5.0)	
-T2c	6 (15.4)	2 (4.9)	8 (10.0)	
-T3a	1 (2.6)	1 (2.4)	2 (2.5)	
Post-prostatectomy Gleason grade (n, %)				
-6	20 (51.3)	23 (56.1)	43 (53.8)	0.894‡
-7	10 (25.6)	7 (17.1)	17 (21.3)	
-8	5 (12.8)	8 (19.5)	13 (16.3)	
-9	4 (10.3)	0 (0.0)	4 (5.0)	
-10	0 (0.0)	3 (7.3)	3 (3.8)	
Post-prostatectomy pathological T stage (n, %)				
-T2a	8 (20.5)	18 (43.9)	26 (32.5)	0.261‡
-T2b	5 (12.8)	4 (9.8)	9 (11.1)	
-T2c	13 (33.4)	8 (19.5)	21 (26.3)	
-T3a	6 (15.4)	5 (12.2)	11 (13.8)	
-T3b	7 (17.9)	6 (14.6)	13 (16.3)	
Surgical margin positivity (n, %)				
-Yes	4 (10.3)	7 (17.1)	11 (13.8)	0.376‡
-No	35 (89.7)	34 (82.9)	69 (86.3)	
Post-prostatectomy PSA recurrence (n, %)				
-Yes	12 (30.8)	14 (34.1)	26 (32.5)	0.747‡
-No	27 (69.2)	27 (65.9)	54 (67.5)	
Median pre-prostatectomy ASA score	2.00	2.00	2.00	0.745§
(25th 75th percentile)	(2.00-3.00)	(1.50-3.00)	(2.00-3.00)	
Median pre-prostatectomy ACCI score	5.00	5.00	5.00	0.437§
(25th 75th percentile)	(4.00-6.00)	(5.00-6.00)	(4.00-6.00)	
Presence of preoperative hypertension (n, %)				
-Present	21 (53.8)	18 (43.9)	39 (48.8)	0.374‡
-Absent	18 (46.2)	23 (56.1)	41 (51.2)	
Presence of preoperative diabetes mellitus (n, %)				
-Present	17 (43.6)	16 (39.0)	33 (41.3)	0.678‡
-Absent	22 (56.4)	25 (61.0)	47 (58.8)	
Presence of smoking (n, %)				
-Present	20 (51.3)	23 (56.1)	43 (53.8)	0.666‡
-Absent	19 (48.7)	18 (43.9)	37 (46.3)	
Intraoperative excessive blood loss (> 1000 ml) (n, %)				
-Present	13 (33.3)	15 (36.6)	28 (35.0)	0.761‡
-Absent	26 (66.7)	26 (63.4)	52 (65.0)	
Prolonged leakage at the anastomotic site (> 100 ml in the drainage tube) (n, %)	9 (23.1)	12 (29.3)	21 (26.2)	0.529‡
-Present	30 (76.9)	29 (70.7)	59 (73.8)	
-Absent				

Continue...

Table 1. Continuation

Parameters	Group I (n = 39)	Group II (n = 41)	Total (n = 80)	P-value
Q max prior to operation for VUAS (ml/s)	8.03 ± 1.53	7.74 ± 1.09	7.88 ± 1.33	0.338†
Postvoid residual volume prior to operation for VUAS (ml)	92.97 ± 9.67	90.02 ± 10.04	91.46 ± 9.91	0.185†
Median time until occurrence of VUAS (months) (25th 75th percentile)	9.00 (6.00-12.00)	10.00 (7.00-12.00)	9.00 (7.00-12.00)	0.433§
Recurrence of VUAS (n, %)				
-Present	8 (20.5)	9 (22.0)	17 (21.3)	0.875‡
-Absent	31 (79.5)	32 (78.0)	63 (78.7)	
Median time until the recurrence of VUAS (months) (25th 75th percentile)	7.00 (6.00-8.75)	9.00 (5.00-10.00)	8.00 (6.00-10.00)	0.373§
Median total number of occurrences of VUAS (25th 75th percentile) minimum-maximum	1.00 (1.00-2.00) 1-3	1.00 (1.00-2.00) 1-3	1.00 (1.00-2.00) 1-3	0.489§
Median VSS score (25th 75th percentile)	5 (4-6)	4 (3-6)	4 (4-6)	0.083§
Median total follow-up period (months) (25th 75th percentile) minimum-maximum	79.00 (23.00-84.00) 12-105	67.00 (62.00-78.00) 18-99	72.00 (57.75-82.75) 12-105	0.467§

ACCI = age-adjusted Charlson comorbidity index; ASA = American Society of Anesthesiologists; BMI = body mass index; PSA = prostate-specific antigen; VSS = Vancouver scar scale, VUAS = vesicourethral anastomotic stenosis.

Group I comprises patients who underwent dilatation using Amplatz renal dilators; Group II comprises patients who underwent endoscopic bladder neck incision and/or resection"

§Mann-Whitney U test; data are expressed as "median (25th percentile-75th percentile)"; ‡Chi-square test; data are expressed as "number (percent)"; †independent-sample t test; data are expressed as "mean ± standard deviation";

P < 0.05 indicates statistical significance; however, there are no significant values in this table.

Table 2. Cutoff values of Vancouver scar scale for predicting stenosis recurrence following two different types of operation for treating for vesicourethral anastomotic stenosis

	Dilatation using Amplatz renal dilators	Endoscopic bladder neck incision and/or resection
Cutoff value	6.5	3.5
Sensitivity (%)	87.3	93.3
Specificity (%)	84.6	80.8
Positive predictive value (%)	85.0	82.9
Negative predictive value (%)	86.9	92.3
Area under receiver operating characteristic curve	0.920	0.949
P	< 0.001*	< 0.001*

*P < 0.05; Asterisk (*) indicates statistical significance.

VUAS is usually seen within six months following RRP.[13,14] In our series, it was observed with a median follow-up of nine months.

Vesicourethral anastomotic stenosis may develop due to fibrosis in the anastomosis line between the bladder neck and urethra. It is thought that tension in anastomosis, postoperative hemorrhage, large-volume blood loss, pelvic hematoma formation, urinary leakage from the anastomosis, disrupted peri-bladder neck vascular supply, overnarrowing of the bladder neck during anastomosis, prolonged catheterization, acute retention after urethral catheter removal, prior radiation or a history of hypertrophic scar formation may cause VUAS.[6,8,13] These factors may cause a peri-anastomotic inflammatory response that results in scar formation.[6] In addition, in the presence of obesity, diabetes mellitus, smoking, advanced age or vascular disease, susceptibility to VUAS increases since there is no adequate microvascular environment for anastomotic healing.[6,15] The surgeon's experience is also one of the known factors playing a role in complications after RRP, and this may affect VUAS rates.[6] In different open RRP series, the VUAS rates have been reported to be 19.8%-22% for high-volume surgeons.[14,16] In our study, all the operations were performed by the same surgical team (approximately 45 RRP procedures per year) and, thus, we tried to exclude the effect of the surgeon's experience.

The most commonly used first-line surgical methods for treating VUAS are dilatation with urethral catheters, rigid bougie dilators or urethral balloon dilators, dilatation using Amplatz renal dilators and endoscopic bladder neck incision or resection.[17] In cases of failure, with repeated interventions such as internal urethrotomy, metallic urethral stent or endourethroplasty using interstitial injection of antiproliferative agents, open surgical treatments may be recommended as the last option for treatment.[13,18] Adding this undesirable complication to the anxiety and mood disorder caused by prostate cancer may affect the person's life even more negatively.

Guidewire-assisted dilatation avoids the complication rates associated with blind dilatation techniques such as false passage, incontinence, impotence or rupture of the rectum.[13,19] Therefore,

Amplatz renal dilators that are used for tract dilatation in percutaneous renal surgeries have begun to be used for dilatation of urethra or bladder neck strictures, as an alternative method.[19] The success rates for this technique have been reported as 73-92.3% at 21-month follow-up.[19] According to our results, the recurrence rates were 20.5% and 21.9%, respectively, in patients who underwent dilatation using Amplatz renal dilators and endoscopic bladder neck incision and/or resection at a median follow-up of 72 months.

The presence of a poorly healed median sternotomy incision scar has also been shown to be associated with poor wound healing in urethral tissue. It has been reported that patients with advanced median sternotomy scars develop longer segmented and frequently recurrent urethral stenosis after urethral manipulations.[20] There have not been enough studies investigating any similar relationship with VUAS, but we observed a strong positive relationship between VSS and development and recurrence of VUAS. Although a cutoff value for the VSS score has not been defined for a description of hypertrophic scars, the most accepted score has been 4, in various studies.[20-22] A maximal abdominal scar width > 10 mm has been found to have an eight-fold greater likelihood of VUAS after open RRP.[8] In accordance with this information, we observed that median VSS scores were higher in patients with recurrence of VUAS (6 versus 3; P < 0.001).

Some authors have stated that although urethral dilatation and endoscopic laser incision and/or resection can significantly cure VUAS, residual fibrotic tissue may be left. Using electrocautery to provide hemostasis has also been associated with new fibrosis triggered by thermal damage.[13,19] This may be a risk factor for development of new fibrosis and recurrent stenosis.[13] Although holmium laser incision or plasma-button vaporization of VUAS has been reported to have significantly higher success rates,[13,14] there have also been studies contradicting this, in which it was reported that there were no significant differences in the results from the holmium laser, electrocautery or cold knife incision.[23] According to our findings, dilatation using Amplatz renal dilators gave rise to less risk of recurrent fibrotic stenosis than did diathermic incision and resection, even in patients with high susceptibility to development of proliferative hypertrophic scars.

The rate of recalcitrant VUAS with more than three unsuccessful endoscopic interventions has been reported to be 25-30%.[24,25] The treatment options should be carefully chosen in cases of refractory stenosis. Patient factors relating to comorbidities, previous interventions or complications, and surgical factors relating to morbidity, surgical expertise or requirement of reconstructive surgical experience need to be taken into account. Therefore, it is important to choose a

Table 3. Factors predicting recurrence of post-prostatectomy vesicourethral anastomotic stenosis

	Univariate model				Multivariate model			
	OR	95% CI		P	OR	95% CI		P
		Lower	Upper			Lower	Upper	
Patient's age	1.095	0.986	1.218	**0.090**				
BMI	1.061	0.932	1.208	**0.373**				
Preoperative PSA level	1.027	0.905	1.164	**0.683**				
Biopsy Gleason grade	1.418	0.881	2.283	**0.150**				
Preoperative clinical T stage	1.517	0.909	2.531	**0.110**				
Post-prostatectomy Gleason grade	1.020	0.671	1.552	**0.924**				
Post-prostatectomy pathological T stage	1.128	0.819	1.555	**0.459**				
Surgical margin positivity	1.515	0.368	6.250	**0.565**				
Post-prostatectomy PSA recurrence	1.727	0.619	4.807	**0.296**				
Pre-prostatectomy ASA score	1.044	0.544	2.004	**0.894**				
Pre-prostatectomy ACCI score	1.225	0.923	1.626	**0.160**				
Presence of preoperative hypertension	1.440	0.570	3.636	**0.440**				
Presence of preoperative diabetes mellitus	1.387	0.547	3.512	**0.491**				
Presence of smoking	1.763	0.841	5.448	**0.266**				
Qmax prior to operation for VUAS (ml/s)	1.164	0.820	1.652	**0.395**				
Postvoid residual volume prior to operation for VUAS (ml)	1.004	0.958	1.052	**0.850**				
Operation type for VUAS	1.154	0.460	2.896	**0.761**				
Time until the occurrence of VUAS (months)	1.865	1.420	2.457	**< 0.001***	1.628	1.137	2.331	**0.008***
VSS score	5.380	2.641	10.958	**< 0.001***	5.380	2.641	10.958	**< 0.001***

OR = hazard ratio; CI = confidence interval; BMI = body mass index; PSA = prostate-specific antigen; ASA = American Society of Anesthesiologists; ACCI = age-adjusted Charlson comorbidity index; VUAS = vesicourethral anastomotic stenosis; VSS = Vancouver scar scale; Qmax: peak flow rate.
*P < 0.05; Asterisk (*) indicates statistical significance.

method in which the likelihood of recurrence may be lower in these patients. Pfalzgraf et al.[26] stated that VUAS recurrence after transurethral incision or transurethral resection was not predictable. In our study, we aimed to predict the more appropriate surgical intervention for preventing recurrent VUAS. Although the two treatments had similar success rates, it seemed that dilatation using Amplatz renal dilators, rather than endoscopic bladder neck incision and/or resection, in patients with VSS scores of 4, 5 and 6 could significantly reduce VUAS recurrence. Contrary to the opinion of Pfalzgraf et al.,[26] our findings showed that it can be predicted which surgical intervention is more appropriate for preventing recurrent VUAS.

When minimally invasive interventions such as endoscopic interventions or dilatation techniques fail, repetition of these interventions subsequently may substantially reduce the success rate of future reconstructive surgeries. Therefore, prediction of VUAS cases with a high likelihood of recurrence may lead to preference of open or perineoscopic reconstruction operations initially.[27] Through this, success rates may further increase and patients may avoid repeated procedures. Although our findings did not allow us to make such estimates directly, our preliminary results suggest that use of VSS in a particular patient group may help predict the surgical intervention method that is more appropriate for preventing VUAS recurrence.

To the best of our knowledge, this was the first study to investigate the relationship between proliferative hypertrophic scar formation and the success of treatment options for VUAS following open RRP. Most studies in the literature have limitations because of small patient populations, retrospective design, heterogeneous patient groups with concomitant urethral strictures and variable definitions of VUAS. Although most studies mentioned above have described absence of recurrence in the first six months after intervention as a criterion for success,[13,14,25,28] we found that any recurrence requiring additional surgical procedures, regardless of the time that had elapsed, was indicative of failure.

Radiotherapy that is used for adjuvant or salvage treatment is also a predisposing factor for development of necrosis and fibrosis of the bladder neck, due to progressive obliterative endarteritis.[29] In our study, we excluded patients who had undergone radiotherapy, and also those with urethral stricture or bladder neck stenosis prior to RRP, in order to form a homogeneous patient group.

Taking a critical view, the utility of VSS may not seem significant enough, given that minimally invasive surgical techniques for prostate cancer that reduce the rate of VUAS have been developed. Nonetheless, although minimally invasive techniques do not give rise to incision lines that are as long as in open surgery, proliferative hypertrophic scars may also develop at the trocar sites in these methods. Therefore, although the rate of VUAS is decreased through minimally invasive surgery, it is still likely to be seen. Based on the relationship between proliferative hypertrophic scar formation and VUAS in our study, we think that our findings may also guide clinicians in choosing a more appropriate surgical intervention that can reduce the likelihood of recurrence, even in cases of VUAS following minimally invasive surgery.

Although our study revealed a novel prediction, its retrospective nonrandomized design with a limited number of patients and a relatively short follow-up period in a single center is its main limitation. Moreover, although our VUAS rates were consistent with traditional open RRP rates, they were higher than what is seen in robotic surgery data, and are too high for a modern series. In addition, performing open RRP despite the current technological advances can be considered to be a serious limitation in this era of uro-technology. On the other hand, robotic surgery is not available in every institution, because of various financial reasons. Therefore, open surgery still remains a commonly used technique in many developing countries, even though it has been reported to have a tenfold greater risk of development of VUAS, compared with minimally invasive surgery. Furthermore, we only compared the two most-used treatment methods in our department. Other popular methods, such as endoscopic holmium laser incision, plasma button vaporization and injection of antifibrotic agents or steroids into the incision site were not used in this study. We also were unable to evaluate the relationship between the success rates of these methods and the presence of proliferative hypertrophic scars. Lastly, in similar studies in the literature, patients with a scar on the anterior chest wall were included because this body area is more likely to develop hypertrophic scar formation. However, we also included patients who had previously developed incision scars for any reason, in areas other than this one. Although we evaluated these scars through VSS, this can be considered to be a limitation in terms of standardization.

CONCLUSION

The VSS score can be used as a prediction tool for choosing a more appropriate method for individualized treatment among patients at higher risk of scarring. We present our findings as "preliminary results" because it was not easy to obtain comprehensive results, due to the limitations of our study. Nevertheless, because the relationship between proliferative hypertrophic scar formation and development of VUAS had not been investigated before, we think that our preliminary results may be a step towards further studies.

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Impact of bundle implementation on the incidence of peri/intraventricular hemorrhage among preterm infants: a pre-post interventional study

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Bundle.

ABSTRACT

BACKGROUND: Peri/intraventricular hemorrhage (PIVH) is a frequent cause of death and morbidity among preterm infants. Few studies have addressed the use of bundles for preventing PIVH.

OBJECTIVE: To evaluate the efficacy of a bundle of interventions designed to decrease the incidence of intraventricular hemorrhage at hospital discharge among preterm infants.

DESIGN AND SETTING: Pre-post interventional study with retrospective and prospective data collection performed before and after bundle implementation in the neonatal intensive care unit of a university hospital.

METHODS: Infants with gestational age < 32 weeks without malformations, who survived > 6 days were included. The bundle consisted of the following actions during the first 72 hours of life: maintenance of head in neutral position with the body in supine position, minimal handling, including delay of lumbar puncture until after 72 hours and absence of respiratory therapy maneuvers. Cranial ultrasound was performed on days 3, 7 and 28, or later if needed. The effect of the bundle was analyzed through logistic regression and results were adjusted for confounding variables.

RESULTS: 167 infants met the inclusion criteria; 146 (87%) were analyzed. Bundle implementation was associated with decreased chances of PIVH at hospital discharge (odds ratio 0.29; 95% confidence interval 0.13-0.65). Cerebrospinal fluid collection within the first 72 hours increased the odds of PIVH of any grade during the hospital stay fourfold, after adjustment for all variables included in the model.

CONCLUSION: Implementation of a bundle of interventions to avoid intraventricular hemorrhage was effective for decreasing the incidence of all grades of PIVH in preterm infants.

INTRODUCTION

The survival of preterm infants reflects the quality of prenatal and labor and delivery care, as well as the infrastructure available for neonatal care. According to a report published by the World Health Organization in 2012, titled "Born Too Soon: The Global Action Report on Preterm Birth",[1] Brazil ranks 10th highest in the number of premature live births and 16th highest in the number of deaths associated with complications of prematurity. Adequate and effective care in the neonatal intensive care unit (NICU) might modify the short, medium and long-term prognoses[2] for infants who require long hospital stays, especially for those who are extremely preterm.

Peri/intraventricular hemorrhage (PIVH) is a frequent cause of death and morbidity among preterm infants and contributes to an adverse neurological prognosis.[3-5] Several studies have sought to identify risk factors associated with PIVH in general, and in grade III and IV lesions in particular,[6] in order to establish preventive strategies for this condition.[7] However, because of the complex and multifactorial etiopathogenesis of PIVH, adoption of preventive measures alone is not expected to have much impact on the incidence of this severe neonatal complication.[8]

The outcomes from interventions aimed at improving the quality of hospital care indicate that the use of bundles, i.e. sets of simultaneously applied measures, reduces the incidence of infections,[9-11] and central catheter-related late neonatal sepsis in particular, along with reducing other conditions particular to preterm infants.[12,13] However, few studies have addressed the use of bundles for prevention of PIVH.[8,14,15] Carteaux et al.[14] implemented a set of practices to reduce the incidence of intracranial hemorrhage and periventricular leukomalacia among very low birth weight infants, although the impact of those measures was not reported. Schmid et al.[8]

implemented a bundle of measures targeting delivery care and the initial care of neonates in the delivery room and neonatal intensive care unit (NICU) that emphasized minimal handling, and they reported that these measures reduced the incidence of PIVH by 50% among preterm infants with birth weight under 1,500 g. A nursing intervention bundle applied in two Dutch centers reduced the risk of severe PIVH, and it was also associated with a lower risk of any degree of IVH, cystic periventricular leukomalacia and/or mortality.[15]

OBJECTIVE

Thus, the aim of the present study was to establish whether a bundle of clinical measures implemented during the first 72 hours of life among preterm infants with gestational ages less than 32 weeks could reduce the incidence of PIVH of any grade during the hospital stay.

METHODS

This was a pre-post interventional study with retrospective (pre) and prospective (post) data collection performed before and after implementation of a bundle of measures at the NICU of a university hospital. The study was approved by the institutional research ethics committee (protocol number: 226.656; approved on March 22, 2013). The study periods were as follows:

1. Data were retrospectively collected before bundle implementation, over a period covering from March 2009 to April 2011. Thus, informed consent for this period was waived.
2. Data were prospectively collected after bundle implementation, from May 2011 to April 2013. For these data, informed consent was required.

All newborn infants with gestational ages less than 32 weeks, as established according to the best obstetrical estimate, without lethal congenital abnormalities or malformations of the central nervous system, were included. Infants who died and/or who underwent surgical procedures within the first 168 hours of life were excluded.

The presence of PIVH was investigated using head ultrasound (US) on days 3, 7 and 28 of life, and later as indicated by the medical staff. The scans were performed using the Acusson X300 US device (Siemens, Erlangen, Germany), with a multifrequency micro-convex 8-5 MHz transducer. The presence and severity of PIVH was assessed in accordance with the methods of Papile.[6] All US examinations were performed by specialized pediatric radiology staff, and the reports were reviewed by the supervising radiologist.

The frequency of PIVH of any grade and the frequency of grade III/IV lesions among newborn infants with gestational ages less than 32 weeks and without malformations, who survived for more than 12 hours, were 64% and 45%, respectively in the NICU of the present study in 2010. Assuming that the bundle of measures would reduce the incidence rates of PIVH of any grade and grade III/IV lesions to the average seen among 20 hospitals included in the Brazilian Network of Neonatal Research[16] (35% and 18%, respectively), with power of 90% and two-tailed alpha error of 5%, the required sample size for the periods before and after bundle implementation was 60 individuals.

The bundle implemented within the first 72 hours of life among all the eligible infants consisted of the following procedures: 1) maintaining the infant in dorsal decubitus and neutral elevated head position;[14,15,17] 2) avoidance of physical therapy maneuvers and aspiration of the tracheal cannula;[18,19] 3) postponing cerebrospinal fluid (CSF) collection for sepsis work-up until after 72 hours of life;[14,20] 5) assessment of daily weight only after the first 72 hours of life; and 6) reinforcement of minimal handling and environmental policies.[14,15]

Demographic data on the mothers and newborn infants were collected. Advanced resuscitation was defined as the need for tracheal intubation with concomitant chest compression and/or medication. Clinical severity was evaluated using the Score for Neonatal Acute Physiology, Perinatal Extension, Version II.[21] Neonatal morbidity was defined as the occurrence of at least one of the following events in the first seven days of life: hypothermia (body temperature < 36 °C); metabolic or respiratory acidosis (arterial blood pH < 7.20); hypocapnia or hypercapnia (pCO_2 < 40 and > 60 mmHg, respectively, in an arterial blood sample); respiratory distress syndrome; air leak syndrome; apnea (pauses > 20 seconds or shorter pauses accompanied by bradycardia and/or cyanosis); hypotension (need for volume expansion and/or use of vasoactive drugs); patent ductus arteriosus (PDA) on echocardiogram requiring pharmacological and/or surgical treatment; hypoglycemia (capillary glycemia < 40 mg/dl); thrombocytopenia (< 150,000/mm); hemorrhagic disorders (active bleeding requiring intervention); and pain (score on validated scales compatible with the presence of pain).

Data collection and monitoring were performed every two days. Adherence to the bundle was defined as keeping the infants in dorsal decubitus with neutral head position and not performing physical therapy maneuvers, cannula aspiration or CSF sample collection within the first 72 hours of life, as documented in the infants' medical records by the medical, nursing and physical therapy staff.

Neonatal characteristics and variables associated with adherence to the bundle, stratified in relation to the presence of PIVH, were analyzed by means of logistic regression for the outcome of PIVH of any grade during the hospital stay. As a sensitivity analysis, PIVH of any grade at three days of age was also analyzed. Two models were fitted for each outcome, in which all variables that had a P-value < 0.20 on univariate analysis were included as independent variables. In addition, model one also included a "period" variable indicating

whether the infants received the bundle. In model two, the "period" variable was removed, and the following bundle-related variables were included: head position (adequate or inadequate); body position (adequate or inadequate); tracheal aspiration (present or absent); respiratory physical therapy maneuvers (present or absent); and CSF sample collection before 72 hours of age (present or absent). Non-significant variables were removed from the model one at a time, and the model goodness-of-fit was tested using the Hosmer-Lemeshow test in SPSS 21.0 0 (IBM SPSS Statistics for Windows, version 21.0; IBM Corporation, Armonk, NY, United States).

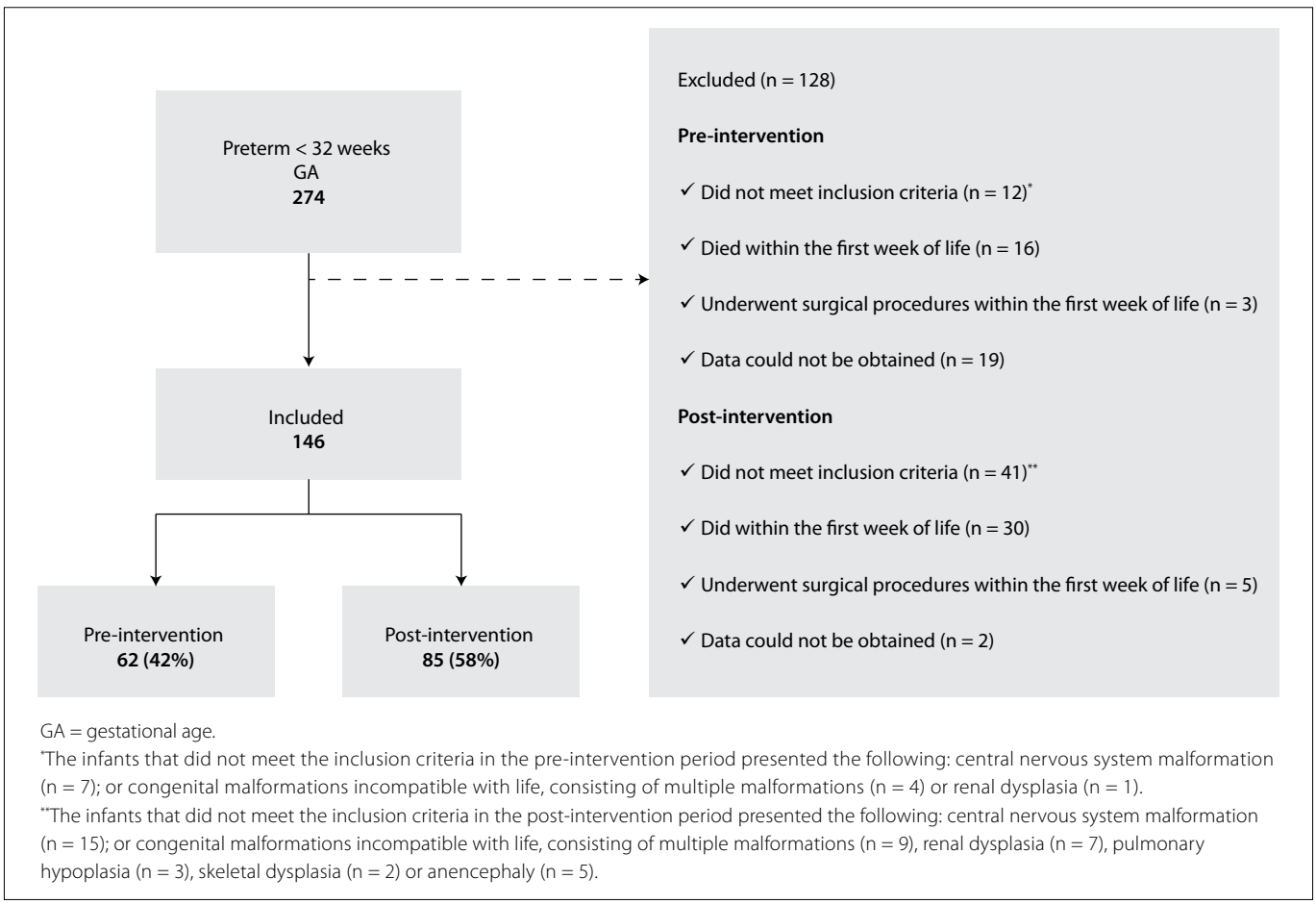
RESULTS

A total of 274 infants with gestational ages less than 32 weeks were born during the study period, and 221 (81%) met the inclusion criteria (**Figure 1**). Of these, 46 (21%) were excluded because they died within the first week of life, and eight (4.5%) were excluded because they underwent surgical procedures. Among the remaining 167 eligible infants, data could not be obtained for 21 (12.6%). Consequently, 146 infants were included in the analysis: 61 (42%) during the pre-intervention period and 85 (58%) during the post-intervention period.

The mothers' and newborn infants' characteristics stratified according to intervention group are described in **Table 1**; no significant differences were found between the groups.

The incidence of PIVH of any grade at three days of age was 41% among the infants in the pre-intervention group and 29% in the post-intervention group (P = 0.146). These values were 5% and 3% (P = 0.281), respectively, for grade III/IV lesions on the third day of life. Comparing the incidence of PIVH during the infants' hospital stay, post-intervention reductions were found both for PIVH of any grade (66% versus 49%; P = 0.05) and for grade III/IV lesions (16% versus 6%; P = 0.03).

The results from the logistic regression analysis performed to investigate risk factors associated with occurrence of PIVH of any grade during the hospital stay are described in **Table 2**. In model one, being born after bundle implementation reduced the odds of PIVH of any grade during the hospital stay by 71% after adjustment for possible confounding variables. When the pre and post-intervention variable was replaced by variables representing the bundle measures, CSF collection within the first 72 hours increased the odds of PIVH of any grade during the hospital stay fourfold, after adjustment for all variables included in the model.



GA = gestational age.
*The infants that did not meet the inclusion criteria in the pre-intervention period presented the following: central nervous system malformation (n = 7); or congenital malformations incompatible with life, consisting of multiple malformations (n = 4) or renal dysplasia (n = 1).
**The infants that did not meet the inclusion criteria in the post-intervention period presented the following: central nervous system malformation (n = 15); or congenital malformations incompatible with life, consisting of multiple malformations (n = 9), renal dysplasia (n = 7), pulmonary hypoplasia (n = 3), skeletal dysplasia (n = 2) or anencephaly (n = 5).

Figure 1. Study population flow chart.

Table 1. Characteristics of 146 newborn infants and their mothers grouped according to study period: before or after implementation of a bundle of measures to prevent peri/intraventricular hemorrhage

	Pre-bundle (n = 61)	Post-bundle (n = 85)	P-value
Maternal characteristics			
Hypertension	23 (37.7%)	28 (32.9%)	0.552[a]
Chorioamnionitis	6 (9.8%)	3 (3.5%)	0.165[b]
Antenatal steroids	47 (77.0%)	60 (70.6%)	0.384[a]
C-section	54 (88.5%)	67 (78.8%)	0.125[a]
Infants' characteristics			
Gestational age (weeks)	29.2 ± 1.8	29.1 ± 2.0	0.762[c]
Gestational age < 28 weeks	11 (18.0%)	24 (28.2%)	0.154[a]
Male gender	36 (59.0%)	39 (45.9%)	0.117[a]
Positive pressure ventilation at DR	33 (54.1%)	54 (63.5%)	0.252[a]
Advanced resuscitation	Zero	2 (2.4%)	0.510[b]
Birth weight (g)	1,200 ± 324	1,230 ± 357	0.781[c]
Birth weight < 1,000 g	16 (26.2%)	27 (31.8%)	0.469[a]
SNAPPE < 20	35 (57.4%)	49 (57.6%)	0.974[a]
Hypothermia at NICU admission	25 (41.0%)	35 (41.2%)	0.981[a]
Events during the first three DOL			
≥ 1 hypothermia episode	47 (77.0%)	68 (80.0%)	0.667[a]
Mechanical ventilation by tracheal cannula	34 (55.7%)	45 (52.9%)	0.738[a]
Acidosis (pH < 7.2)	7 (11.5%)	18 (21.2%)	0.125[a]
Arterial pCO_2 > 60 mmHg	4 (6.6%)	10 (11.8%)	0.292[a]
MAP >10 cmH_2O	8 (13.1%)	4 (4.8%)	0.072[a]
≥ 1 surfactant dose	28 (45.9%)	41 (48.2%)	0.781[a]
Tracheal tube change	2 (3.3%)	7 (8.2%)	0.305[b]
≥ 1 apnea episode	19 (31.1%)	34 (40.0%)	0.273[a]
Systemic hypotension	16 (26.2%)	27 (31.8%)	0.469[a]
PDA pharmacological closing	20 (32.8%)	3 (3.5%)	**< 0.001[a]**
Hypoglycemia	6 (9.8%)	5 (5.9%)	0.527[b]
Thrombocytopenia < 150,000/mm^3	18 (29.5%)	26 (30.6%)	0.888[a]
Opioid analgesia	20 (32.8%)	38 (44.7%)	0.147[a]
Adherence to bundle in the first three DOL			
Supine body positioning	18 (29.5%)	71 (83.5%)	**< 0.001[a]**
Neutral head positioning	16 (26.2%)	69 (81.2%)	**< 0.001[a]**
Tracheal aspiration	32 (52.5%)	33 (38.8%)	0.102[a]
Respiratory physical therapy maneuvers	12 (19.7%)	zero	**< 0.001[a]**
CSF collection	31 (50.8%)	9 (10.6%)	**< 0.001[a]**
Deaths during hospital stay	6 (9.8%)	6 (7.1%)	0.547[a]

[a]chi-square test; [b]Fisher's exact test; [c]t test; DR = delivery room; SNAPPE = score of clinical severity during the first 12 hours of life; moderate hypothermia: axillary temperature < 36 °C; NICU = neonatal intensive care unit; DOL = days of life; MAP = mean airway pressure; systemic hypotension: need for vasopressors or volume expansion; PDA = persistent ductus arteriosus; CSF = cerebrospinal fluid.

Table 2. Logistic regression analysis to identify factors associated with the dependent variable, i.e. peri/intraventricular hemorrhage of any grade during the hospital stay

	Odds ratio	95% CI	P-value
Model 1[a]			
Post-bundle period	0.289	0.128-0.653	0.003
C-section	0.166	0.053-0.515	0.002
Gestational age < 28 weeks	3.581	1.313-9.765	0.013
Thrombocytopenia < 150,000/mm^3	3.134	1.246-7.881	0.015
Systemic hypotension	4.664	1.768-12.301	0.002
Model 2[b]			
C-section delivery	0.191	0.061-0.598	0.004
Gestational age < 28 weeks	4.403	1.578-12.283	0.005
Systemic hypotension	4.824	1.820-12.788	0.002
Thrombocytopenia < 150,000/mm^3	3.487	1.361-8.936	0.009
CSF collection	4.102	1.634-10.298	0.003

95% CI = 95% confidence interval; CSF = cerebrospinal fluid.

[a]Model 1: adjusted for infant gender, cesarean delivery, SNAPPE (score of clinical severity during the first 12 hours of life) < 20, antenatal corticoids, 5-minute Apgar score < 7, birth weight < 1,000 g, ventilation through tracheal cannula during the first three days of life, acidosis episode within the first three days of life, one apnea episode within the first three days of life, pharmacological ductal closing within the first three days of life, and use of opioid analgesia during the first three days of life (Hosmer-Lemeshow: P = 0.341).

[b]Model 2: this model initially included the same variables as Model 1, but afterwards, "bundle period" was removed, and variables relating to adherence to the bundle during the first three days of life (body positioning, head positioning, tracheal aspiration, physical therapy and CSF collection) were introduced (Hosmer-Lemeshow: P = 0.389).

The results from the sensitivity analysis performed to investigate risk factors associated with occurrence of PIVH of any grade at three days of age showed that after adjustment for gestational age, mode of delivery, and systemic hypotension in the first three days of life, being born after bundle implementation reduced the odds of having PIVH of any grade at three days of age by 68% (odds ratio, OR 0.32; 95% confidence interval, CI 0.14-0.75). When the pre and post-intervention variable was replaced by variables representing the bundle measures, maintenance of neutral head position reduced the odds of PIVH of any grade at three days of age by 68% (OR 0.32; 95% CI 0.13-0.77), after adjustment for confounders.

DISCUSSION

This observational study showed that after adjustment for confounding variables, being born after bundle implementation reduced the odds of PIVH of any grade at three days of age and during the hospital stay by approximately 70%. Among the bundle measures, maintenance of head neutral position stood out as a protective factor against occurrence of PIVH at three days of age, and delaying CSF collection until a more stable period of the neonatal cardiopulmonary transition, i.e. after the first 72 hours of life, was protective against occurrence of PIVH during the hospital stay. The outcome of any PIVH was used in the analysis on associated risk factors because we had few infants with PIVH grades III/IV. By preventing any grade of PIVH, we were also preventing severe PIVH as a consequence. The number of deaths did not increase between the two periods.

The results from the present study corroborate data in the literature indicating that a set of simultaneous measures aimed at improving the quality of neonatal care might have a significant impact with regard to PIVH prevention. In 2003, Carteaux et al.[14] implemented a set of practices at five institutions to reduce the incidence of intracranial hemorrhage and periventricular leukomalacia in very low birth weight infants. These practices included antenatal betamethasone administration; optimization of peripartum management; optimization of direct clinical management by neonatologists and trained nurses; implementation of measures to minimize pain and stress responses; maintaining neutral head position in the first days of life; judicious treatment of hypotension by means of fluid volume therapy followed by use of inotropic agents as needed; judicious use of indomethacin to help close cases of PDA; optimization of respiratory management; limited use of sodium bicarbonate; and judicious postnatal use of dexamethasone. While difficulties in adhering to these suggested practices have been reported,[22] their impact on the incidence of PIVH has not yet been elucidated.

In 2013, Schmid et al.[8] showed that a program of preventive measures within perinatal care reduced the incidence of PIVH from 22% to 10% among very low birth weight preterm infants. De Bijl-Marcus et al., in 2020, published the results from a bundle of nursing interventions that consisted of posture interventions and avoidance of rapid intravenous/arterial flushes and rapid arterial blood withdrawal.[15] Use of the bundle was associated with lower risk of developing any degree of PIVH, cystic periventricular leukomalacia and/or mortality (adjusted OR 0.42; 95% CI 0.27 to 0.65). [15] Other studies, such as the one conducted by Lee et al.,[13] sought to improve the quality of care delivered and reduce occurrences of PIVH grades III/IV and/or leukomalacia as a secondary outcome among premature infants with gestational ages less than 29 weeks. The practices implemented to reduce severe neurological injury consisted of delayed cord clamping, antenatal use of magnesium sulfate, minimal use of volume expanders and minimal use of inotropes. However, the results did not show any significant reduction in severe neurological injury.

This study, as well as the study conducted by Schmid et al.,[8] focused predominantly on measures aimed at stabilizing infants during the period of cardiopulmonary transition, when infants are vulnerable to hemodynamic fluctuations that impact the germinal matrix.[23] Despite the positive result, it should be highlighted that the incidence of PIVH at the NICU studied here was much higher than the incidence of 20-25% reported in the United States for infants with birth weight < 1,500 g.[24] Measures aimed at improving the quality of hospital care may have greater impact on conditions of higher prevalence.

In designing this study, it was decided to exclude infants who died within the first 168 hours of life because death and PIVH are competing risks. The best strategy for analyzing competing risks is to use composite outcomes, but these are difficult to use and lead to errors of interpretation and sample size calculation.[25] Moreover, composite outcomes are generally inadequate, thus implying that the results apply to the individual components of the composite outcome rather than only to the overall composite.[26] Since nearly all occurrences of PIVH develop within the first week after birth, it was therefore decided, in this study, to exclude infants who died before the occurrence of PIVH. We also excluded infants who underwent surgical procedure during this same period, because the procedure itself and the anesthetic procedure might have biased our outcome.

With regard to the mechanisms underlying PIVH, turning the infant's head to one side might occlude or obstruct drainage of the ipsilateral jugular vein, which might consequently increase local venous congestion.[17] The results from the present study stress the relevance of this pathophysiological mechanism, given that after adjustment for possible confounding factors, the protection afforded by neutral head position during the first 72 hours of life was significant. Romantsik et al. conducted a systematic review to assess whether head midline position would be more effective than any other position for preventing or extending PIVH and they did not find any significant differences in the outcomes.[27]

They included a total of 110 infants in their review, from two randomized controlled trials, and found that the difference in the risk of PIVH, comparing the supine midline head position with the supine rotated head position, was 0.03 (95% CI: -0.13 to 0.18).[27] The results from this systematic review did not provide a definitive answer to the review question.[27] Another review of the literature was conducted by Malusky and Donze[17] to evaluate changes in cerebral hemodynamics in response to position changes. They found evidence to recommend a midline head position during the first 72 hours of life among infants with gestational ages of less than 32 weeks.[17] Some studies have indicated that it is important to maintain an elevated position, in addition to the midline neutral position.[28] The protocol at the NICU of the present study is to admit and maintain all preterm infants in a position of head elevation (approximately 15°).

CSF collection requires considerable postural manipulation, including the position of the infant's head, which might result in fluctuations in cerebral blood flow. Some studies have shown that during CSF collection in newborn infants, the arterial blood partial pressure of oxygen decreases and that of carbon dioxide increases.[20,29] These factors, together with the pain caused by the procedure,[30] might alter cerebral blood flow. A retrospective study that included 106,461 very low birth weight infants found an association between lumbar puncture for CSF collection in the first three days of life and occurrence of PIVH grades III/IV.[31] At birth, the risk of PIVH grades III/IV was more than double for infants who received the procedure (adjusted OR 2.64, 95% confidence interval 1.96-3.54).[31]

The results from the present study suggest that care practices that can minimize fluctuations in cerebral blood flow among very low birth weight preterm infants in the first days of life might result in significant reductions in intracranial hemorrhage during that period and throughout the hospital stay. Despite this finding, postponing the diagnosing of early meningitis may be an undesirable effect of postponing lumbar puncture. One third or more of infants with meningitis have a negative blood culture.[32,33] However, the incidence of early onset meningitis is much lower than the incidence of late onset meningitis (1.1/1000 versus 13.9/1000 in very low birth weight infants in 2005 and 2001, respectively).[32-34] The consequences of postponing CSF collection in infants with suspected early onset sepsis has not been studied. Therefore, the risk-benefit relationship of early CSF collection needs to be individually balanced.

The present study had several limitations, and the main one among these was its methodological design. Because it was a cohort study involving two periods of time, the changes introduced in neonatal care between the periods may have been confounding factors. In this regard, the main change in the NICU between the two periods was the introduction of functional echocardiography, which became routine for assessing the presence and repercussions of PDA. As a result, the number of infants requiring pharmacological or surgical treatment for PDA was significantly reduced, as their treatment became more conservative, which could have influenced the incidence of PIVH. For this reason, the statistical analysis took this change into consideration, and the analysis was also adjusted for prenatal, delivery and postnatal factors that would affect the pathogenesis of PIVH. Although the two cohorts represent clinical practices that are now more than five years old, these practices are still up-to-date and the comparison between these two periods can help clinicians to better understand the impact of these practices. Another limitation was that the diagnosis of PIVH was not made by a single US technician. Nevertheless, as the study was conducted in a teaching hospital and, thus, the final US reports were systematically reviewed by the professor in charge of teaching the technique for head US, the diagnosis can be considered to have been uniform throughout the study.

CONCLUSIONS

These limitations notwithstanding, the present study demonstrated that a set of measures to prevent PIVH in preterm infants with gestational age less than 32 weeks was effective in decreasing the incidence of all grades of intraventricular hemorrhage. Implementation of these measures mainly requires education for the NICU staff regarding the need for care practices that minimize fluctuations in cerebral blood flow. These measures are low-cost and easy to implement, although they are difficult to maintain in the long run because consistent implementation requires staff to be continuously reminded of their value.

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Impact of home-based aerobic training combined with food orientation on food consumption, daily physical activity and cardiorespiratory fitness among breast cancer survivors: six-month clinical trial

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ABSTRACT

BACKGROUND: Anticancer treatment gives rise to adverse effects such as increased pain and changes to body weight and menstrual cycles, with negative effects on activities of daily living.

OBJECTIVE: To analyze the effect of food orientation combined with supervised (face-to-face, FF) versus home-based (HB) aerobic training on lifestyle (food consumption and daily physical activity (PA) levels), body composition, metabolic profile and cardiorespiratory fitness, among breast cancer survivors.

DESIGN AND SETTING: Clinical trial study (six months) conducted at a public university in Presidente Prudente, Brazil.

METHODS: Twenty-three female breast cancer survivors (40-75 years old) were allocated to aerobic training groups, either FF or HB. Both groups were trained and received food orientation. They were evaluated through a dietary record, ergometric treadmill test and blood test and the Baecke questionnaire.

RESULTS: After six months, both groups had reduced their lipid levels, total energy consumption and poly-unsaturated fat intake, and had increased their PA levels and treadmill test durations. However, only the HB showed reduced carbohydrate percentage and increased folic acid; and only the FF showed reduced lipid, saturated fat and sodium levels, along with increased carbohydrate and protein levels. No differences in body composition or metabolic profile were found.

CONCLUSIONS: These results demonstrated the feasibility of HB aerobic training. In isolation, HB showed greater regulation of carbohydrate percentage and increased folic acid levels. Moreover, these breast cancer survivors presented improvements in food consumption, PA levels and cardiorespiratory fitness, while also maintaining their body composition and metabolic profile after the intervention, independent of the group.

CLINICAL TRIAL REGISTRATION: NCT03494400.

INTRODUCTION

Hormone therapy is an adjuvant treatment used by breast cancer patients to reduce the risk of tumor recurrence through hormonal blocking, among those with positive hormonal receptors.[1] Among the different types of hormone therapy, aromatase inhibitors and tamoxifen are the ones most frequently applied to breast cancer patients. Aromatase inhibitors are considered to be more efficient than tamoxifen among menopausal women. Although there is clinical evidence to support the use of hormone therapy, a variety of adverse effects among patients have been reported, such as bodyweight changes, menstrual cycle alterations, pain and risk of uterine cancer.[2]

On the other hand, food orientation allied with physical activity (PA) has been demonstrated to improve quality of life among breast cancer survivors.[3] Combination of these two interventions has also been found to be advantageous with regard to cancer patients' body composition and metabolic profile.[4] These results were obtained through home-based interventions. Recently, this type of intervention was used among breast cancer patients.[4] Nevertheless, it is less commonly used among patients who are undergoing hormone therapy.

Home-based interventions can be developed in different areas and places, such as public squares and patients' homes. Hence, this approach has also been used to increase adherence.[5]

Moreover, technology has enabled monitored home-based training sessions.[6] However, previous studies that involved home-based training did not provide good descriptions of protocol progression and control over training intensity within this method.[3,4] Our study contributes to this information, and also compares use of the same protocol in a face-to-face group.

Aerobic training has been the form of exercise most recommended for breast cancer patients, due to its safety.[7] Furthermore, it can alter their metabolism, as demonstrated through a study on fat mass reduction and lower-limb lean mass increments among 38 obese women who were breast cancer survivors. These women performed three months of aerobic training in which they walked more, did static stretching and were invited to do moderate-intensity exercise at home.[8]

Conversely, some studies are still showing controversial results. In one such study, 22 overweight or obese black breast cancer survivors who underwent an aerobic intervention combined with nutritional counseling for 12 weeks did not show any body weight reduction.[9] These results demonstrate that there is a lack of consensus in the literature about prescription of aerobic training to improve the metabolic profile and reduce the bodyweight of breast cancer patients. However, aerobic training increases the level of physical activity and cardiorespiratory capacity.[9] Although the effect of home-based training among patients with breast cancer has been already researched, little has been explored regarding the effect on women undergoing hormone treatment.

OBJECTIVE

The aim of this study was to analyze the effect of food orientation combined with face-to-face versus home-based aerobic training on lifestyle (food consumption and daily physical activity level), body composition, metabolic profile and cardiorespiratory fitness among women undergoing hormone therapy for breast cancer.

METHODS

Subjects

Twenty-three women without current aerobic training who were undergoing hormone therapy (either still in treatment or with treatment concluded) for breast cancer, consisting of use of either tamoxifen or aromatase inhibitors, volunteered to participate in this study. The women who had concluded their treatment had had at least five years of hormone therapy. To be included, the participants needed to have not had any aerobic training for at least three months before the intervention. Potential participants were excluded if they presented any mental disorder or physical condition that would not allow them to perform the aerobic training. In addition, any women who were incapable of verbal communication or had physical impairments or were pregnant or breastfeeding at that time were also excluded. Participants were also excluded if they withdrew from the training or suffered any physical injuries. The women were allocated either to a face-to-face training group (FF) (n = 10) or to a home-based training group (HB) (n = 13).

This study was approved by the Research Ethics Committee of the School of Science and Technology, São Paulo State University (Universidade Estadual Paulista "Júlio de Mesquita Filho", UNESP), in Presidente Prudente, Brazil, under protocol number 78971417.9.0000.5402 (approved February 26, 2018), and was registered at clinicaltrials.gov under the number NCT03494400 (April 11, 2018). All the procedures were conducted in accordance with the Declaration of Helsinki. Thus, potential participants were informed of the aim and procedures of the study, with a complete explanation, and those who agreed to participate signed a written informed consent statement.

To recruit potential participants, phone numbers of female breast cancer patients who were undergoing hormone therapy were obtained from cancer hospitals. Social media were also used to publicize the study, in order to facilitate inclusion of women living in nearby municipalities or who were not on the phone lists. All the participants were blindly coded and allocated 1:1 with sequence boundaries in the random sequence generator random.org.[10] The sample size was calculated using statistical software (G-power 3.1; Düsseldorf, Germany). This revealed that with eight participants, a medium effect size of 0.60 would be achieved,[11] with α error probability of 0.05, power (1-β error probability) of 0.8 and correlation of 0.5, in repeated-measurement analysis of variance (ANOVA) on within-between interaction; and with non-sphericity correction of one, for two groups. There were two analyses over the course of the study.

Outcomes

The participants' clinical characteristics were verified at the baseline through an anamnesis. All evaluations were carried out before and after the 24-week intervention.

Lifestyle

The participants' nutritional status was determined through a dietary record, which was applied on three occasions: on two workdays and on one weekend day. This dietary record, which consisted of recording all food consumed throughout the day, was collected at the baseline and after the 24 weeks of the intervention.[12] The software Avanutri Revolution Package, version 4.0 (Avanutri Informatics Ltda, Rio de Janeiro, Brazil) was used to calculate the dietary record.

In order to evaluate the daily physical activity (PA) level, the Baecke questionnaire was applied. This questionnaire has been validated for the Brazilian adult population.[13] It contains three domains, but the working PA domain was not used in this study since most of the participants were retired or had stepped down due to their health condition.[14,15]

Body composition

Anthropometric measurements were made on a mechanical scale (Filizola) to the nearest 0.1 kg; and on a fixed stadiometer (Sanny) to the nearest 0.1 cm or with a measuring tape (Sanny) to the nearest 0.1 cm. The body mass index was also calculated.[16]

A bioelectrical impedance device (BIA Analyzer, Nutritional Solutions, Harrisville, MI, United States) was used to obtain resistance and reactance data. The participants received recommendations regarding clothing, food and drug use, to be evaluated.[17,18] The bioelectrical impedance analyzer data were used to calculate fat free mass (kg).[19] The percentage of fat mass was also calculated.[19] For the purposes of the present study, obesity was defined as a fat mass percentage ≥ 25%.[20]

Metabolic profile

The participants' metabolic profile was analyzed by assaying their glycemia, insulin, triglyceride, total cholesterol and cholesterol fraction levels. For this, blood samples were collected in vacuum tubes with gel without anticoagulant. An enzymatic colorimetric kit was used and the samples were processed in an Autohumalyzer A5 device (Human Gesellschaft für Biochemica und Diagnostica mbH, Wiesbaden, Germany).[21] The participants were recommended to fast for 12 hours before the blood test, which was done at a specific laboratory (Unilab, Presidente Prudente, São Paulo, Brazil). The metabolic profile was classified as normal or altered.[22]

Cardiorespiratory capacity

The modified Naughton test was performed on an ergometric treadmill (Inbramed ATL 2000; Inbrasport, Porto Alegre, Brazil), with a maximum capacity of 180 kg, inclination of 26% and velocity of 24 km/h, in a climate-controlled laboratory. This ramp test involved incremental increases in velocity and inclination, and each stage was maintained for two minutes.[26] The test was ended when the participant reached 85% of her maximum heart rate, as predicted for her age, or when she showed signs for which the test needed to be halted, or when she asked for the test to be stopped because of fatigue.[26]

Aerobic training

The aerobic intervention combined with food orientation lasted for 24 weeks. The aerobic training followed a recommended duration of 150 minutes per week.[23] Nonetheless, progressively higher loads were used in order to achieve physiological and metabolic adaptations.[24]

The aerobic training protocol for the FF was undertaken on an ergometric treadmill (Movimento, LX-160, Equipamento de Fitness, Pompeia, São Paulo, Brazil) in an air-conditioned laboratory. The participants trained three times a week on non-consecutive days (Monday, Wednesday and Friday). The intensity of the training was controlled using a heart rate monitor (HR102; Oregon Scientific, São Paulo, Brazil) and was adjusted for the maximum heart rate (HR_{max}), according to age (220-age).[25,26] The degree of perceived exertion was also recorded at the end of each training session, in order to assess the intensity of the training.[26] Over the course of the intervention, the participants went through an adaptation process and three progressive stages (**Table 1**).

The aerobic intervention for the HB was undertaken in a variety of environments. These included places near the participants' homes, public squares and/or inside their homes.[6] The intensity of each training session and the controlled adjustments to the aerobic training were monitored using the rate of perceived exertion[27] and HR_{max}.[28] The same protocol as used for the FF group to increase the intensity of the training was also used for the HB group (**Table 1**).

The participants were encouraged to walk or run at least three times per week. They were also monitored and followed up every 14 days by an exercise specialist from a laboratory. The distance walked or run was verified using a specific application (Google Maps GPS; or Runtastic, Pasching, Austria, 2009).

Food orientation

Both FF and HB received dietary recommendations for breast cancer survivors,[7,29,30] before the intervention began and in each month of the intervention, provided by a specialized nutritionist. The nutritionist gave information on how to choose good-quality economic foods and on how to prepare and adapt meals according to their energy value and nutrient, fiber and vitamin content, through cellphone communication and in-person meetings.

Statistical analysis

Descriptive statistics were calculated: means, confidence intervals and absolute and relative frequencies. Data normality and variance homogeneity were verified through the Shapiro-Wilk

Table 1. Aerobic training protocol for the supervised (face-to-face) group

Stages	Weeks	Session duration (minutes)	Intensity (% HRmax)	Rate of perceived exertion
Adaptation	1-2	30	50 to 60	11-13 (slight to somewhat heavy)
Stage 1	3-4	40	50 to 60	11-13 (slight to somewhat heavy)
Stage 2	5-12	50	60 to 70	13-15 (somewhat heavy to heavy)
Stage 3	13-24	50	70 to 89	15-17 (heavy to very heavy)

HR_{max} = maximum heart rate.

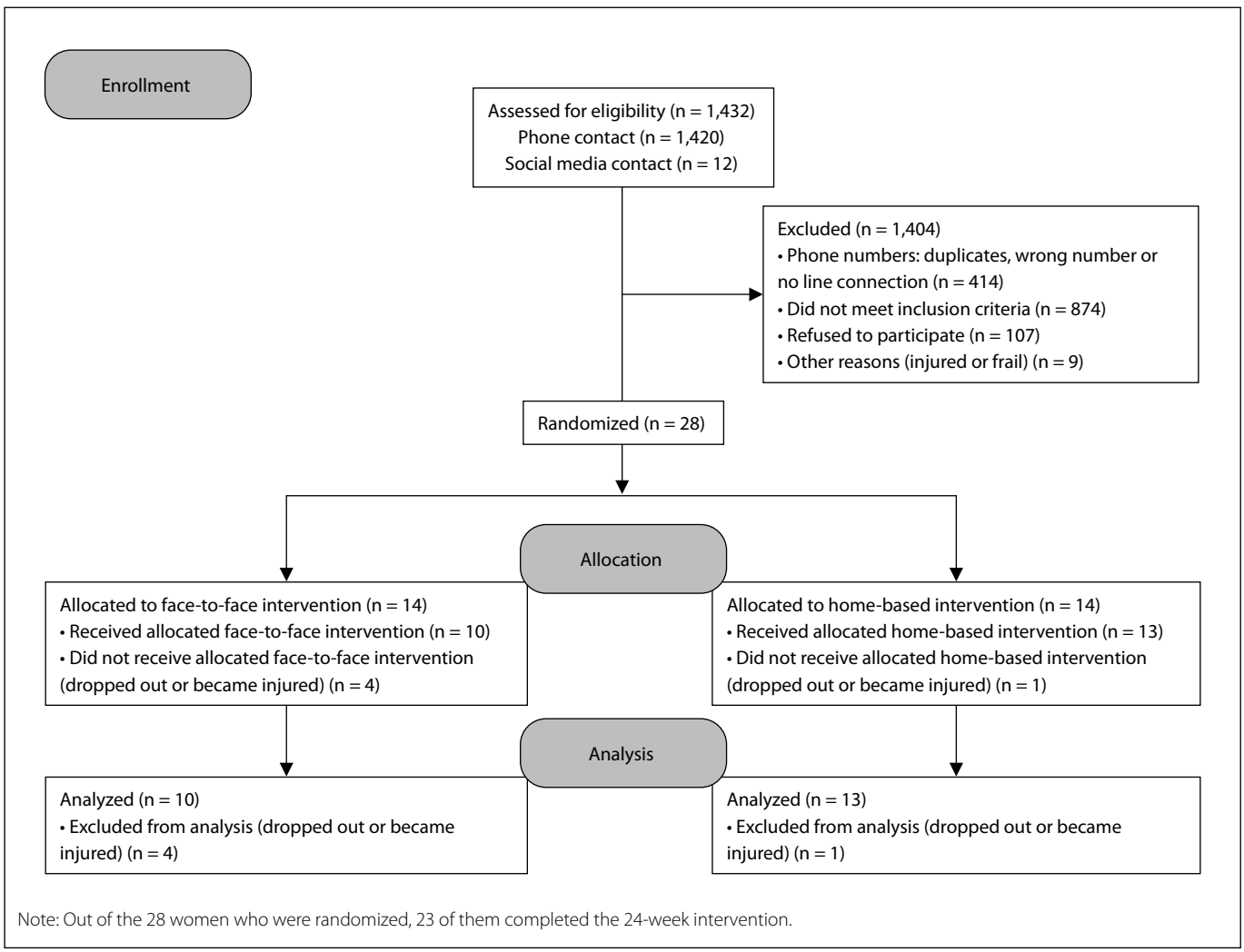
and Levene tests, respectively. The participants' characteristics were analyzed using Student's t test for body mass index and Fisher's exact test for menopause status, medications, chemotherapy and/or radiotherapy utilization, cancer recurrence and/or metastases, time and type of hormone therapy used, with comparisons between FF and HB.

Repeated ANOVA measurements (within-between interactions) were calculated to assess food consumption, daily PA level, body composition and metabolic profile. Subsequently, the Bonferroni post-hoc test was used to verify any statistical differences. The chi-square test and Fisher's exact test were used to verify body composition and metabolic profile classification at the baseline and after the 24 weeks of the intervention. The chi-square test was used to analyze total cholesterol, low-density lipoprotein-cholesterol (LDL-C), non-high-density lipoprotein-cholesterol (non-HDL-C), triglycerides and glycemia; while Fisher's exact test was used to analyze HDL-C and insulin. The effect size was calculated by means of ηp^2. The SPSS 21.0 software (SPSS Inc., Chicago, IL, United States) was applied to perform the statistical analysis. A statistical difference was considered to be present when $P < 0.05$.

RESULTS

Twenty-eight women undergoing hormone therapy for breast cancer participated in this study, and 23 of them completed the 24-week intervention (**Figure 1**). It was observed that the participants in the FF and HB groups were similar at the baseline. Nevertheless, the type of hormone therapy used differed between the groups (P = 0.036) (**Table 2**). All the participants had undergone breast cancer surgery.

We observed that the participants' lipid consumption (g) presented reductions, as shown in the post-hoc test: for FF, P = 0.001; and for HB, P = 0.008. The percentage of lipid consumption decreased only for FF (P = 0.002). The carbohydrate percentage presented interaction (f = 7,216; P = 0.023; $\eta p^2 = 0.419$) and difference in the time analysis (f = 5.012; P = 0.049; $\eta p^2 = 0.334$), with increased levels in FF (P = 0.007). The groups differed at the baseline (P = 0.022) (**Table 3**).



Note: Out of the 28 women who were randomized, 23 of them completed the 24-week intervention.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

The total energy consumption (kcal) and polyunsaturated fat (g) showed reductions in the FF group (P = 0.003; P = 0.018), as also did HB (P = 0.010; P = 0.047), in the post-hoc test. The FF group presented an increase in protein (%) (P = 0.005) and a reduction in saturated fat (g) (P = 0.016). The sodium level (mg) was influenced over time (f = 15.134; P = 0.003; $\eta p^2 = 0.602$), with a reduction for FF (P = 0.010), such that there was a difference between the groups at the end of the 24-week intervention (P = 0.027). Conversely, the carbohydrate percentage (P = 0.029) presented a reduction and folic acid (mg) presented an increase (P = 0.018) in HB (**Table 3**).

We observed increases in physical exercise levels, with regard to the dimensions of both leisure PA and locomotion PA, in both the FF group (P = 0.004; P = 0.024) and the HB group (P = 0.035; P = 0.040) (**Table 4**). The duration of the treadmill test showed a difference in the time analysis (f = 10,811; P = 0.008; $\eta p^2 = 0,519$), with different increases in FF (P = 0.010) and in HB (P = 0.038) (**Table 5**).

Body composition and metabolic profile did not present significant differences (**Table 4**). Nonetheless, the alterations in the metabolic profile, independent of the training group, demonstrated that the majority of the participants were within the normal range at the baseline, except for LDL-C (39.1%) and non-HDL-C (26.1%). It was also observed that after the 24-week intervention, there were more participants with a metabolic profile that was considered normal, except for glycemia and insulin (**Table 5**).

DISCUSSION

In this study, the nutritionist's recommendations were given in person and online via smartphones. It is worth mentioning that in the literature, it has been established that informative interventions combined with aerobic training seem to be more efficient with regard to improving quality of life, compared with interventions alone.[3]

Hence, food orientation seems to be a means for changing habits. On the other hand, changes in dietary habits might also be due to alterations related to physical exercise, which generate improvements in the anti-inflammatory process. Consequently, leptin and insulin signaling in conjunction with the central nervous system improve the signaling of the satiety command in the hypothalamus.[31]

Table 2. Anthropometric and clinical characteristics among the breast cancer survivors

Variables	Face-to-face group (n = 10)	Home-based group (n = 13)	P-value
Age (years)	61.91 (56.87-66.95)	55 (50.27-60.23)	0.050
Body mass index (kg/m²)	30.98 (27.53-34.42)	29.17 (26.71-31.63)	0.348
Menopause, n (%)			
30-39 years	2 (18.2)	0	0.549
40-49 years	6 (54.5)	8 (66.7)	
≥ 50 years	3 (27.3)	3 (25)	
No information	0	1 (8.3)	
Treatment combinations completed			
Chemotherapy + radiotherapy	4 (36.4)	6 (50)	0.680
Without combination	7 (63.6)	6 (50)	
Chemotherapy completed			
Yes	6 (54.5)	7 (58.3)	1.000
No	5 (45.5)	5 (41.7)	
Radiotherapy completed			
Yes	7 (63.6)	10 (83.3)	0.371
No	4 (36.4)	2 (16.7)	
History of cancer recurrence or metastasis			
Yes	1 (9.1)	3 (25)	0.590
No	10 (90.9)	9 (75)	
Hormone therapy phase			
Treatment	6 (54.5)	11 (91.7)	0.069
Concluded	5 (45.5)	1 (8.3)	
Hormone therapy type			
Aromatase inhibitor	8 (72.7)	4 (33.3)	**0.036**
Tamoxifen	2 (18.2)	8 (66.7)	
Used both	1 (9.1)	0	

Values are expressed either as mean (confidence interval) or as absolute frequency (relative frequency).
Statistical tests: Student's t test (age and body mass index) or Fisher's exact test (menopause, treatment combinations, chemotherapy, radiotherapy, cancer recurrence or metastasis and hormone therapy and type of hormone therapy); significance level: P-value < 0.05.

Our results showed that total energy consumption (kcal) decreased, both in FF and in HB. This finding corroborated the data in the literature. A feasibility study among 22 overweight and obese black female breast cancer survivors who participated in an aerobic intervention for 12 weeks found that reductions in energy intake and fat consumption occurred.[9]

Another noteworthy finding in this study was the decreases in macronutrient intake, such as lipid (g) and polyunsaturated fat (g) consumption. These data indicate that our intervention enabled adjustment of fat consumption in both groups and adjustment of lipid consumption in FF.[32]

We observe broader alterations in the FF group, which included simultaneously increased protein (%) and carbohydrate (g) intake, along with reduced lipid (%) and saturated fat (%) levels. However only HB showed a carbohydrate reduction (%). Especially for FF, these results indicated that the balance in macronutrient consumption was enhanced. This was possibly because the adjustments that macronutrients were able to provide to the liver and muscle fat became better. In this regard, overfeeding on sucrose and fat, combined with low protein content, has been seen to increase storage of intrahepatocellular and intramyocellular lipids, consequently increasing fat accumulation in the liver and muscles.[33]

The sodium (mg) consumption was also reduced in both groups, which seems to be a prevention factor against breast cancer recurrence. A cohort study carried out among South African women showed that there was an association between salty foods and the risk of breast cancer development during the post-menopause period.[34]

We observed that in the HB group, the amount of folic acid intake was enhanced. In both groups, folic acid patterns were within normality after the intervention. Folic acid is composed of vitamin B, which is essential for biological reactions since folates provide carbon for deoxyribonucleic acid (DNA) biosynthesis and thus assist in

Table 3. Food consumption among breast cancer survivors who underwent aerobic training combined with food orientation

Variables	Face-to-face group (n = 10)		Home-based group (n = 13)					ηp^2
	Baseline	24 weeks	Baseline	24 weeks	Time	Group	Interaction	
Total energy consumption (kcal)	1960.20 (1606.81-2313.58)	1583.36 (1327.61-1839.11)#	1982.75 (1780.18-2185.32)	1634.27 (1418.40-1850.13)#	**0.001**	0.842	0.842	0.694
Carbohydrates (g)	50.32 (46.19-54.46)*	59.09 (54.14-64.03)#	57.30 (51.70-62.90)	57.38 (51.78-62.98)	**0.049**	0.353	**0.023**	0.334
Lipids (g)	67.79 (50.03- 85.55)	34.74 (22.55-46.93)#	57.36 (44.99-69.72)	43.10 (28.70-57.51)#	**< 0.001**	0.908	**0.039**	0.761
Protein (g)	94.56 (75.74-113.39)	86.08 (70.76-101.40)	82.89 (70.85-94.94)	79.63 (67.08-92.19)	0.298	0.413	0.506	0.108
Carbohydrates (%)	242.96 (205.46-280.46)	231.60 (197.18-266.02)	283.74 (244.80-322.68)	231.95 (201.67-262.23)#	**0.025**	0.362	0.089	0.409
Lipids (%)	30.27 (25.31-35.24)	19.11 (13.99-24.24)#	25.78 (21.15-30.40)	23.00 (17.19-28.82)	**0.002**	0.913	**0.013**	0.616
Protein (%)	19.40 (17.52- 21.29)	21.80 (19.54-24.07)#	16.92 (14.26-19.58)	19.61 (17.14-22.09)	**0.020**	0.139	0.863	0.435
Saturated fat (g)	27.70 (18.79-36.60)	15.31 (8.50-22.13)#	23.64 (17.79-29.48)	19.58 (15.14-24.01)	**0.003**	0.980	0.137	0.605
Polyunsaturated fat (g)	18.41 (11.32-25.49)	9.71 (4.33-15.09)#	14.45 (10.71-18.18)	10.90 (6.60-15.20)#	**0.004**	0.697	0.178	0.576
Monounsaturated fat (g)	9.29 (4.58-14.01)	5.60 (2.88-8.32)	9.19 (5.30-13.08)	8.68 (5.91-11.45)	0.256	0.196	0.327	0.127
Cholesterol (mg)	265.70 (184.81-346.59)	314.91 (154.37-475.45)	253.10 (146.49-359.71)	181.29 (134.43-228.14)	0.818	0.112	0.201	0.006
Fiber (g)	17.69 (12.43-22.95)	20.87 (18.48-23.26)	16.17 (10.98-21.37)	19.03 (15.31-22.75)	0.179	0.498	0.896	0.172
Protein (g/kg)	1.31 (1.0272-1.5964)	1.18 (0.99-1.36)	1.21 (1.00-1.43)	1.16 (0.95-1.37)	0.256	0.720	0.481	0.127
Sodium (mg)	1671.39 (1004.06-2338.71)	601.73 (405.78-797.69)#*	1650.70 (980.25-2321.16)	1226.74 (780.68-1672.80)	**0.003**	0.302	0.246	0.602
Potassium (mg)	1950.06 (1503.57-2396.55)	2017.01 (1659.52-2374.49)	1691.75 (1168.86-2214.64)	1853.23 (1496.25-2210.22)	0.582	0.410	0.723	0.031
Folic acid (mg)	137.65 (83.69-191.60)	170.88 (125.74-216.03)	107.83 (72.01-143.65)	170.09 (139.65-200.53)#	**0.014**	0.540	0.330	0.468
Calcium (mg)	664.54 (415.00-914.08)	600.01 (421.36-778.65)	567.33 (417.00-717.66)	517.49 (338.52-696.46)	0.408	0.445	0.887	0.069
Phosphorus (mg)	1126.37 (875.75-1376.99)	1164.84 (988.64-1341.05)	940.83 (760.85-1120.80)	908.63 (762.38-1054.88)	0.953	0.113	0.586	< 0.001
Iron (mg)	17.33 (14.04-20.62)	16.29 (12.66-19.91)	14.61 (11.79-17.42)	13.44 (10.10-16.78)	0.313	0.204	0.965	0.101

Values are expressed as mean (confidence interval). #Statistical difference within group; *statistical difference between groups; statistical test: ANOVA (within-between interactions) and thereafter the Bonferroni post-hoc test; effect size: ηp^2; significance level: P-value < 0.05.

maintaining the gene balance. Furthermore, folate deficiency is associated with cardiovascular and brain diseases, and also cancer.[35] Folic acid concentrations in the range of 18-32 μmol/l have less association with the risk of development of breast cancer in patients ≤ 50 years old, except in those who carry the gene 677 Ncc.[35] However, the researchers in that study did not analyze the values in patients with breast cancer.

In the literature, it has been proposed that changes to food habits through aerobic home-based training interventions may be a differential in clinical research. This may be due to changes in consumption of fiber and processed meat, along with better choice of purchases, such that vegetables, whole grains, proteins and legumes are bought instead of sweets and processed snacks.[36] Therefore, aerobic home-based interventions that are monitored online with nutritional counselling seem to have positive effects on food habits, compared with FF interventions.[36]

In the present study, similar results for FF and HB were observed regarding increases in PA levels and maintenance of body composition and metabolic profile. These results are in accordance with those from a study in which 100 women with breast cancer were

Table 4. Daily physical activity level, body composition and metabolic profile among breast cancer survivors who underwent aerobic training combined with food orientation

Daily physical activity level	Face-to-face (n = 10)		Home-based (n = 13)					ηp^2
	Baseline	24 weeks	Baseline	24 weeks	Time	Group	Interaction	
Exercise and leisure physical activity	2.18 (1.87-2.49)	2.64 (2.26-3.01)#	2.27 (2.07-2.48)	2.61 (2.42-2.80)#	**0.004**	0.801	0.472	0.583
Activities of locomotion	1.95 (1.53-2.38)	2.43 (2.06-2.81)#	2.02 (1.67-2.38)	2.36 (2.15-2.58)#	**0.005**	1.000	0.574	0.566
Cardiorespiratory fitness								
Test time (minutes)	6.36 (4.88-7.84)	7.45 (5.97-8.94)#	6.45 (5.49-7.42)	7.18 (5.91-8.45)#	**0,008**	0,915	0,307	0,519
Body composition								
Weight (kg)	73.78 (65.55-82.02)	73.66 (64.70-82.63)	69.53 (64.33-74.73)	69.28 (65.11-73.45)	0.765	0.333	0.888	0.009
Waist circumference (cm)	90.14 (83.14-97.13)	91.03 (84.03-98.02)	84.81 (80.14-89.48)	84.31 (80.22-88.40)	0.740	0.192	0.163	0.011
Fat-free mass (kg)	40.18 (37.17-43.19)	40.20 (36.94-43.47)	39.39 (37.63-41.15)	39.32 (37.45-41.20)	0.914	0.616	0.826	0.001
Fat mass (%)	44.96 (42.07-47.84)	44.75 (41.73-47.77)	42.93 (39.45-46.40)	43.02 (40.19-45.85)	0.900	0.240	0.731	0.002
Metabolic profile								
Total cholesterol (mg/dl)	190.82 (172.49-209.15)	189.55 (173.12-205.97)	176.55 (159.25-193.84)	169.55 (150.88-188.21)	0.299	0.177	0.590	0.107
HDL-C (mg/dl)	58.45 (49.05-67.86)	56.09 (49.29-62.89)	57.64 (49.48-65.79)	58.09 (49.78-66.40)	0.551	0.914	0.354	0.037
LDL-C (mg/dl)	107.35 (90.75-123.95)	110.62 (94.14-127.09)	96.89 (80.61-113.17)	89.81 (70.77-108.85)	0.570	0.235	0.249	0.033
Non-HDL-C (mg/dl)	132.36 (114.07-150.66)	133.45 (115.66-151.25)	118.91 (100.40-137.41)	111.36 (92.13-130.59)	0.368	0.210	0.358	0.081
Triglycerides (mg/dl)	139.00 (106.81-171.19)	123.25 (96.11-150.38)	122.00 (91.33-152.67)	120.91 (93.03-148.79)	0.429	0.643	0.152	0.064
Glycemia (mg/dl)	101.03 (89.18-112.88)	107.0364 (95.62-118.46)	94.75 (68.03-121.46)	90.53 (75.67-105.38)	0.827	0.333	0.091	0.005
Insulin (mcIU/ml)	15.69 (11.64-19.74)	18.63 (12.71-24.54)	11.83 (7.47-16.19)	11.79 (8.14-15.44)	0.106	0.136	0.212	0.239

Values are expressed as mean (confidence interval). #Intra-group difference; statistical test: analysis of variance (within-between interactions) and thereafter the Bonferroni post-hoc test; effect size: ηp^2; significance level: P-value < 0.05.
HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein cholesterol.

Table 5. Assessment of metabolic profile in breast cancer survivors who underwent aerobic training combined with food orientation, independent of training groups

Metabolic profile	Baseline		24 weeks		P-value	ηp^2
	Altered	Normal	Altered	Normal		
Total cholesterol (mg/dl)	10 (43.5)	13 (56.5)	7 (30.4)	16 (69.6)	0.359	0.135
HDL-C (mg/dl)	2 (8.7)	21 (91.3)	1 (4.3)	22 (95.7)	1.000	0.088
LDL-C (mg/dl)	14 (60.9)	9 (39.1)	12 (52.2)	11 (47.8)	0.552	0.088
Non-HDL-C (mg/dl)	17 (73.9)	6 (26.1)	14 (60.9)	9 (39.1)	0.345	0.139
Triglycerides (mg/dl)	8 (34.8)	15 (65.2)	7 (30.4)	16 (69.6)	0.753	**0.046**
Glycemia (mg/dl)	7 (30.4)	16 (69.6)	8 (34.8)	15 (65.2)	0.753	**0.046**
Insulin (mcIU/ml)	1 (4.3)	22 (95.7)	3 (13)	20 (87)	0.608	0.145

Values are expressed as absolute frequency (relative frequency). Statistical test: chi-square test (total cholesterol, LDL-C, non-HDL-C, triglycerides and glycemia) or Fisher's exact test (analysis on HDL-C and insulin); effect size: ηp^2; significance level: P-value < 0.05.
HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein cholesterol.

assessed. The sample was separated into three groups: one of them received counselling via telephone, another received on-site recommendations and the third was a control group. The two intervention groups received counselling aimed at decreasing their energy intake, and underwent regular aerobic PA combined with behavioral therapy, for six months.[4] The telephone counselling and on-site groups showed similar results. A significant reduction in body weight was detected, thus differing from the control group, which remained unchanged throughout the intervention.[4] However, weight reduction was only identified when there was a comparison with the group without intervention.[4] Conversely, our study did not have a group without intervention, because the goal was to compare intervention models. These results highlight that HB intervention seems to be efficient among women with breast cancer.

Our data indicated that changes in lifestyle occurred, along with increased PA levels and improved food consumption. However, these improvements did not provide body weight loss. The results from this study are in agreement with data in the literature, in which no significant improvements in body composition were found after six months of aerobic intervention and nutritional counselling, among 61 breast cancer women undergoing chemotherapy.[37] Therefore, it appears that difficulty in reducing body weight and improving body composition, after an aerobic intervention combined with food orientation, is present at different stages of breast cancer.

Regarding the effects of hormone therapy on body weight gain, no significant differences between aromatase inhibitors and tamoxifen were observed in comparison with a placebo.[38] On the other hand, use of aromatase inhibitors seems to cause less body weight increase than does estrogen receptor selective modulator.[38] This demonstrates that endocrine agents might not be the only cause of body weight gain, considering that other events may occur concomitantly, such as chemotherapy and menopause. All of these other events may encompass factors related to body weight increase.[38] Moreover, the aging process could be another factor, given that middle aged women's body weight increases by about 0.5 kg per year.[39] In contrast, maintenance of body composition and metabolic profile could be positive for women undergoing hormone therapy for breast cancer, when these variables are within the recommended values.

In this study, most of the participants were within the recommended range of metabolic profile.[22] This may have influenced maintenance of this parameter without the need for metabolic adjustments caused by the aerobic intervention and food orientation. However, the training volume might not have been efficient with regard to ameliorating the metabolic profile.[24] Nevertheless, practicing moderate to vigorous PA for ≥ 150 minutes per week has been correlated with better levels of HDL-C and triglycerides.[40]

Clinically, cancer survivors show metabolic alterations, as well as dysfunction or increased cardiac overload, in comparison with individuals of a similar age without a diagnosis of cancer.[41] In order to test the fitness level of our participants, we used the modified Naughton test, which is recommended for individuals with chronic conditions, older adults and individuals with low physical activity levels.[26] The duration of the stress test is a parameter for estimating cardiopulmonary capacity.[42] The results from our study showed that the number of stages completed during the test increased in both groups, which suggests that among women undergoing hormone therapy for breast cancer, not only supervised aerobic training but also a home-based approach can improve cardiorespiratory capacity.

Some limitations of the present study need to be acknowledged. These include prescription of training on the basis of HRmax, which may present variability between participants of a mean of 12 heartbeats/minute.[26] On the other hand, use of the perceived exertion rate was helpful for the home-based training protocol. Additionally, the sample size was another limitation in this study, owing to the difficulty in recruiting women with breast cancer who were undergoing hormone therapy, in a city of approximately 208,000 inhabitants. Nevertheless, a medium effect size was predominant among the study variables and we were able to investigate the feasibility of an intervention.

We suggest that multicenter studies should be conducted on this population, with analysis on inflammatory cytokines, in order to better comprehend the nutritional alterations caused by the relationships of body composition and metabolic profile with the central nervous system.

CONCLUSION

The aerobic intervention combined with food orientation was a feasible strategy for promoting improvements in food consumption, daily PA and cardiorespiratory fitness, and for maintaining body composition and metabolic profile, among women undergoing hormone therapy for breast cancer.

The groups also stood out individually, such that in the FF group, there was greater regulation of macronutrients and, in the HB group, the folic acid level increased and the percentage of carbohydrates decreased. These results demonstrated the feasibility of HB aerobic training, as a complementary treatment for breast cancer survivors.

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Effects of participation level and physical activity on eating behavior and disordered eating symptoms in the Brazilian version of the New Moves intervention: data from a cluster randomized controlled trial

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ABSTRACT

BACKGROUND: Childhood and adolescent obesity is a worldwide public health concern. The New Moves program aims to change eating behavior (EB) and physical activity (PA).

OBJECTIVE: To evaluate the effectiveness of an intervention and predictors of better outcomes relating to EB and PA levels.

DESIGN AND SETTING: Secondary data from a cluster randomized controlled trial in 10 public schools in São Paulo, Brazil.

METHODS: 270 female adolescents, aged 12 to 14 years, were analyzed. Participation levels were categorized as presence in 1 to 9 sessions or 10 to 17 sessions, or control. Effectiveness was evaluated through improvement in disordered EB (DEB) and EB. Predictors of better outcomes relating to PA levels were evaluated through clustering of individual characteristics that affected changes in PA scores.

RESULTS: Participation level was not significantly associated with changes in DEB or EB. Girls with higher body mass index percentile (BMI-P) percentile tended to have increases in sedentary lifestyles through the program. Girls with less body image dissatisfaction presented higher increases in daily PA. Girls with higher BMI-P percentile and higher self-esteem showed reductions in sedentary lifestyles. The program seemed to have more effect on daily PA among older girls than among younger girls.

CONCLUSIONS: This program could be used as a structured action plan in schools, with the aims of improving eating behaviors and physical activity, in addition to promoting self-acceptance. The results indicate the importance of evaluating determinants of adherence, as these metrics might influence the effectiveness and future design of lifestyle programs.

BRAZILIAN REGISTRY OF CLINICAL TRIALS: RBR-6ddpb3.

INTRODUCTION

Pediatric obesity is a worldwide health concern, and the majority of overweight or obese children live in low-to-middle income countries.[1-3] Studies on low-income individuals[4] and school-based interventions in low-to-middle income countries[5,6] have demonstrated improvements in eating behavior (EB), physical activity (PA) and body weight. Traditional preventive measures against obesity that focus on weight seem to be ineffective and harmful to the participants. These programs contribute to eating and weight concerns, body image dissatisfaction, low self-esteem and unhealthy weight control practices. Such behaviors are considered to be risk factors for weight instability and development of eating disorders (ED).[7,8]

Obesity and ED result from cultural contexts that motivate an unhealthy relationship with food, EB and PA. In addition to these factors, this cultural context discourages respect for the diversity of body size.[9] Obesity and ED share psychosocial and behavioral risk factors, which suggests that integrated interventions would lead to better outcomes.[9] These integrated interventions can include overlapping of problems and involvement of similar risk factors (diet and weight). They make use of the economic efficiency of addressing two conditions in a single intervention.[10]

The New Moves program is an integrated intervention based on social cognitive theory, which is one of the most common theoretical frameworks used in interventions that have the aim of changing EB and PA.[11-13] This program was designed in the United States focusing on adolescent

females and it incorporates issues relating to eating disorders and obesity. It has a dynamic multi-component that includes factors that can predict body satisfaction, eating behaviors and patterns, weight control practices and PA levels. Positive outcomes were found among female adolescents in the United States, with improvements in sedentary lifestyles, eating patterns, unhealthy weight control behaviors and body/self-image.[11]

Considering that none of the previous intervention programs involved an after-school approach and that none of the studies with individuals from low socioeconomic backgrounds[5,6] discussed the effect of participation level on the programs, a gap in the literature currently exists.

OBJECTIVE

We aimed to evaluate the effectiveness of an intervention and the predictors of better outcomes relating to eating behaviors and PA levels.

We hypothesized that 1) girls with higher participation level would show significant improvements in those outcomes after the phase 1 (P1) intervention; and 2) their levels of body image dissatisfaction and self-esteem, their age and their nutritional status would enable prediction of PA levels and sedentary lifestyles.

METHODS

Study design

This study consisted of an exploratory analysis on a previously conducted cluster randomized controlled trial of the Brazilian New Moves program (BNMP). This program was conducted among girls aged 12 to 14 years old, at ten public schools in the central and southern areas of the city of São Paulo.[14] The randomization of the original trial was performed at the school level to prevent contamination across students, between the intervention and observation arms. There was no blinding regarding intervention assignments or assessment, but blinding was present during data analysis. The analyses followed an intention-to-treat protocol that involved a sensitivity analysis in which all the subjects were included regardless of their length of follow-up or intervention. A total of 270 adolescent girls who practiced less than one hour of moderate to vigorous-intensity PA per day[15] were randomized, among whom 131 were allocated to the intervention arm and 139 to the control arm. All the adolescents completed the baseline and endpoint assessments of P1 and the endpoint assessment of P2 (after nine weeks).

The BNMP consists of eight behavioral objectives that can be accessed at www.newmovesonline.com. However, in this study we focused on four behavioral objectives: (1) to be more physically active; (2) to increase fruit and vegetable intake; (3) to limit consumption of sugar-sweetened beverages; and (4) to eat breakfast every day. The BNMP was adapted for use as a nine-week intervention phase (P1) with 17 sessions that was followed, after a holiday interval, by an additional nine-week maintenance phase (P2) with 9 sessions, thus totaling 26 sessions. Adolescent girls were included from 2014 to 2015.

PA sessions were scheduled twice a week, and nutrition and social support components were held on those same days. All of these elements were conducted by trained healthcare professionals, including psychologists, dietitians and PA professionals.

The Institutional Review Board of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP), Brazil, approved our study on September 30, 2015 (CAAE: 06460112.6.0000.5505). Informed assent and consent forms were signed by the adolescents and their parents/guardians, respectively, before implementation of any study protocol. We registered the trial at the Brazilian Registry of Clinical Trials in September 2015 (RBR-6ddpb3).

Participation level

The participation level was assessed by categorizing the number of times a participant was present in sessions promoted by the study intervention. This was considered in terms of three groups: control group, presence in 1 to 9 sessions and presence in 10 to 17 sessions. The exploratory analysis broke the randomization, so that participants in the intervention groups who did not participate in the intervention activities were analyzed as controls.

Socioeconomic status (SES)

The "Brazilian Economic Classification" was used to categorize students based on their economic status. This classification is based on possession of items (e.g. television, radio or automobile) and the head of the family's education level. From this, a score was generated and the participants were stratified according to monthly gross family income. The sum of these scores was used to determine the family's purchasing power, which was categorized ranging from A1 to E.[16] Based on Brazil's monthly minimum wage (1 monthly minimum wage = US$ 249.50 at the time of writing this article, the categories are classified as A1/A2 = 11 minimum wages; B1 = 6 minimum wages; B2 = 3.12 minimum wages; C1 = 1.86 minimum wages; C2 = 1.27 minimum wages; and D/E = 0.89 minimum wages.

Body mass index (BMI)

BMI was calculated as the weight in kilograms divided by the height in meters squared. Weight was measured by trained study staff using a digital scale, while height was measured with a portable stadiometer. Based on BMI-P percentiles (BMI-P) standardized according to age and sex, the participants were classified as defined by the World Health Organization (2007),[17] as underweight or at

risk (BMI-P ≤ 15), normal weight (15 < BMI-P < 85), overweight (85 ≤ BMI-P < 97) or obese (BMI-P ≥ 97).

Disordered eating behaviors (DEB)

Disordered eating behaviors (DEB) were assessed using the following three scales.

Body Shape Questionnaire (BSQ) - Brazilian Portuguese version:[18] This is a self-reported scale with the aim of assessing body image dissatisfaction. It presents good internal consistency (Cronbach's alpha = 0.96) and reliability (r = 0.91; P < 0.001). The questionnaire consists of a 34-item self-reported scale that uses six Likert categories going from "never" to "always", in which the higher the score is, the greater the degree of dissatisfaction with body image is. The scores were classified as "no dissatisfaction", "slight dissatisfaction", "moderate dissatisfaction" and "serious dissatisfaction".[19]

Weight Control Behaviors Scale (WCBS) - Brazilian Portuguese version:[20] This scale is an internally reliable and valid instrument that is used to assess factors representing healthy and unhealthy weight control behaviors. Out of the items on this scale, we used only the following nine items that assessed unhealthy weight control behaviors (UWCB): fasting, skipping meals, dieting, taking diet pills, making oneself vomit, using diuretics, using laxatives, using food substitutes like powdered/special drinks and smoking cigarettes. For each item, the participants responded with a "yes" or "no" response to indicate whether they had performed the behavior with the intent of losing weight in the past month. The internal consistency among these nine items was adequate (Cronbach's alpha = 0.66). Through this scale, we aimed to assess unhealthy weight-control behaviors.

Rosenberg Self-Esteem Scale (RSES):[21] This is a 10-item self-administered scale with items used as four-point Likert categories ranging from strongly agree to disagree, in which higher scores indicate higher self-esteem. Its construct validity shows a significant positive correlation with social support and its internal consistency has been reported as 0.68. With this scale, we aimed to assess self-worth and feelings about the self.

Although BSQ, WCBS and RSES are self-reported scales, we noticed in a pre-test study that the girls were having difficulties in filling out these questionnaires. We therefore trained the research staff to ask questions, without giving any interpretation of these questions.

Eating behaviors (EB)

To assess EB, we evaluated changes in fruit, vegetable and sugar-sweetened beverage intake, and the frequency of breakfast intake. Fruit and vegetable intake was assessed using the following questions, "Thinking back over the past week, how many servings of fruit did you usually eat on a typical day?" and "Thinking back over the past week, how many servings of vegetables did you usually eat on a typical day?" The response options for both questions went from "none," to "five or more servings/day." Last week's intake of regular soda and artificial juices was assessed using the following response options, which were converted to a mean intake/day: never = 0; once or twice a week = 0.2; three or four times a week = 0.5; once a day = 1; twice a day = 2; three times a day = 3; four times/day = 4; or five or more times/day = 5. The question relating to breakfast intake was, "During the past week, on how many days did you eat breakfast?" and the response options went from "none" to "seven days".

Physical activity level

The participants were provided with accelerometer devices (model GT3x, version 4.4.0; ActiGraph, Pensacola, FL, United States). They were instructed to fasten the elastic tape to their hips while keeping the instrument on their right side, to use it for seven consecutive days and only to remove it while showering. Data extraction and validation were conducted using the Actilife software, version 6.11.3 (ActiGraph, Pensacola, FL, United States).

Metabolic equivalents (METs) were evaluated as the rate of energy expenditure at rest. The accelerometer-related measurements of PA data corresponded to an index that was composed of a two-factor structure: daily PA (DPA) (Cronbach's alpha = 0.94) and sedentary activity (Cronbach's alpha = 0.79). Both structures have good factor loadings, internal reliability scores and appropriate validity across a range of self-reported PA measurements.[22]

The DPA index included the total time spent on moderate to vigorous PA (MVPA), total step count, Freedson bouts, METs and total time spent on mild-intensity PA. The sedentary activity index referred to sedentary lifestyles and included the following: total number of sedentary breaks, number of sedentary bouts, duration of sedentary activities and time spent doing vigorous and very vigorous PA.[22]

Statistical analysis

Our exploratory analysis started with an evaluation of distributions, frequencies and percentages for each of the numerical and categorical variables of this study. The categorical variables were evaluated for near-zero variation,[23] or categories with only a small percentage of response that could potentially bias our models. An extensive graphical exploratory analysis was used for both univariate analysis and bivariate associations between potential outcomes and the frequency of participation in study-related activities. Missing data were explored using a combination of graphical displays involving univariate, bivariate and multivariate methods. Imputation was performed using a k-nearest neighbors algorithm (n = 5).[24]

The association between participation level and outcome measurements was assessed using generalized estimating equations that adjusted for baseline variables, to account for each school level. In accounting for each school, we automatically controlled for the confounding of zero participation among those in the control group, compared with the intervention groups. We included both groups (control and intervention) while adjusting for their differences based on statistical considerations, thus providing greater statistical power for finding predictors of engagement, if they were present. The participation level was assessed by categorizing the count of the number of times a participant was present in the sessions, which was categorized into three groups. These groups were created to have approximately equal numbers of observations for each of the categories. The results were expressed as predicted means with 95% confidence intervals and were deemed statistically significant when the confidence intervals did not overlap between different estimates.

We also used regression trees (recursive partitioning) to evaluate how the clustering of individual characteristics affected the change in PA scores over time. The predictors included age, BMI-P, BSQ score, METs and RSES scale. The outcomes included the DPA and sedentary lifestyles. Regression trees represent the best cutoff points for predictor values in the context of a given outcome after previous features have been taken into account. This method allowed us to evaluate variables not only in isolation but also as a sequence. To avoid overfitting, we applied a cost-complexity strategy using weakest-link pruning by successively collapsing the internal node that produces the smallest per-node increase in the cost complexity criterion. When overfitting was detected, those nodes were removed. Otherwise, they were left intact. We also provided a graphical representation of each model. All analyses were performed using the R statistical language.[25]

RESULTS

Out of the overall sample (n = 270), 65.2% of all the subjects did not participate in any sessions, 15.2% participated in 1 to 9 sessions and 19.6% participated in 10 to 17 sessions. **Table 1** shows the baseline characteristics of the participants in each group. Analysis of variance (ANOVA) and chi-square analyses were conducted to determine whether the groups differed in any of the variables with continuous or categorical data, respectively. At the baseline, these groups differed in only three variables: age, SES and breakfast habits. Regarding the demographics of age and SES, these potentially confounding variables were entered as covariates in the remaining analyses.

To evaluate the association between the participation level and the outcome measurements, we used the three categories representing the participation level by means of a generalized estimating equation to account for the clustering effect within each school. The participation level did not result in statistically significant differences concerning outcome measurements, including body image dissatisfaction, self-esteem, unhealthy weight-control behaviors, BMI-P and EB measurements (frequency of breakfast and fruit, soda and artificial juice intake per day) (**Table 2**).

Based on a previously validated sensor-based index,[22] we used generalized estimating equations to identify predictors of change in daily PA and sedentary lifestyles between the baseline and 17 weeks. All the scores were normalized to a 0-100 scale, which was then used to determine the predicted means for the change in daily PA and sedentary lifestyles. Out of the 270 participants in the trial, 75 were excluded because of lack of data recording devices, or because they missed the orientation and training day when the devices were distributed, or because some data was found to be missing at the time of data extraction from the device. The analysis was conducted with a final sample of 195 participants, given that only these girls presented MET data. We found that the differences in participation level relating to 1 to 9 and 10 to 17 sessions gave rise to statistically significant associations with increases in sedentary lifestyle (P = 0.027 and P = 0.039, respectively) (**Table 3**).

To better understand how the clustering of individual characteristics might affect their change in daily PA scores (DPAS) over time, we used regression tree analysis (recursive partitioning). We found that METs ≥1.02 was the first node separating those with higher or lower changes in DPAS. Individuals with lower METs showed a reduction in DPA, while individuals with higher METs showed an increase in DPA. At a METs cutoff point of 1.07, individuals with higher METs showed an increase in DPA, while individuals with lower METs showed a decrease in DPA. The second node in the tree was age. Accordingly, participants with METs between 1.02 and < 1.07 and age ≥14.6 years old demonstrated an increase in DPA, while participants with the same METs but who were younger than 14.6 years old showed a decrease in DPA. The third node in the tree was body image dissatisfaction (BSQ), which was associated with girls younger than 14.6 years old and METs between 1.02 and < 1.07. The cutoff point for BSQ was 64.5. Girls with body image dissatisfaction showed small changes in DPA, while those with less body image dissatisfaction showed an increase in DPA (**Figure 1**).

In evaluating predictors of changes in sedentary lifestyles (sedentary score, SS), METs were the first node in the regression tree. Girls with higher METs showed a reduction in SS, while those with lower METs showed an increase in SS. Also, girls with lower METs (< 1.09) showed an increase in the SS, while those with higher METs only showed a subtle increase in SS. The second node in the tree was BMI-P. Girls with lower METs and BMI-P less than P85 showed a reduction in SS, compared with those with BMI-P ≥P85, who showed an increase in SS. Girls with BMI-P ≥P85 and higher RSES showed a reduction in SS, while those with lower RSES showed an increase in SS (**Figure 2**).

DISCUSSION

Our study demonstrated that the participation level in the BNMP did not affect DEB and EB. Also, we observed a negative effect on PA levels (an increase in sedentary lifestyles). In brief, girls with less body image dissatisfaction presented higher increases in daily PA, while for those with more body image dissatisfaction, the program had almost no effect on daily PA. The program seemed to have more effect on daily PA among older girls than

Table 1. Participant characteristics stratified according to participation level

Variable	Total (270)	Control** (176)	1 to 9 sessions** (41)	10 to 17 sessions** (53)	P-value
Age	13.4 (± 0.64)	13.5 (± 0.64)	13.3 (± 0.66)	13.1 (± 0.54)	< 0.001
Weight	53.3 (± 12.2)	53.75 (± 12.6)	51.32 (± 11. 6)	53.45 (± 11.7)	0.497
Height	1.58 (± 0.06)	1.58 (± 0.07)	1.57 (± 0.06)	1.57 (± 0.06)	0.181
Body mass index percentile	21.35 (± 4.4)	21.348 (± 4.5)	20.8 (± 4.2)	21.6 (± 4.2)	0.626
Body mass index percentile category					
Underweight or at risk (< P15)	26 (9.6%)	17 (9.7%)	5 (12.2%)	4 (7.6%)	0.978
Normal weight (P15-P85)	151 (55.9%)	100 (56.8%)	22 (53.7%)	29 (54.7%)	
Overweight (P85-P97)	59 (21.9%)	37 (21%)	9 (22%)	13 (24.5%)	
Obese (> P97)	34 (12.6%)	22 (12.5%)	5 (12.2%)	7 (13.2%)	
Socioeconomic status					
A2	7 (2.6%)	6 (3.4%)	0 (0%)	1 (1.9%)	0.004
B1	23 (8.5%)	14 (8%)	2 (4.9%)	7 (13.2%)	
B2	76 (28.1%)	61 (34.7%)	10 (24.4%)	5 (9.4%)	
C1	104 (38.5%)	56 (31.8%)	20 (48.8%)	28 (52.8%)	
C2	54 (20%)	38 (21.6%)	7 (17.1%)	9 (17%)	
D	6 (2.2%)	1 (0.6%)	2 (4.9%)	3 (5.7%)	
Rosenberg Self Esteem Scale					
Low self-esteem	8 (2.96%)	6 (3.43%)	2 (4.88%)	0 (0%)	0.322
Medium/high self-esteem	261 (96.7%)	169 (96.6%)	39 (95.1%)	53 (100%)	
Body Shape Questionnaire					
No dissatisfaction	167 (61.9%)	117 (66.5%)	23 (56.1%)	27 (50.9%)	0.11
Slight dissatisfaction	52 (19.3%)	26 (14.8%)	13 (31.7%)	13 (24.5%)	
Moderate/serious dissatisfaction	51 (18.9%)	33 (18.7%)	5 (12.2%)	13 (24.5%)	
Unhealthy Weight-Control Behaviors*					
No unhealthy weight-control behavior	190 (70.4%)	117 (66.5%)	31 (75.6%)	42 (79.2%)	0.261
1-3 unhealthy weight-control behaviors	73 (27.1%)	55 (31.2%)	8 (19.5%)	10 (18.9%)	
More than 5 unhealthy weight-control behaviors	7 (2.6 %)	4 (2.3%)	2 (4.9%)	1 (1.9%)	
Binge eating	39 (14.4%)	21 (7.8%)	10 (3.7%)	8 (2.9%)	0.127
Last week – fruits per day					
None	48 (17.8%)	31 (17.6%)	11 (26.8%)	6 (11.3%)	0.739
1 portion	65 (24.1%)	44 (25%)	10 (24.4%)	11 (20.8%)	
2 portions	84 (31.1%)	54 (30.7%)	10 (24.4%)	20 (37.7%)	
3 portions	41 (15.2%)	26 (14.8%)	6 (14.6%)	9 (17%)	
More than 3 portions	32 (11.9%)	21 (11.9%)	4 (9.8%)	7 (13.2%)	
Last week – vegetables per day					
None	71 (26.3%)	44 (25%)	16 (39%)	11 (20.8%)	0.223
1 portion	76 (28.1%)	48 (27.3%)	12 (29.3%)	16 (30.2%)	
2 portions	64 (23.7%)	40 (22.7%)	8 (19.5%)	16 (30.2%)	
3 portions	34 (12.6%)	25 (14.2%)	5 (12.2%)	4 (7.5%)	
More than 3 portions	25 (9.3%)	19 (10.8%)	0 (0%)	6 (11.3%)	
Last week – breakfast (number of days)	3.87 (± 2.7)	4.51 (± 2.59)	2.15 (± 2.49)	3.06 (± 2.46)	< 0.001
Last week frequency of regular soda/day	0.86 (± 1.3)	0.86 (± 1.32)	0.99 (± 1.36)	0.77 (± 1.18)	0.714
Last week frequency of artificial juice/day	1.23 (± 1.51)	1.14 (± 1.4)	1.16 (± 1.48)	1.6 (± 1.83)	0.242

Results are demonstrated as mean ± standard deviation, or crude number and percentage.

*Number of unhealthy weight control methods used by each participant, including fasting, skipping meals, dieting, vomiting, along with use of diet medications, diuretics, laxatives, nutritional replacements or cigarettes.

**Control group: participants who were absent from the program interventions; 1 to 9 sessions: participants who were present in 1 to 9 sessions of the program; 10 to 17 sessions: participants who were present in 10 to 17 sessions of the program.

Table 2. Association between frequency of sessions and predicted means of outcome measurements (n = 270)

Outcome measurements	Control** (n = 176)	1 to 9 sessions** (n = 41)	10 to 17 sessions** (n = 53)
Body mass index percentile	0.31 (0.11, 0.5)	0.44 (0.1, 0.78)	0.41 (0.09, 0.74)
Body shape questionnaire	-4.7 (-10.52, 1.07)	-6.8 (-15.21, 1.57)	-9.43 (-17.9, -0.99)
Rosenberg Self Esteem Scale	**0.93 (0.42, 1.44)**	**1.05 (0.27, 1.84)**	**0.8 (0.07, 1.53)**
Unhealthy weight-control behaviors*	0.004 (-0.15, 0.16)	-0.28 (-0.52, -0.05)	-0.23 (-0.44, -0.03)
Last week frequency			
Breakfast	-0.07 (-0.38, 0.25)	-0.41 (-0.96, 0.13)	-0.08 (-0.54, 0.38)
Fruits per day	-0.27 (-0.45, -0.09)	0.03 (-0.3, 0.36)	0.1 (-0.17, 0.37)
Vegetables per day	-0.05 (-0.23, 0.14)	-0.2 (-0.49, 0.1)	-0.16 (-0.44, 0.11)
Regular soda	-0.18 (-0.42, 0.06)	-0.05 (-0.41, 0.31)	-0.20 (-0.56, 0.15)
Artificial juice	0.24 (-0.07, 0.55)	0.09 (-0.33, 0.52)	-0.08 (-0.55, 0.39)

Results are demonstrated as predicted means with 95% confidence intervals.

*Number of unhealthy weight control methods used by each participant, including fasting, skipping meals, dieting, vomiting, along with use of diet medications, diuretics, laxatives, nutritional replacements, or cigarettes.

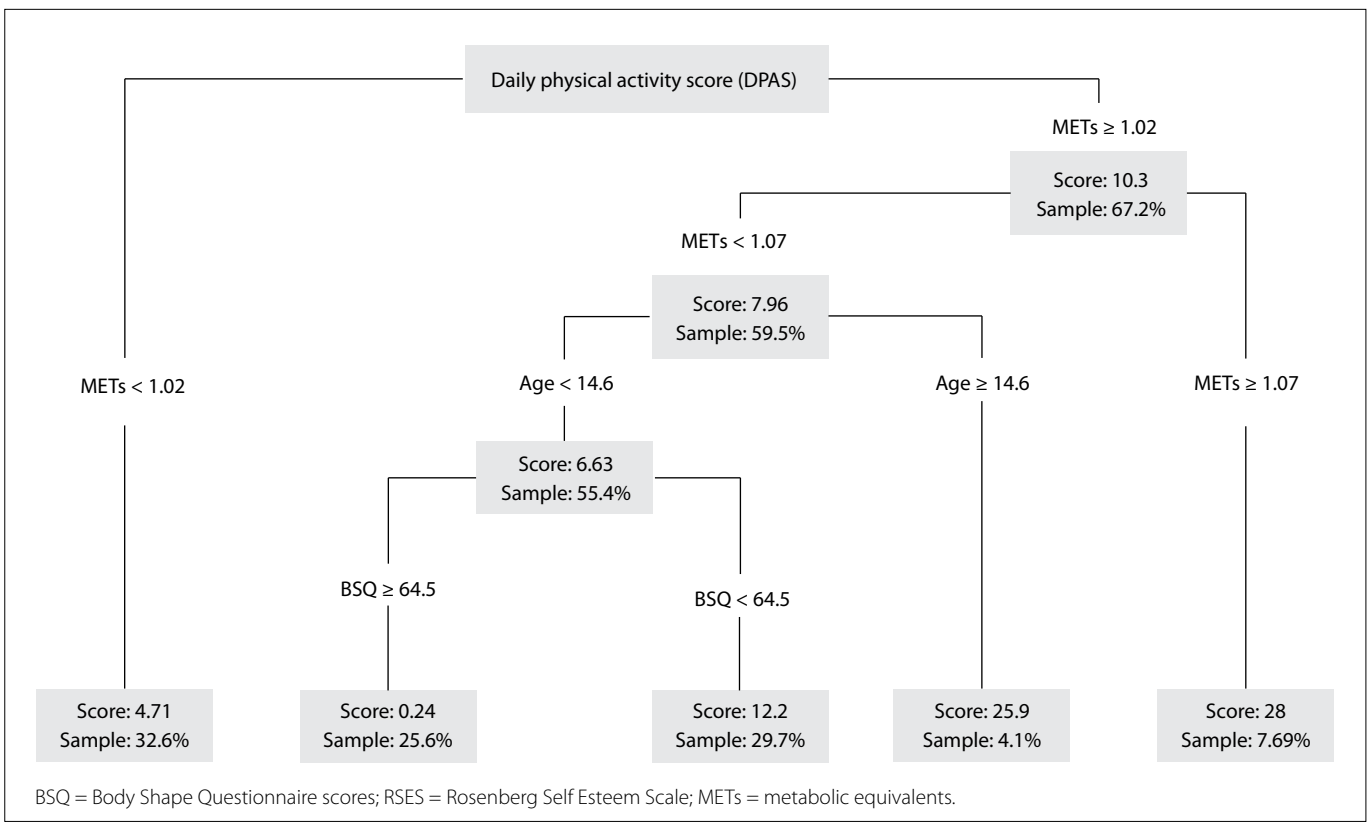
**Control group: participants who were absent from the program interventions; 1 to 9 sessions: participants who were present in 1 to 9 sessions of the program; 10 to 17 sessions: participants who were present in 10 to 17 sessions of the program.

Table 3. Changes in daily physical activity and sedentary activity (n = 195)

Participation level	Daily physical activity	P-value	Sedentary activity	P-value
Control*	2.83 (-3.99, 9.66)		-3.89 (-12.3, 4.53)	
1 to 9 sessions*	7.32 (-0.174, 14.8)	0.435	12.1 (4.11, 20.1)	0.027
10 to 17 sessions*	3.8 (-4.67, 12.3)	0.885	13 (2.1, 23.9)	0.039

Results are demonstrated as predicted means with 95% confidence intervals.

*Control group: participants who were absent from the program interventions; 1 to 9 sessions: participants who were present in 1 to 9 sessions of the program; 10 to 17 sessions: participants who were present in 10 to 17 sessions of the program.



BSQ = Body Shape Questionnaire scores; RSES = Rosenberg Self Esteem Scale; METs = metabolic equivalents.

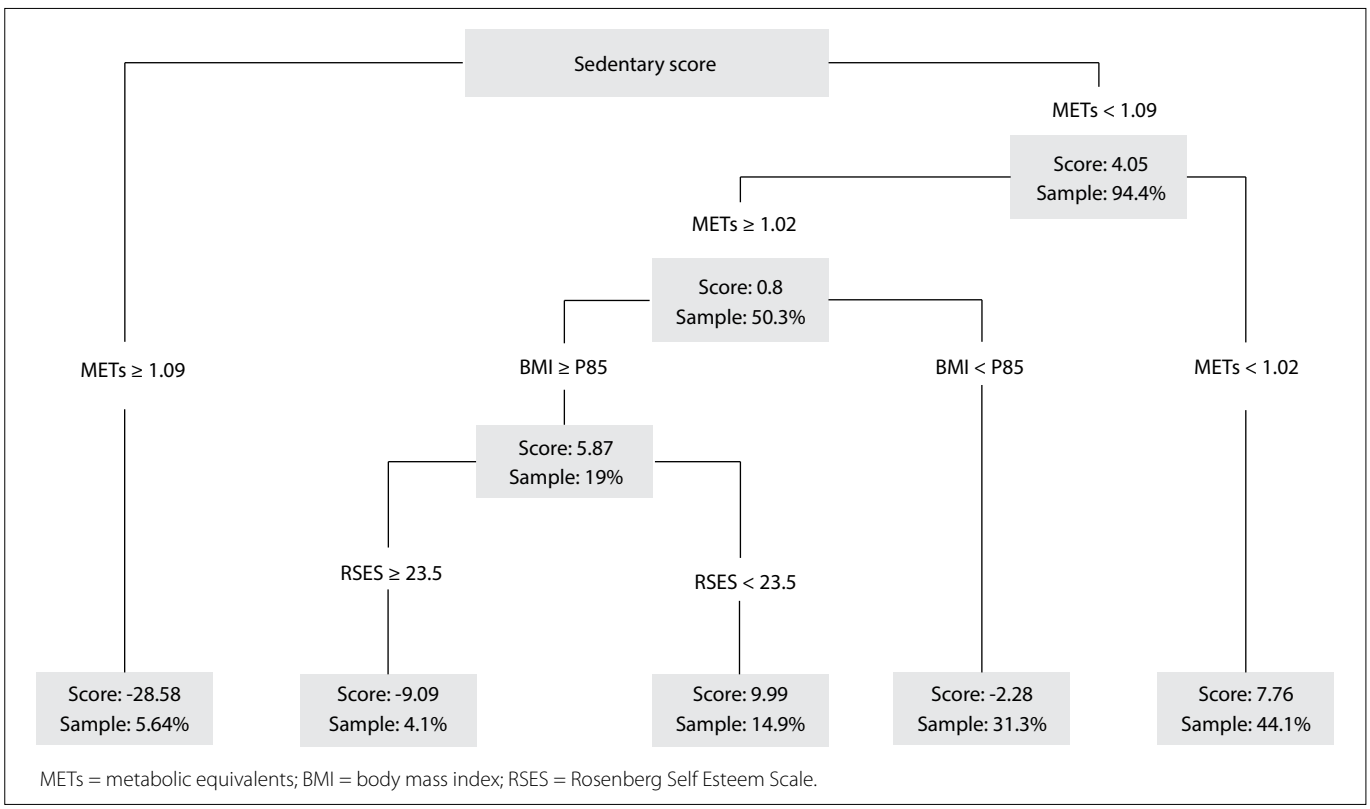
Figure 1. Regression tree of daily physical activity score changes (n = 195).

among younger girls. Therefore, girls with higher BMI-P tended to have increasingly sedentary lifestyles, while eutrophic girls tended to reduce sedentary lifestyles. Those with higher BMI-P and higher self-esteem showed reductions in sedentary lifestyles, while those with higher BMI-P and lower self-esteem showed increases in sedentary lifestyles.

For the program to be successful, participation by everyone involved in the environment of these girls is necessary. Part of the program consists of communication with parents, so that they may motivate teenagers to improve their PA lifestyle. During the intervention, absence of parent and teacher involvement was observed. There was no motivation for PA at school, even though it formed part of the students' curriculum. Souza et al.[26] demonstrated that, both for children and for adolescents, the main adherence factors for PA were motivation and support from friends or parents, pleasure in doing PA and the opportunity to be with and play with other children and adolescents. Ceschini et al.[27] and Moraes et al.[28] demonstrated high prevalence of physical inactivity among adolescents, and the factors associated with this were gender (girls were more inactive than boys), age, lower socioeconomic status, geographical region of the city of São Paulo, daily time spent watching television and being obese.

One potential protective factor against body dissatisfaction is greater amounts of PA, given that this has been correlated with satisfaction with body image, self-esteem, reduced risk of ED and psychological benefits.[29] In our sample, being an older girl, with less dissatisfaction with body image, normal BMI-P and better self-esteem was predictive of higher PA levels and less sedentary behavior. Girls with more body satisfaction may be more engaged in PA for reasons of fun and socialization, while girls who are dissatisfied with their bodies aim to change their weight and shape. For older girls, there was better understanding of healthcare, while younger girls were more motivated to play than to practice PA. Girls with higher BMI percentiles had more sedentary habits than did eutrophic girls, and this was a possible explanation for being overweight. Girls with higher self-esteem tended to be better motivated to exercise than did those with low self-esteem. Moreover, PA interventions were associated with increased self-concept and self-worth among children and adolescents.[30]

No improvement in EB was observed, given that socioeconomic issues and food availability may influence such habits. One possible explanation for this is that marketing of food and beverages may influence children's food choices, preferences and consumption, especially with regard to foods that are high in energy density and poor in micronutrients.[31] Another possible explanation is that manufactured products, with low monetary value and low dietary value, are preferred over healthy foods.[32] Data from the latest 2008/2009 Brazil Household Budget Survey found that low-income



METs = metabolic equivalents; BMI = body mass index; RSES = Rosenberg Self Esteem Scale.

Figure 2. Regression tree of sedentary score changes (n = 195).

communities tend to buy fewer fruits, vegetables, tubers and roots in a week than do the middle and upper classes. This may be consequent to a lack of food and nutrition education in public schools and for the overall community, which would develop skills and knowledge and allow these communities to choose and consume their foods safely and appropriately.[33]

Effective procedures and designs for programs targeting multicomponent behaviors among low-income individuals[4] are still a challenge because these are not maintained over the long term. Certain limitations can influence the effectiveness of such programs.[4,34,35] These limitations have been described as insufficient knowledge and understanding within the school community (participants, teachers, etc.) about the importance of healthy lifestyles.[36]

The strengths of our study are its use of reliable measurements for DEB and accelerometer devices for measuring PA levels. Nonetheless, our results should be interpreted in the light of some limitations of this study: 1) the sample was composed of adolescent girls, thus preventing generalization to adolescent boys; 2) the participants' education levels and ages are likely to have been an interpersonal barrier to innovative intervention; 3) Twenty-eight percent of the girls who were initially randomized to the intervention arm completed all the assessments but did not participate of the sessions, which thus represents low adherence and will have impacted on the effectiveness of the program.

CONCLUSIONS

This program could be used as a structured action plan in schools, with the aims of improving eating behaviors and physical activity, in addition to promoting self-acceptance. Moreover, it could be implemented in a personalized and interactive manner, with weekly messages on mobile devices. As discussed by López-Guimerà et al.,[37] in interactive programs like New Moves, it is also important to monitor adherence to activities.

With regard to future work, researchers are encouraged to address the issue of adherence in after-school programs and to involve school staff in the development of further interventions. Moreover, through adding qualitative data to evaluations, insights that would enhance the likelihood of successful intervention may be gained.

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Association between vitamin D levels and lower-extremity deep vein thrombosis: a case-control study

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ABSTRACT

BACKGROUND: Vitamin D has relationships with pathogenesis and inflammation pathways in many diseases. Its deficiency may make clinicians think not only of supplementation but also of presence of other diseases.

OBJECTIVE: To investigate the relationship between vitamin D levels and deep vein thrombosis (DVT), given that reduced levels are related to increased risk of cardiovascular diseases.

DESIGN AND SETTING: Case-control study conducted in the cardiovascular surgery and family medicine departments of a hospital in Turkey.

METHODS: A total of 280 participants were included: 140 each in the DVT and control groups. Basic clinical characteristics, comorbidities and serum 25-hydroxyvitamin D (25(OH)D) levels were recorded and then compared between the groups. Serum 25(OH)D levels were also evaluated separately in three subgroups (sufficient, insufficient and deficient).

RESULTS: Serum 25(OH)D levels were significantly lower in the DVT group than in the controls ($P < 0.001$). Females in the DVT group had lower 25(OH)D levels than those in the control group ($P = 0.002$). Nonetheless, the median 25(OH)D level (16.41 ng/ml) of the control group was still below the reference value. Logistic regression analysis showed that 25(OH)D was a significant predictor of DVT. Weight, height and body mass index, which all presented interaction, were significant in the logistic regression analysis but not in individual analyses.

CONCLUSION: The serum vitamin D levels of DVT patients were lower than those of controls. If the results obtained from our study are supported by further large-scale randomized controlled trials, vitamin D replacement may be brought into the agenda for protection against DVT.

INTRODUCTION

Vitamin D is a fat-soluble vitamin that is synthesized non-enzymatically in the skin and metabolized in the liver and kidneys. It arranges the immune response of the body, acts as a steroid hormone and plays a crucial role in mineral homeostasis and skeletal health.[1] Serum vitamin D levels in the range 30-60 ng/ml (75-150 nmol/l) are considered normal. Deficiency of vitamin D is associated with a variety of bone disorders (rickets, osteoporosis or osteomalacia), skin diseases and autoimmune disorders.[1,2] It also causes increased risk of cardiovascular diseases such as myocardial infarction (MI), heart failure and coronary artery disease.[2-5] Furthermore, deficiency of vitamin D has been reported in arterial diseases, including aortic aneurysm, peripheral arterial disease, arterial calcification and hypertension.[6-9]

Deep vein thrombosis (DVT) is characterized by thrombus formation, usually in the lower-extremity deep venous system, which causes obstruction or occlusion of blood flow in veins. It is considered to be the third most common cardiovascular disease, after ischemic heart diseases and cerebrovascular events.[10] Although the medical and interventional treatment options for deep vein thrombosis have improved nowadays, it continues to pose a serious problem, especially in cases with inadequate treatment. It can lead to pulmonary thromboembolism, venous gangrene, chronic venous insufficiency and post-thrombotic syndrome.[11] The most well-known factors in the etiology of lower-extremity deep vein thrombosis are genetic predisposition, malignancy, history of surgical operation, immobilization, trauma, bone fractures, long journeys and oral contraceptive use.[12] Nevertheless, there may also be other factors that play a role in the etiopathogenesis of deep vein thrombosis.

OBJECTIVE

There are very few studies in the existing literature on the topic of the association between vitamin D levels and lower-extremity deep vein thrombosis. Therefore, we designed this study to investigate whether deficiency of vitamin D is associated with lower-extremity deep vein thrombosis.

METHODS

Ethical considerations

Ethical approval regarding this study was obtained from the institutional ethics committee (decision: 4/17; date: March 28, 2018). All the participants in this study were only included after written informed consent had been obtained from them. All procedures performed in this study were compatible with the ethical standards of the institutional research committee and with those of the Declaration of Helsinki and its comparable ethical standards.

Study design and participants

This was a case-control study that was conducted in the cardiovascular surgery and family medicine departments of our hospital between January 2018 and December 2018. A total of 280 participants were included in the study and were divided equally into two groups: the study group (n = 140) and the control group (n = 140).

The study group consisted of patients who had been admitted to the cardiovascular surgery department and had been diagnosed as presenting lower-extremity deep vein thrombosis. The patients with this condition had had signs and symptoms such as pain and swelling in the leg at the time of admission. After the initial examination on patients whose clinical condition had given rise to a suspicion of deep vein thrombosis, lower-extremity venous duplex ultrasonography was routinely carried out in order to confirm the final diagnosis. All the patients with lower-extremity deep vein thrombosis received anticoagulant therapy consisting of warfarin sodium, low molecular weight heparin or new oral anticoagulant agents such as rivaroxaban.

On the other hand, individuals who were admitted to the family medicine department for a routine check-up and consented to participate in the study were enrolled in the control group. All the participants' demographic and basic clinical characteristics, their comorbid diseases and some laboratory parameters (including vitamin D levels) were noted and then compared between the groups. Findings of any significant variations between the study and control groups, especially with regard to vitamin D levels, were examined in the study. Participants with a family history of venous thromboembolism (VTE) and those who had previously been diagnosed with this condition, individuals who had suffered liver or kidney failure, pregnant women, individuals who had undergone major surgery or trauma in the previous three months and those who had been receiving vitamin D supplementation or hormone replacement therapy over the previous two years were excluded from the study.

Determination of vitamin D levels

Venous blood samples were taken from the subjects enrolled in the study. The samples were placed in sterile standard tubes. Plasma levels of 25-hydroxyvitamin D (25(OH)D), which is a marker for vitamin D status, were measured by means of chemiluminescence immunoassay. All the samples were analyzed within one hour of collection. The levels of 25(OH)D were categorized into three groups: i) Sufficient group, 25(OH)D > 30 ng/ml; ii) Insufficient group, 25(OH)D = 20-30 ng/ml; and iii) Deficient group, 25(OH)D < 20 ng/ml.

Statistical analysis

The normality of the variables was evaluated using the Anderson-Darling test. Descriptive statistics were acquired. Data were expressed as number (%) or median (minimum-maximum). Continuous variables were compared using the Mann-Whitney U-test. Categorical data (two-way tables) were evaluated using the chi-square test. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values of 25-hydroxyvitamin D for deep vein thrombosis from the area under the curve (AUC). The ROC curve analysis was performed using the "OptimalCutpoints" library (version 1.1-4), which was described by López-Ratón et al. for the R software (version 3.4).[13]

Multiple explanatory variable logistic regression analysis was then conducted. The initial model was fitted with inclusion of all significant independent variables. Following this, a backward-elimination approach in a multiple explanatory variable logistic regression model was conducted to evaluate the model for potential confounding effects. In this model, the factors/covariates were taken away one at a time, starting with the factor/covariate that had the largest P value, until all remaining factors had a two-tailed P-value < 0.05. The goodness of fit was tested using the Hosmer-Lemeshow test. The single and multiple explanatory variable logistic regression analysis methods were used. In the single explanatory variable logistic regression analysis, we estimated the odds ratios (OR) with 95% confidence intervals (CI) for deep vein thrombosis, for each study variable, and the significance level of each factor/covariate was determined. The analyses were performed in R (R Core Team, 2014).[14]

RESULTS

The study group consisted of 71 males and 69 females, while the control group consisted of 67 males and 73 females. The mean age of the patients with deep vein thrombosis was found to be

58.36 ± 16.36 years, while it was 57.95 ± 16.01 years in the control group (P = 0.814). The 25(OH)D levels of the patients with deep vein thrombosis were found to be significantly lower than those of the control group: median 9.14 (minimum-maximum: 4.2-82.5) versus 16.41 (4.2-70.7) ng/ml; P < 0.001. Female patients in the study group had significantly lower 25(OH)D levels than those in the control group: median 7.34 (minimum-maximum: 4.20-79.80) versus 12.57 (4.20-70.71) ng/ml; P = 0.002 (**Table 1**). Similarly, male patients in the study group had significantly lower 25(OH)D levels than those in the control group: median 10.59 (minimum-maximum: 4.20-56.21) versus 22.12 (4.20-82.51) ng/ml; P < 0.001.

Regarding cutoff values, significant differences were found between the study and control groups. Higher number of patients in the deep vein thrombosis group were found to have vitamin D deficiency, in comparison with the healthy participants, whereas the control group was found to have a greater number of participants with sufficient vitamin D (**Tables 1** and **2**) (P < 0.001). As shown in **Table 3**, the 25(OH)D level in the deep vein thrombosis patients was mostly deficient, compared with the sufficient and insufficient subgroups (P < 0.001).

The results from the logistic regression analysis that was performed in order to determine independent predictors of deep vein thrombosis are presented in **Table 4**. According to this logistic regression analysis, 25(OH)D was shown to be a significant predictor of deep vein thrombosis. In addition, body mass index, weight and height, which all presented interaction, were also significant in the logistic regression analysis, but not in individual analyses. 25(OH)D was found to be a significant variable in ROC analysis (**Figure 1**).

Consequently, serum 25(OH)D values are thought to have diagnostic value for predicting deep vein thrombosis, but height, weight and body mass index have no combined diagnostic value for predicting deep vein thrombosis.

DISCUSSION

In the current study, we compared the 25(OH)D levels of healthy participants with those of patients diagnosed with deep vein thrombosis. It was found that deep vein thrombosis was more common among patients who had significantly decreased 25(OH)D levels and vitamin D deficiency.

Vitamin D deficiency is a major health problem affecting many people worldwide. The frequency of vitamin D deficiency in healthy individuals in Middle Eastern countries has been reported to be 30-50%.[15-16] Although there is no consensus on the definition of vitamin D deficiency, the majority of authors have reported that 25(OH)D levels below 20 ng/ml can be considered to constitute vitamin D deficiency. It has been indicated that for individuals to remain healthy, their serum 25(OH)D levels need to be continually above 30 ng/ml.[1,17]

Vitamin D has antithrombotic properties, and the major mechanisms reported for these properties include upregulation of thrombomodulin and downregulation of tissue factor. This also increases the levels of interleukin 10 (IL-10), which is an anti-inflammatory cytokine.[15] It has been reported that greater exposure to ultraviolet B light improves vitamin D status, which positively affects anticoagulant properties and cytokine profile.[18] Since vitamin D levels have been shown to be inversely related to plasminogen activator inhibitor-1 (PAI-1) levels, vitamin D is also associated with fibrinolytic activity and vascular endothelial integrity.[19] Therefore, it

Table 2. Assessment of vitamin D measurements

25(OH)D level	DVT group (n = 140)	Control group (n = 140)	Total (n = 280)
Sufficient (25(OH)D > 30 ng/ml)	9 (6.4%)	29 (20.7%)	38 (13.6%)
Insufficient (25(OH)D = 20-30 ng/ml)	14 (10.0%)	36 (25.7%)	50 (17.9%)
Deficient (25(OH)D < 20 ng/ml)	**117 (83.6%)**	**75 (53.6%)**	**192 (68.6%)**

DVT = deep vein thrombosis; 25(OH)D = 25-hydroxyvitamin D.
Data are expressed as number (%) for categorical variables.

Table 1. Demographics, clinical characteristics and vitamin D status of the participants

Characteristic	DVT group (n = 140)	Control group (n = 140)	P-value
Age (years)	60 (20-91)	60 (20-90)	0.814
Female gender, n (%)	69 (49.3%)	73 (52.1%)	0.720
Height (cm)	168 (145-190)	167 (138-191)	0.079
Weight (kg)	77 (55-120)	75 (40-122)	0.056
BMI (kg/m^2)	27.3 (19.5-44.1)	27.0 (18.2-39.4)	0.335
Obesity, n (%)	35 (25.0%)	32 (22.8%)	0.779
Diabetes mellitus, n (%)	17 (12.1%)	23 (16.4%)	0.393
Hypertension, n (%)	22 (15.7%)	19 (13.6%)	0.735
Hyperlipidemia, n (%)	12 (8.6%)	12 (8.6%)	1.000
Smoking, n (%)	36 (25.7%)	36 (25.7%)	1.000
25(OH)D level (ng/ml)	**9.15 (4.20-82.51)**	**16.41 (4.20-70.77)**	**< 0.001**

DVT = deep vein thrombosis; BMI = body mass index; 25(OH)D = 25-hydroxyvitamin D.
Data are expressed as median (minimum-maximum) for continuous variables or number (%) for categorical variables.

Table 3. Demographics, clinical characteristics and vitamin D status of the participants in the deep vein thrombosis (DVT) subgroups based on 25-hydroxyvitamin D (25(OH)D) status

Characteristic	Sufficient (n = 38)	Insufficient (n = 50)	Deficient (n = 192)	P-value
Age (years)	59 (22-84)	63 (38-90)	61 (20-91)	0.500
Female gender, n (%)	20 (52.6%)	18 (36.0%)	104 (54.2%)	0.071
Height (cm)	167 (145-187)	165 (145-180)	168 (138-191)	0.227
Weight (kg)	77 (48-116)	75 (44-114)	76 (40-122)	0.916
BMI (kg/m^2)	28.2 (18.2-37.1)	27.6 (19.3-38.8)	27.0 (19.5-44.1)	0.281
Obesity, n (%)	11 (28.9%)	17 (34.0%)	39 (20.3%)	0.096
Diabetes mellitus, n (%)	3 (7.9%)	8 (16.0%)	29 (15.1%)	0.474
Hypertension, n (%)	4 (10.5%)	5 (10.0%)	32 (16.7%)	0.367
Hyperlipidemia, n (%)	1 (2.6%)	8 (16.0%)	15 (7.8%)	0.500
Smoking, n (%)	12 (31.6%)	8 (16.0%)	52 (27.1%)	0.188
25(OH)D level, n (%)	**9 (23.7%)**	**14 (28.0%)**	**117 (60.9%)**	**< 0.001**

BMI = body mass index; 25(OH)D = 25-hydroxyvitamin D.

Data are expressed as median (minimum-maximum) for continuous variables or number (%) for categorical variables.

Table 4. Logistic regression analysis to determine independent predictors for deep vein thrombosis (DVT)

	P-value	Odds ratio (95% CI)
Age	0.440	1.0063 (0.9904, 1.0225)
Gender	0.442	0.8168 (0.4875, 1.3685)
Height	**0.010**	1.2718 (1.0472, 1.5445)
Weight	**0.022**	0.7976 (0.6501, 0.9786)
BMI	**0.015**	1.9402 (1.0988, 3.4258)
Obesity	0.684	1.2052 (0.4897, 2.2962)
Diabetes mellitus	0.126	0.5800 (0.2871, 1.1719)
Hypertension	0.680	1.1612 (0.5701, 2.3649)
Hyperlipidemia	0.734	0.8548 (0.3466, 2.1079)
Smoking	0.953	0.9830 (0.5524,1.7491)
25(OH)D	**< 0.001**	**0.9501 (0.9272, 0.9536)**

CI = confidence interval; BMI = body mass index; 25(OH)D = 25-hydroxyvitamin D.

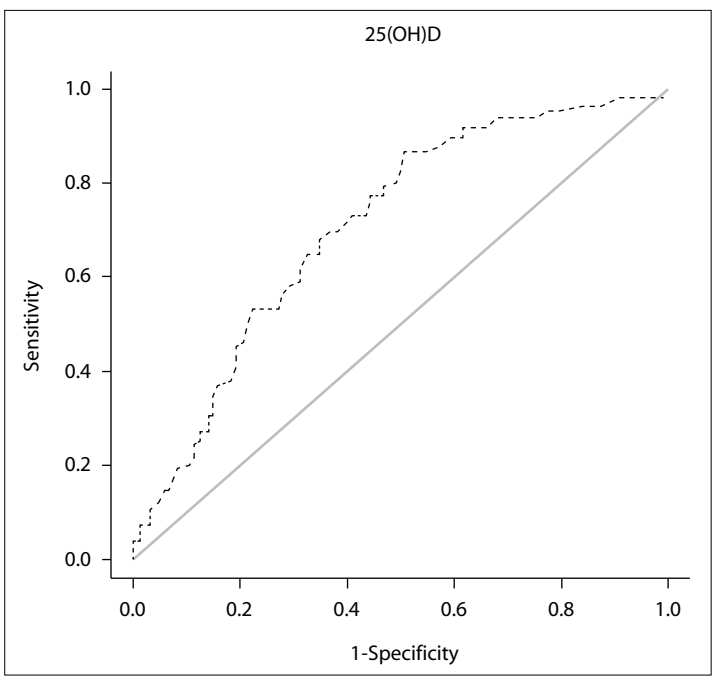

Figure 1. Receiver operating characteristic (ROC) curve showing the diagnostic value of serum 25-hydroxyvitamin D (25(OH)D) for predicting deep vein thrombosis (DVT).

is possible that vitamin D has positive effects on both thrombosis and fibrinolysis. High prevalence of vitamin D deficiency was found in all seasons among 478 subjects diagnosed with acute myocardial infarction (MI), although the deficiency was lower in summer than in winter.[4]

The major risk factors for myocardial infarction consist of atherosclerosis and formation of thrombi and emboli. Inflammation plays an essential role in the basis for risk factor pathogenesis, and vitamin D deficiency increases inflammation. Thus, vitamin D supplementation may reduce these factors.[20] Vitamin D also decreases endoplasmic reticulum stress and oxidative stress of endothelial cells, thereby reducing the risk of atherosclerosis and thrombosis.[21]

Only a very limited number of studies in the existing literature have investigated the relationship between vitamin D levels and venous thromboembolism (VTE). Moreover, to the best of our knowledge, there is only one study in the literature that has examined the association between vitamin D and lower-extremity deep vein thrombosis. Khademvatani et al. studied the relationship between vitamin D status and idiopathic lower-extremity deep vein thrombosis in a case-control study on 82 deep vein thrombosis patients. They reported that low levels of 25(OH)D were related to occurrences of idiopathic lower-extremity deep vein thrombosis.[22] In another study, Wu et al. investigated whether low serum 25(OH)D levels were related to increased incidence of deep vein thrombosis in patients with ischemic stroke. They concluded that low levels of 25(OH)D were independent predictors for deep vein thrombosis in patients with ischemic stroke.[23] Moreover, these authors also indicated that the findings of their study revealed the critical role played by 25(OH)D in the pathogenesis of deep vein thrombosis. On the other hand, the Tromsø Study examined whether high 25(OH)D levels were related to decreased risk of VTE in a prospective population-based study with 6,021 participants. The study revealed that serum vitamin D level was not related to future risk of deep vein thrombosis.[24]

However, in a large-scale observational study including 18,791 participants, it was observed that the risk of deep vein thrombosis became higher with decreasing terciles of seasonally arranged plasma 25(OH)D concentrations. It was concluded that randomized controlled trials were required in order to test the question of causality and whether vitamin D supplementation was essential in the overall population, or only in selected patient groups, to reduce the risk of deep vein thrombosis.[25]

The most important limitations of the present study were the retrospective nature of its data collection, its single-centered design and its limited data evaluation.

CONCLUSION

Our study demonstrated that the serum vitamin D levels of patients with lower-extremity deep vein thrombosis were lower than those of the control subjects. This result suggests that vitamin D deficiency may play a role in the etiopathogenesis of deep vein thrombosis. If the results obtained from our study are supported by further large-scale randomized controlled trials, vitamin D replacement may be brought into the agenda relating to protection against deep vein thrombosis.

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Can physical activity levels and relationships with energy expenditure change the clinical aspects of sarcopenia and perceptions of falls among elderly women? Observational cross-sectional study

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Energy expenditure.

ABSTRACT

BACKGROUND: Physical activity (PA) is an effective strategy for managing sarcopenia in the elderly, but few studies have addressed PA levels regarding age-related changes.

OBJECTIVE: To ascertain the effects of elderly women's PA levels on sarcopenia, physical performance, handgrip strength and perception of the risk of falling, and their relationship with energy expenditure.

DESIGN AND SETTING: Observational cross-sectional study conducted in the southern region of the city of São Paulo, Brazil.

METHODS: Forty-seven elderly women were evaluated and divided into three groups: low PA (n = 13); moderate PA (n = 16); and high PA (n = 18). Their PA levels were investigated through the International Physical Activity Questionnaire (IPAQ); sarcopenia index, through dual-energy radiological absorptiometry; physical performance through the Timed Up & Go test; handgrip strength, using a digital dynamometer; and perception of the risk of falling, through the Fall Risk Awareness Questionnaire.

RESULTS: High PA level indicated higher skeletal muscle mass index, physical performance and IPAQ score, compared with low and moderate PA levels. Multiple linear regression analysis showed that higher IPAQ energy expenditure at high and moderate PA levels was a good predictor of higher physical performance and increased perception of the risk of falling.

CONCLUSION: Elderly women classified as having high PA level showed improvements in sarcopenia, handgrip strength, physical performance and perception of the risk of falling. The IPAQ energy expenditure of the elderly women with high and moderate PA levels was a good predictor of physical performance and improved perception of the risk of falling.

INTRODUCTION

A sedentary lifestyle is the primary risk factor for muscle weakness.[1] Sarcopenia, defined as the loss of muscle mass and function, affects quality of life and increases the risk of physical limitations and disability among older adults.[1,2] Currently, epidemiological statistics show that sarcopenia affects about 50% of elderly people, depending on the country, ethnicity of the patient, diagnostic criteria and healthcare setting.[1-4] Overall, the prevalence among men is about 25% and among women, 20%.[2,5] Thus, loss of muscle mass appears to be an inevitable part of the aging process, especially with decreasing physical performance with aging.[5-9] Scientific evidence has shown that sarcopenia begins to develop between the ages of 30 and 40 years. It progresses with muscle mass declining by an average of 8% per decade between the ages of 40 and 70 years, and accelerates to 15% per decade from the age of 70 years onwards, with variation between men and women.[8,10]

Sarcopenia is associated with functional decline, falls, disabilities and fractures, increased mortality among older adults and increased medical expenditure.[1-5] This disease has many causes, including genetics, nutritional deficiencies, metabolic disturbances, inflammation through production of proinflammatory cytokines by adipose tissue, physical inactivity[4,11-14] and physical limitations.[15-18] Among all these risk factors, research has shown that the greatest cause of sarcopenia is insufficient physical activity and lack of exercise with advancing age, and this has attracted the attention of science and healthcare professionals who are involved in its treatment.[4,5,12-15]

Physical activity (PA) and exercise training have great value in maintenance and augmentation of muscle strength. Increased physical performance enables prevention or treatment of sarcopenia among elderly people.[14,19,20-22] One of the mechanisms relating to the protective effect of PA against sarcopenia is the ability of PA to minimize the effects of muscle apoptosis, which causes decreases in the number and size of muscle fibers.[10,19-22] In addition, sarcopenia is associated with falls and fractures among older adults, with elevated risk of mortality, given the effect of vitamin D on muscle strength and physical performance, which depend on the PA level demonstrated by elderly people.[4,23]

Nevertheless, only a few studies have focused on the relationship between sarcopenia and physical activity levels in the geriatric population, especially with regard to clinical variables relating to the diagnosis of sarcopenia, such as physical performance, handgrip strength and balance. In a cross-sectional study on community-dwelling older adults in Korea, it was found that moderate-to-vigorous physical activity was associated with a reduced risk of sarcopenia.[24] In another study, it was observed that a higher level of PA (accelerometer-determined) was associated with greater lean mass percentage and greater lower-limb strength.[25] However, contradictorily, other studies did not show any association between light/moderate/vigorous physical activity and sarcopenia.[26] Moreover, physical activity (light/moderate/vigorous) did not seem to prevent the loss of muscle mass.[27]

There thus seems to be an issue that needs to be resolved regarding inconsistent findings relating to the effect of general physical activity on sarcopenia. Furthermore, only a few studies have examined the incidence rate of sarcopenia,[28–30] of which only one study looked at its incidence in relation to physical activity.[28] In addition, a few studies have used dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis to assess muscle mass.[28–30]

The differential that was proposed for the present study was that it should characterize physical activity levels and their association with clinical variables (using a simple and reliable questionnaire) through which the diagnosis of sarcopenia could become established. Thus, DXA, physical performance and handgrip strength and their relationship with energy expenditure would be investigated, following the recommendations of the European Working Group on Sarcopenia in Older People (EWGSOP). Furthermore, perceptions of the risk of falling, a critical factor for prevention of fractures and consequently mortality among elderly women, would be assessed. Better understanding of these factors might promote improvements in rehabilitation processes through activity and exercise, thereby creating strategies that would, in fact, be pragmatic with regard to prevention or treatment of sarcopenia due to advancing age.

OBJECTIVE

The objective of the present study was to ascertain the effects of different levels of physical activity practice among elderly women on their clinical characteristics, physical performance, sarcopenia, handgrip strength and perception of the risk of falling, and the relationships of these factors with energy expenditure. The hypothesis was that elderly women who practiced vigorous physical activity would effectively gain better physical performance, thus improving their sarcopenia, handgrip strength and perception of the risk of falling, which might be related to higher energy expenditure.

METHODS

Study design and participants

This study had a cross-sectional and observational design. Fifty elderly women who were in care at the Beneficent Society for Healthcare for the Elderly of the Southern Region, São Paulo, Brazil, were evaluated, but three of them were excluded from the study because they did not attend the DXA examination. The study was approved by the Departmental Research Committee of the Universidade de Santo Amaro (UNISA) (registration number: 2.991.135; date: October 10, 2018, in accordance with relevant guidelines and regulations. All the elderly women provided their informed consent in writing before they underwent assessment.

The eligibility criteria for this study were that the participants needed to be elderly people practicing PA, aged 60 years or older. The exclusion criteria comprised presentation of vestibulocochlear diseases, uncontrolled cardiac and/or respiratory arrhythmias, convulsive and neurological syndromes and musculoskeletal disorders such as diabetic neuropathies, osteoarthritis, rheumatoid arthritis, limiting tissue lesions (cutaneous ulcers of any etiology) and functional impairment, especially of the lower limbs. In addition, use of prostheses and/or orthoses in the lower limbs, or occurrence of fractures within the last six months, were also considered to be exclusion criteria. Thus, good general health (without any diagnosis of mental illness or signs and symptoms of depression) was necessary in order to prevent bias in interpreting the evaluations.

The elderly women selected were divided into three groups: low PA: n = 13; moderate PA: n = 16; and high PA: n = 18. The PA level was measured by means of the International Physical Activity Questionnaire (IPAQ). IPAQ facilitates estimation of time spent walking, engaging in moderate and vigorous intensity PA, or sitting, both during the week and on weekends. It covers multiple domains: work, travel, housekeeping and leisure in one typical week or the last seven days. Detailed information on duration (minutes/day) and frequency (days/week) was collected for the different dimensions of physical and sedentary activity in all domains. In this, the activities performed for at least ten continuous minutes in the previous week were considered. Intensity, expressed in terms of working metabolic equivalents (METs), was

determined in accordance with the guidelines for data processing and analysis that form part of IPAQ.[31,32]

To calculate PA scores in the different domains mentioned above, the following formula was used: Intensity (METs) * Duration (minutes/day) * Frequency (days/week). The total PA score was generated as the sum of the scores (work + travel + domestic + leisure) in METs/minute/week and the final classification of PA levels was obtained using the SAS statistical software, version 9.1 (SAS, Raleigh, NC, United States).

Evaluation and clinical diagnosis of sarcopenia

The clinical and laboratory diagnosis of the skeletal muscle mass index (i.e. presence of sarcopenia) was made by means of lunar DXA examination (model DPX-MD; General Electric Company, United States), in order to characterize the sarcopenia profile of the elderly women. The parameters considered for the diagnosis of sarcopenia were ≤ 7.0 kg/m^2 for men and ≤ 6.0 kg/m^2 for women.[6,33] This calculation was performed by means of the software inserted into the device and was called the skeletal muscle mass index. It was defined as the sum of the appendicular lean mass (as a volume) in the arm and leg segments, divided by the height squared.

Physical performance and balance evaluation

Physical performance was determined using the Timed Up and Go (TUG) test, which provides an assessment of gait speed and dynamic balance. The TUG test measures the time spent in the tasks of standing up from a chair (from a seated position), walking three meters along a path marked out on the floor, turning round, walking along the same path back to the chair and sitting down again, with one's back resting against the back of the chair.

The test began with the subject sitting correctly on a stable chair that had armrests and a seat back (the subject's hips and back were leaning fully on the chair); the subject could use the arms of the chair to help in moving from the sitting position to the standing position and vice versa. At a signal from the evaluator (who started the timer concomitantly), the subject stood up, walked (at his or her usual pace) to a marked point, walked around it, returned and sat down on the chair again (the timer was stopped when he or she was in the correct sitting position, with arms resting on the chair armrests, at the end of the walk). The instruction given was for the elderly person to perform the task safely, as quickly as possible, wearing their usual shoes. For greater measurement accuracy, no bracing device for walking (walking stick, walker, etc.) or assistance from another person during the test course was allowed.[33,34]

The test results were classified as follows. Times of between 11 and 20 seconds were considered to be normal for frail elderly or disabled patients. Times that were greater than or equal to 20 seconds were taken to indicate impaired physical and balance performance that required appropriate intervention.[33,34]

Handgrip strength assessment

Handgrip strength, in kg, was measured using a digital dynamometer (Model SH5001; Saehan Corporation, Yangdeok-Dong, Masan, South Korea). The test was performed with the elderly person sitting on a chair without armrests, with the shoulder slightly adducted and the elbow of the dominant arm flexed at 90°, and with the forearm and wrist in a neutral position. The elderly individual was instructed to press the dynamometer as hard as possible twice, with a two-minute interval between the attempts. The highest force value obtained was recorded. Elderly individuals with values below 30 and 20 (kg), for men and women respectively, were classified as having low muscle strength.[35,36]

Fall risk assessment

The FRAQ-Brazil (Fall Risk Awareness Questionnaire) is a questionnaire that assesses the perception of risk of falling among individuals over 65 years of age, which has been validated for Brazilian culture.[37] The questionnaire contains 26 objective multiple-choice questions and two open-ended questions, and is divided into two sections. The first section, with three questions, is applied by the interviewer him/herself, and the second section, with 25 questions, is answered individually by the interviewee him/herself. Each of the 26 multiple choice questions has only one correct answer. Because one question about medication contains eight correct answers and another question does not include feedback, the questionnaire scores can range from 0 to 32 points. The higher the number of points is, the better the elderly person's perception of the risk of falling will be.[37]

Statistical analysis

The sample-size calculations to determine that the sample should comprise 50 elderly people were based on an equation for the correlation coefficient (between the DXA test and MET, obtained for studying PA). A moderate effect size (F = 0.25), 80% power and a 5% significance level were used in the calculation. However, we ended up with a total of only 47 participants, since three elderly women who had previously been evaluated did not show up on the day and time scheduled for the DXA test. The groups of PA levels were compared for each of the dependent variables by means of analysis of variance, followed by Tukey's post-hoc test. Multiple linear regression analysis was performed, considering the level of energy expenditure from the IPAQ (MET/min/week) in relation to the dependent variables evaluated, with a significance level of 5%. The statistical analysis was performed using SPSS v17.0 (SPSS, Chicago, IL, United States).

RESULTS

The elderly people who were evaluated were similar regarding their anthropomorphic characteristics, between the different levels of PA considered, as shown in **Table 1**.

Table 2 shows that the sarcopenia index at the high PA level indicated greater skeletal muscle mass than at the moderate and low PA levels. Another important observation, in relation to the IPAQ score, was that the energy expenditure and physical performance of the elderly people practicing high PA produced increases in these variables, compared with the elderly people practicing moderate and low PA. Regarding the other clinical variables, i.e. the perception of risk of falls and handgrip strength at different levels of PA, no significant differences were observed, as shown in **Table 2**.

In the multiple linear regression analysis, it was observed that only physical performance and the perception of the risk of falling showed strong relationships with higher IPAQ score (MET/min/week), corresponding to moderate or high PA levels (**Table 3**). In addition, there was no positive relationship between IPAQ energy expenditure and the sarcopenia index and/or handgrip strength (**Table 3**).

Table 1. Means and standard deviations of the elderly women's anthropometric characteristics, compared between their levels of physical activity (PA): low, moderate or high

Anthropometric variables	Low PA (n = 13)	Moderate PA (n = 16)	High PA (n = 18)	P
Age (years)	73.4 ± 7.8	72.9 ± 5.4	69.9 ± 7.3	0.349
Height (m)	1.5 ± 0.7	1.5 ± 0.8	1.5 ± 0.5	0.130
Body mass (kg)	64.3 ± 11.6	71.5 ± 14.2	62.9 ± 9.9	0.112
Body mass index (kg/m^2)	28.3 ± 3.9	28.9 ± 5.3	27.6 ± 4.3	0.739
Lean mass (kg)	35.6 ± 5.5	40.5 ± 8.2	36.8 ± 5.0	0.088
Fat mass (kg)	26.6 ± 7.6	28.6 ± 10.0	23.9 ± 7.0	0.353
Arterial hypertension	58%	50%	42%	-
Diabetes mellitus	25%	23%	14%	-

Analysis of variance test, with Tukey's post-hoc test. P < 0.05 was taken to indicate a statistical difference (but there were no significant results).

DISCUSSION

The main result from this study was that the loss of skeletal muscle mass (as measured using the sarcopenia index) in the high PA level group was lower than in the moderate and low PA level groups. Thus, the skeletal muscle mass of this group of elderly women with high PA was greater. Another important point was that the energy expenditure and physical performance were greater among the elderly women practicing high PA, compared with the moderate and low PA level groups. A further extremely valuable finding was the relationship between higher energy expenditure (as shown through the IPAQ), which corresponded to high and moderate PA levels practiced by these elderly subjects, and better perception of the risk of falling and increased physical performance.

The differential and clinical relevance of the present study was that it showed that practicing PA at different levels influenced the sarcopenia index of the elderly women evaluated, as measured through the DXA laboratory examination. A high PA level corresponded to an increased skeletal muscle mass index, in comparison with the groups with low and moderate PA levels. Current research suggests that, in particular, practicing PA is an effective supportive intervention for retarding reduction of muscle mass and strength in the elderly and, in addition, for promoting improvement in musculoskeletal functioning while performing activities of daily life.[14,19,20-22]

Table 2. Means and standard deviations from the skeletal muscle mass index, Timed Up and Go (TUG) test, Fall Risk Awareness Questionnaire (FRAQ) and handgrip strength evaluations of the elderly women, compared between their levels of physical activity (PA): low, moderate or high

Clinical variables	Low PA (n = 13)	Moderate PA (n = 16)	High PA (n = 18)	P
IPAQ score (MET/min/wk)	840.8 ± 778.5	4788.0 ± 1906.9	5289.0 ± 2742.5	0.990$^{1-2}$ 0.010^{1-3*} 0.266$^{2-3}$
Skeletal muscle mass index (sarcopenia) (kg/m^2)	5.7 ± 0.6	6.0 ± 0.4	6.3 ± 0.3	0.245$^{1-2}$ 0.010^{1-3*} 0.007^{2-3*}
Timed Up and Go (TUG) test (seconds)	12.2 ± 1.8	12.0 ± 4.2	13.3 ± 2.4	0.071$^{1-2}$ 0.042^{1-3*} 0.086$^{2-3}$
Fall Risk Perception Questionnaire (FRAQ) (score)	20.0 ± 3.6	21.3 ± 2.8	21.0 ± 2.5	0.341$^{1-2}$ 0.212$^{1-3}$ 0.102$^{2-3}$
Handgrip strength (kg)	15.7 ± 3.7	17.1 ± 7.1	17.8 ± 4.8	0.153$^{1-2}$ 0.357$^{1-3}$ 0.099$^{2-3}$

MET = working metabolic equivalent; min = minutes; wk = week.
Analysis of variance test, with Tukey's post-hoc test. *P < 0.05 was taken to indicate a statistical difference.

In the literature, a recent systematic review showed that individuals who were considered to be physically active presented lower risk of developing sarcopenia during the aging process,[38] but it did not provide any description of the associated level of PA. In the present study, it was observed that, to prevent or alleviate the onset of sarcopenia, a high level of PA practice was necessary. This finding is especially relevant for the elderly in Brazil, where there is a lack of studies on the influence of different levels of PA practice among elderly women for preventing muscle loss.

Another important finding was that the energy expenditure verified through the IPAQ (MET/minute/week) for the high PA level group was greater, with better physical performance. This can be explained by the effect of the intensity of high PA practice on improving the aerobic conditioning of the elderly. This shows the importance of increasing the PA intensity for prevention of sarcopenia and the risk of falling, in view of the positive association between sarcopenia and falls and fractures among older adults.[38-41] The findings from the present study were concordant with those of some reviews and clinical studies, in which the effectiveness of aerobic exercise of 30 to 60 minutes for preventing the risk of dynapenia, sarcopenia, and associated weaknesses in the elderly was revealed.[2,4,5,39] In addition, it has also been shown in the literature that prolonged periods of sedentary behavior among the elderly do not substantially increase energy expenditure above resting levels (< 1.5 units of metabolic work equivalent, METs). This leads to impaired muscle functioning[40,42] and performance in the elderly.[41-43]

In this study, all the elderly people performed aerobic exercises, resistance exercises and walking as their PA practice. Only those who were considered to have high PA levels were able to improve their muscle mass loss and physical performance. This was concordant with the findings of Santos et al., who showed that insufficient leisure-time PA practice was associated with sarcopenia in individuals aged 50 years or over.[14] Although those authors did not evaluate elderly people, the results from the present study emphasize the effectiveness of high PA levels for prevention of sarcopenia. This finding with regard to higher intensity of PA, in association with anaerobic exercise (i.e. for 60 minutes, twice a week), was also observed in some other studies,[2,39,40] thus confirming the association of these two factors with long-term improvement of sarcopenia.

Another extremely valuable finding was that physical performance and the perception of the risk of falling had positive relationships with the IPAQ energy expenditure consumption (MET/minute/week), which corresponded to moderate and high PA levels practiced by the elderly women. On the other hand, Aggio et al. did not find any association or relationships between sedentary patterns and sarcopenia among men aged 70 to 92 years.[44] In the present study, only elderly women were evaluated and it was possible to establish a cause-effect relationship between increased energy expenditure (moderate and high PA levels) and better perception of the risk of falling and increased physical performance among them. These relationships support development of pragmatic and effective strategies for prevention of falls and their consequences among elderly women. These consequences include higher numbers of hospitalizations, which generate high healthcare costs and high mortality rates resulting from femur fractures, and decreased PA resulting from restrictions on its practice.[38-41,44,45]

Through gaining an understanding that moderate or high PA is related to better physical performance and perception of the risk of falling, elderly people's fear of falling may be reduced. It may help combat loss of independence and the ability to perform activities of daily living normally, which arise through limitations on

Table 3. Multiple linear regression analysis on IPAQ energy expenditure (MET/min/week) at different levels of physical activity (PA) (low, moderate or high), in relation to the skeletal muscle mass index (sarcopenia), Timed Up and Go (TUG) test, Fall Risk Awareness Questionnaire (FRAQ), and handgrip strength evaluations among the elderly women

Clinical variables	Physical activity	Beta coefficient	Confidence interval (95%)	Standard deviation	T	P	R; R2
Skeletal muscle mass index (sarcopenia) (kg/m^2)	Low	0.650	5.33; 6.06	0.6	1.7	0.102	0.42; 0.12
	Moderate	-0.221	5.79; 6.21	0.4	-0.4	0.693	0.10; -0.05
	High	0.595	6.15; 6.44	0.3	0.4	0.652	0.13; -0.07
Timed Up and Go (TUG) test (seconds)	Low	-0.329	11.10; 13.28	1.8	-1.7	0.101	0.42; 0.13
	Moderate	-0.293	9.76; 14.24	-4.2	-3.4	0.003*	0.65; 0.39
	High	-0.762	12.10; 14.49	2.4	-1.5	0.007*	0.41; 0.10
Fall Risk Perception Questionnaire (FRAQ) (score)	Low	0.770	17.82; 22.18	3.6	0.7	0.994	0.02; -0.07
	Moderate	0.148	19.80; 22.79	2.8	2.6	0.016*	0.55; 0.26
	High	0.417	19.76; 23.24	2.5	1.9	0.007*	0.41; 0.09
Handgrip strength (kg)	Low	0.690	13.46; 17.93	3.7	0.6	0.516	0.17; -0.03
	Moderate	-0.145	13.31; 20.88	7.1	-0.8	0.385	0.21; -0.01
	High	-0.762	15.41; 20.18	4.8	-1.52	0.156	0.42; 0.10

Multiple linear regression; *P < 0.05 was taken to indicate a statistical difference.

T = t-statistic, calculated as t* = (sample coefficient - hypothesized value)/standard error of coefficient; R; R^2 = coefficient of correlation; coefficient of determination.

practicing PA.[26,27,30,46] Scientific evidence has increasingly shown that practicing PA is very effective in preventing falls, since it increases muscle strength and improves balance, flexibility, motor coordination and proprioception.[2,4,14,46]

The contribution that this study has made to was to show that moderate and high levels of PA made a difference through improving the perception of the risk of falling, and thus through maintaining elderly people's perceptive self-care for better fall prevention. The practical implications of this study are the following:

a) High physical activity levels gave rise to increases in the skeletal muscle mass index and physical performance. Poor levels of these clinical characteristics are associated to sarcopenia in elderly women;
b) High and moderate physical activity levels (energy expenditure in MET/minute/week) were a good predictor of improved physical performance and better perception of the risk of falling among elderly women;
c) Public health interventions aimed at encouraging moderate and high levels of physical activity may increase physical performance and reduce the risk of falling, thus reducing the onset of sarcopenia in elderly women.

The limitation of this study was that it did not evaluate the dynamic balance between the levels of PA and sarcopenia, to better understand falls among the elderly people evaluated here. Future studies addressing variables relating to kinematic and dynamic balance, according to the PA levels of elderly people as they age, may further enhance the understanding of the association of these variables with the sarcopenia index and with falls.

CONCLUSION

Elderly women classified as presenting high levels of PA showed improvements in sarcopenia, handgrip strength, physical performance and perception of the risk of falling. The IPAQ energy expenditure of the elderly women with high and moderate PA levels was a good predictor of physical performance and of improved perception of the risk of falling.

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The role of the surgeon in treating patients with lung cancer. An updating article

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ABSTRACT

Lung cancer is a type of neoplasia with one of the highest incidences worldwide and is the largest cause of mortality due to cancer in the world today. It is classified according to its histological and biological characteristics, which will determine its treatment and prognosis. Non-small cell lung cancer accounts for 85% of the cases, and these are the cases that surgeons mostly deal with. Small cell lung cancer accounts for the remaining 15%. Surgery is the main method for treating early stage lung cancer, and lobectomy is the preferred procedure for treating primary lung cancer, while sublobar resection is an alternative for patients with poor reserve or with very small tumors. Surgeons need to be trained to use the resources and techniques available for lung resection, including less invasive approaches such as video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), and need to be familiar with new oncological approaches, including curative, adjuvant or palliative treatments for patients with lung cancer.

INTRODUCTION

Lung cancer is the type of neoplasia responsible for the greatest number of deaths in Brazil and worldwide. Estimates from 2018 showed that lung cancer was among the forms with highest incidence, with 2.1 million new cases worldwide.[1]

The survival rate is low because lung cancer is diagnosed late and symptoms in the initial stages of the disease go unnoticed or do not exist.[2] However, recently, a variety of advances have been changing this panorama, especially due to prospective studies on screening for lung cancer by means of low-dose chest computed tomography.[3,4]

Surgeons need to be aware that these studies have shown reductions in mortality due to lung cancer through use of screening protocols in at-risk populations, thereby increasing the number of diagnoses made at initial stages, in asymptomatic individuals. The survival of patients with advanced disease has also improved significantly over recent years, especially through the introduction of targeted molecular therapies and immunotherapy.[5]

MAIN SUBTYPES

Lung cancer is subdivided into two major groups according to its histological characteristics, biological behavior, treatment and prognosis: non-small cell lung cancer (NSCLC), which accounts for 85% of the cases of malignant lung neoplasia; and small cell lung cancer (SCLC), which accounts for the remaining 15%.

Most cases of NSCLC are diagnosed at an advanced stage. This means that the survival rates are low, and this is seen especially in emerging countries, where scarcity of resources have the consequence that the main treatments are unavailable because of the high costs of tests and medications.[6] Among cases of NSCLC, there are two main types: adenocarcinoma and squamous (or epidermoid) carcinoma.[7] Squamous carcinoma accounts for 30% of NSCLC and was one of the most common types until the middle of the 1980s. This was the type most linked to tobacco smoking.[8]

INITIAL ASSESSMENT OF PATIENTS WITH LUNG CANCER

Patients should be assessed by means of a detailed history and physical examination. They should be actively questioned about any history of smoking (even if this was passive smoking), exposure to toxic agents, oncological antecedents, family history of cancer and any signs

and symptoms such as weight loss without apparent cause, loss of appetite, coughing, coughing with blood, hoarseness, dyspnea or chest pain, among others.[1,9,10]

Unfortunately, for most patients, their diagnosis is only made when the disease causes symptoms, i.e. when it is at an advanced stage. At this time, curative treatment is often no longer possible. Approximately 70% of the patients diagnosed with lung cancer in Brazil present locally advanced or metastatic disease.[6]

The diagnostic method should be chosen bearing in mind the patient's clinical condition, comorbidities, risk relating to invasive procedures and possibility of making the diagnosis and staging in a single procedure, with the aim of avoiding unnecessary invasive tests.[8] The greater the amount of material that can be obtained and the better the definition of the staging that can be achieved within a single method, the better it will be for the patient.[11] Some studies have shown that patients with lung cancer have better survival when therapeutic decisions are made by a multidisciplinary team.[12] This is our opinion as well.

In addition to thoracic and upper abdominal computed tomography, the patient's clinical staging should be complemented through positron emission tomography–computed tomography (PET-CT) and magnetic resonance imaging (MRI) of the brain.

The test that is indicated when patients present with an initial peripheral lesion in one of the lungs is CT-guided needle biopsy. This method presents a diagnostic yield of up to 90%.[13] On the other hand, central lesions are better evaluated by means of video-bronchoscopy, which enables a diagnosis and surgical planning. The diagnostic yield of bronchoscopy for central lesions is around 85%, when five or more fragments from the lesion are obtained.[11]

In the case of lesions associated with enlarged or PET-positive mediastinal lymph nodes, the methods that are indicated may be echobronchoscopy (EBUS) and/or mediastinoscopy. In patients with suspected metastatic lesions, the metastatic site should be targeted for biopsy. If it is proved that the suspected metastatic site is from a primary lung cancer, the diagnosis and staging are provided at the same time.[13]

STAGING

Lung cancer staging is directly related to the patient's prognosis. This staging is based on the combination of three characteristics: size of the primary tumor and its invasion of adjacent structures (T); presence and extent of affected lymph nodes (N); and presence or absence of metastatic disease (M). This is the TNM staging system.

The TNM system (**Table 1**) has the objective of unifying the overall language of staging, thereby facilitating communication within care and academic studies.[14] It also aids in selecting patients as candidates for surgical resection, radiotherapy, systemic treatment (chemotherapy, targeted therapy and immunotherapy) or combinations of two or more of these types of treatments.[15]

SURGICAL TREATMENT

Surgical treatment for lung cancer was first reported in 1933, when Evarts Graham performed the first left-side monoblock pneumonectomy, to resect a pulmonary tumor.[16] Removal of the entire lung was the preferred procedure over the next 20 years, but this approach presented high rates of complications, including respiratory insufficiency, and deaths.

Pulmonary lobectomy with lymphadenectomy then became the gold standard for treating lung cancer in its initial stages.[17] It was popularized through the studies conducted by William Cahan, published in 1962.[16]

Subsequent studies have shown the feasibility of sublobar resection for treating lung cancer in its early stages. In 1995, a randomized prospective study on lobectomy versus sublobar resection among patients in clinical stage IA of lung cancer was published. Lobectomy presented better results regarding local control and survival beyond two years after surgery.[18]

Criticisms of this study were made more recently, under the allegation that it was conducted in the pre-PET-CT era using old tomographs with poor anatomical definition. A further criticism was that patients with tumors of diameter up to 3.0 cm had been included in that study. Nonetheless, lobectomy continued to be the standard procedure for treating NSCLC, accompanied by hilar and mediastinal lymphadenectomy. Patients who are candidates for pulmonary resection need to be carefully selected, through evaluation of the histology of the tumor and the anatomical extent of the disease, and whether the patient is in a clinical condition to tolerate the proposed procedure. Patients who might benefit from the procedure include those with NSCLC in stages I and II and a limited group of patients with disease in stage III.[19] Patients with SCLC in stage I may also undergo lobectomy and hilar and mediastinal lymphadenectomy, after invasive staging of the mediastinum to confirm that they have disease staged as N0.

Sublobar resection in the initial stages of lung cancer is a surgical option for treating primary pulmonary adenocarcinoma,

Table 1. Lung cancer stage grouping (eighth edition)[14]

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	1A1	IIB	IIIA	IIIB
	T1b	1A2	IIB	IIIA	IIIB
	T1c	1A3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Adapted from the article "The eighth edition TNM stage classification for lung cancer: What does it mean on main street?".[14]

especially for lesions smaller than 2.0 cm.[20] However, this approach is still based on data from non-randomized studies.

The literature on sublobar resection for treating lung cancer only includes patients with adenocarcinoma. Other histological types should not enter within the criteria discussed above because of lack of support from scientific studies.[21]

The surgical approaches most commonly used for sublobar resection comprise wedge resection and segmentectomy. The former consists of removal of a pulmonary tumor together with a surrounding margin of normal lung tissue and is not an anatomical resection. On the other hand, segmentectomy is an anatomical resection in which one or more pulmonary parenchymatous segments are included, with dissection of segmental bronchovascular elements, together with intraparenchymatous, hilar and mediastinal lymph nodes.[22] The approach of sublobar resection is not considered oncologically appropriate if any of the lymph nodes (intralobar, hilar or mediastinal) are found to be compromised by cancer.

In a multicenter prospective randomized study by Altorki et al. on 697 patients, the results from sublobar resection and lobectomy to treat peripheral tumors smaller than 2 cm were compared. It was demonstrated that perioperative morbidity and mortality did not differ among patients with NSCLC clinically staged as T1aN0, between those who underwent lobar resection and those who underwent sublobar resection.[23] The survival results from that study, which are expected to be released in 2021, are keenly awaited.

The extent of adequate margins for sublobar resection continues to be discussed. In one study, it was recommended that the margins needed to be at least volumetrically greater than the largest diameter of the primary tumor.[24] In some other studies, it was suggested that tumor margins > 1 cm were associated with significantly lower recurrence rates, in comparison with margins < 1 cm, in cases of primary tumors up to 1.0 cm in diameter.[20]

One important point to be taken into consideration in this scenario is the histological subtype of the adenocarcinoma. In the most recent classification of the World Health Organization, five main types of adenocarcinoma were established, namely: lepidic, acinar, papillary, micropapillary and solid.[25] The lepidic type corresponds to adenocarcinoma *in situ* (or noninvasive). The last two subtypes (micropapillary and solid) correlate with worse prognosis, according to some studies. For some authors, these are also associated with higher rates of local recurrence in patients who undergo sublobar resection, by means of a form of local spreading through air spaces (STAS).[26]

The pathological definition of STAS is the presence of adenocarcinoma cells or groups of cells that have detached and become distant from the primary tumor, in alveolar spaces. It is known that some tomographic images correlate with certain subtypes of pulmonary adenocarcinoma, especially between ground-glass lesions and lepidic (noninvasive) adenocarcinomas. The other types of lesion are invasive and are characterized as solid nodules in tomographic examinations.

The micropapillary and solid subtypes seem to be more linked to STAS. In this regard, some authors have published data showing higher rates of local recurrence among patients undergoing sublobar resection, even at the initial stages of the disease.

Thus, lobectomy continues to be the standard procedure for treating primary pulmonary carcinoma. Sublobar resection is an alternative for patients with poor reserve or with tumors at a very early stage, generally with an invasive component smaller than 1.0 cm.[27]

Some authors have suggested that patients presenting peripheral pulmonary nodules with a ground-glass component that does not disappear during the follow-up are highly likely to have adenocarcinoma. This presentation should draw the surgeon's attention. A purely ground-glass lesion may evolve to a so-called semi-solid lesion (i.e. one with an invasive component). When this occurs, it becomes clearer that this carcinoma is turning aggressive and should be biopsied or surgically excised. If ground-glass lesions are manifested after resection of the lung cancer, this may be suggestive of recurrence of the neoplasia, or asynchronous multifocal disease.[28]

Dissection of hilar and mediastinal lymph nodes has become mandatory within the surgical treatment of lung cancer, given that is very important for staging, prognosis and treatment strategy. Nowadays, the presence of N1 or N2 lymph nodes determines that the surgeon will refer the patient to an oncologist, for assessment of adjuvant treatment.

The guidelines of the European Society of Thoracic Surgeons (ESTS) recommend sampling or dissection of lymph nodes in all patients with lung cancer who are candidates for surgical resection. Systematic evaluation of lymph nodes has been shown to be more effective than selective evaluation of lymph nodes. To obtain benefits from staging, it is recommendable to perform complete resection of the lymph nodes and the surrounding tissue, if feasible.[29]

In cases in which computed tomography or PET-CT shows suspicious mediastinal lymph nodes, invasive mediastinal staging becomes mandatory, with the initial objective of ruling out false positive results from imaging. Equally important, in addition to confirming whether N2 lymph nodes are compromised by neoplasia, is to be sure that the case is not one of occult N3. It is now known that the presence of N3 is a contraindication for surgical treatment, given that micrometastatic disease is highly likely to already be present.[14]

The presence of metastases in lymph nodes (either hilar or mediastinal) is a strong marker for the existence of micrometastatic disease. In these circumstances, and especially in situations of N2, there is a need for adjuvant or neoadjuvant chemotherapy. This should be defined together with the oncologist.

The main role of lymphadenectomy is well portrayed in a prospective study in which surgeons were asked to place lymph nodes

that had been removed during the surgery, in specimen containers that had previously been labeled with the number of the lymph node chain, in accordance with the map of the International Association for the Study of Lung Cancer (IASLC). This method was tested and compared with what was done routinely by each surgeon in that service. The survival curves from the study showed significant differences in survival in favor of patients who underwent lymphadenectomy using so-called "lymph node kits".[30] Another study with an impact on this topic was conducted using the Surveillance, Epidemiology and End Results (SEER) database. The authors reviewed more than 24,000 cases of patients operated due to lung cancer. Those with the largest numbers of lymph nodes evaluated had better long-term survival.[31]

In services in which detection of cancerous mediastinal lymph nodes before surgery leads to neoadjuvant treatment, invasive staging of the mediastinum is practiced routinely. According to the ESTS guidelines, this staging is indicated for all cases of clinical N2 through imaging, cases of clinical N1 through imaging, cases of central tumors and cases of peripheral tumors of major diameter greater than 3.0 cm.[23]

In our service, all of these cases are discussed in multidisciplinary meetings, but we tend to recommend neoadjuvant therapy in these cases, provided that the staging is single-station N2. This is our limit for considering surgery as part of the curative treatment for these patients. For those presenting multiple-station N2, we follow the treatment protocol of the PACIFIC study, with definitive chemoradiotherapy followed by consolidative immunotherapy.[32]

It needs to made clear that we recommend invasive staging of the mediastinum before starting the treatment, and after multidisciplinary discussion. We agree with the ESTS guidelines that state that an abnormal mediastinum (suspected on computed tomography or PET-CT) should be confirmed through cytological or histological tests (endosonographic methods with cytological analysis and cell blocking, or surgical methods). In patients with a normal mediastinum, invasive staging of the mediastinum is recommended because of the possibility of occult N2, except in cases of peripheral tumors smaller than 3.0 cm (cT1N0). In cases of central tumors with the suspicion of N1 and in peripheral tumors larger than 3.0 cm, we think that procedures to exclude pathological involvement of the lymph nodes should be performed via endosonography (EBUS and/or EUS), or via surgical methods (mediastinoscopy, videomediastinoscopy, videothoracoscopy or anterior mediastinotomy).[29]

This approach has the main aim of ruling out situations of multiple-station N2, extracapsular invasion and N3 disease. We believe that these conditions are contraindications for surgery.

In situations of N2 disease, several approaches have garnered support in the literature. In some services, surgery up-front combined with adjuvant chemotherapy is recommended (IALT, JBR.10, ANITA).[33] In other services, neoadjuvant systemic treatment followed by surgery is indicated. In our department, our preference is for neoadjuvant treatment after multidisciplinary discussion of the cases.

Surgical techniques for pulmonary resections have evolved, to include less invasive approaches. Video-assisted thoracic surgery (VATS) has become the preferred procedure for patients with NSCLC in early stages.[34,35] VATS presents advantages regarding postoperative recovery, with fewer short-term complications, without prejudice to the oncological results. It is also a less painful procedure, with shorter hospital length of stay and, consequently, lower hospital costs.[36–38]

A meta-analysis conducted in 2012 showed that lobectomy through VATS yielded better perioperative outcomes than did lobectomy via thoracotomy. For instance, perioperative morbidity was significantly lower when VATS was used, including less occurrence of complications (prolonged air escape, pneumonia and sepsis) and shorter hospitalization.[38] Although surgery using VATS demonstrates benefits, most patients who would be eligible for this minimally invasive procedure are still not treated in this manner.[37,39]

More recently, although no data have yet been published, the VIOLET study was presented at a IASLC meeting. In this prospective randomized study on surgical treatment for early-stage lung cancer, conducted in the United Kingdom, VATS was compared with thoracotomy for lobectomy. Despite a few methodological criticisms, this study was well designed, and demonstrated that morbidity was lower when VATS was used, with the same oncological results as when open surgery was used.[40]

Even today, most pulmonary lobectomies are performed through thoracotomy, both in developed and developing countries. This is because of limitations on financial resources that cause difficulty in implementation of VATS.[35] It is also due to lack of training in this technique in many centers, with a long learning curve for most surgeons.

In Brazil, the outcomes from VATS lobectomies have been favorable regarding the surgical technique, complication rates and survival, as shown in a recent study by Tsukazan et al.[41] However, even though the VATS approach is well established, it is still not the method most used in Brazil, given the scarce availability of resources and regional difficulties imposed by funding, considering that this type of procedure involves use of surgical staplers designed especially for minimally invasive surgery.[42]

The proportion of lung cancer patients who receive surgical procedures with curative intent in Brazil remains small: approximately 25% of all the patients diagnosed. This is due to the influence of factors such as presence of advanced disease at the time of diagnosis, poor performance status among the patients, presence of comorbidities and socioeconomic factors.[43–45]

Robotic surgery is the most recently introduced minimally invasive technique for treating lung cancer. Robotic platforms provide magnified three-dimensional visualizations of the surgical field that allow surgeons to perform complex delicate operations by means of small incisions. The equipment consists of a computer console at which the surgeon is positioned during the surgical procedure, where he or she manipulates robotic arms by means of the handles installed on the console. The robotic instruments have various degrees of movement resembling those of the human wrist. The computer converts the movements of the surgeon's hands into the same movements of the instruments.

The first reports on robotic surgery were from 2002. Studies have shown that general thoracic procedures can be performed safely with robotic tools, thus enabling precise dissection in areas that are difficult to access.[46]

Studies comparing lobectomy via thoracotomy, VATS and robotics have demonstrated that minimally invasive techniques present better results relating to length of hospital stay, mortality and postoperative complications.[45] Some reviews using databases in the United States have, however, questioned the efficacy of this methodology. In a study on 15,502 patients who underwent pulmonary resection, either via VATS or robotics, the duration of the operation was longer in the cases of robotics-assisted surgery and the costs were higher, in comparison with other techniques.[47]

Table 2 presents brief definitions of the different surgical techniques, with their benefits and limitations.

FUTURE PERSPECTIVES

Assured access to healthcare services, with detection of early-stage lung cancer, may completely change the perspectives for and the progression of the disease. Incorporation of new technologies for minimally invasive surgery (VATS/RATS) has become a reality, in particular through research on new robotic platforms. Nonetheless, even in this scenario, treating multiple synchronic lung cancers remains a challenge, and these cases deserve a multidisciplinary approach.

Technology is helping to improve the results from surgical treatment of lung cancer, through use of three-dimensional planning. This can be used both for locating and assessing pulmonary nodules and for reconstruction of the thoracic wall when its resection and reconstruction are necessary.[48]

Concerning systemic therapy, a multicenter prospective randomized study on targeted adjuvant therapy was published recently. In this, patients undergoing surgery and who presented EGFR mutations were randomized to receive either osimertinib or placebo. The patients who received the medication presented an advantage regarding disease-free survival.[49]

With regard to advanced disease, an article published in the New England Journal of Medicine in which the SEER (surveillance epidemiology and end results) database was analyzed in the United States showed that there was an increase in cancer-specific survival relating to NSCLC between the years 2013 and 2016, after the introduction of targeted therapies and immunotherapy for these patients.[5] Moreover, the concept of oligometastatic disease has been established, and surgeons need to be aware of this. It is possible that surgeons will take on increasing participation in approaches to treating patients with oligometastatic disease. Surgery may have a role in consolidation of local disease after initial systemic therapy.[50]

CONCLUSION

Surgery is the cornerstone of treatment of early-stage lung cancer and, in selected cases, of locally advanced disease. It has a role, albeit less frequently, in cases of oligometastatic disease.

Table 2. Brief definitions of the surgical techniques with their benefits and limitations[15]

Surgical techniques			
Surgical options	**Brief definition**	**Benefits**	**Limitations**
Wedge resection: Typically done via video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracoscopic surgery (RATS).	Small nonanatomical wedge is removed. Smaller than segmentectomy.	Preferred in patients with poor pulmonary reserve. Fewer complications and shorter hospital stays.	Generally not used for tumors > 4 cm. Location of tumor may preclude use of this option. May be associated with higher rate of local recurrence.
Segmentectomy: May be done via VATS and RATS.	Segment of lung is removed but not an entire lobe.	Larger parenchymal margins, and yields greater number of lymph nodes.	Larger than wedge resection but less than lobe. If margins are not clear, lobectomy may be needed.
Lobectomy	Removal of an entire lobe of lung, together with regional lymph nodes.	Gold standard for non-small cell lung cancer. Removal of entire lobe.	Preserves pulmonary function.
Pneumonectomy	Removal of entire lung and its lymph nodes.	Option when cancer involves proximal vascular structures or bronchi.	Higher mortality rate. More complications.

Adapted from the article "Surgical Treatment of Lung Cancer".[15]

For early-stage disease (I and II), the surgical approach continues to be lobectomy with hilar and mediastinal lymphadenectomy. Sublobar resection is reserved for patients whose physiological reserves are too poor for lobectomy, or for patients with very small tumors (or a small solid part of the tumor). Indications for lymphadenectomy remain valid: this serves for staging and also has an impact on survival, and for recommending adjuvant treatment.

For patients in stage IIIA, a multimodal approach should be discussed in a multidisciplinary setting. Invasive staging of the mediastinum preceding the definitive surgical treatment or treatment with concomitant chemoradiotherapy is recommended, followed by consolidative immunotherapy.

Surgeons have a role in treatments for patients with oligometastatic disease, both for resection of primary tumors and for staging of the mediastinum before consolidative treatment. They therefore need to be familiar with the new technologies and new oncological approaches, in every scenario (curative or palliative). This makes surgeons key specialists in multidisciplinary groups that discuss treatments for patients with lung cancer.

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- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details

to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be

declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.

11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the "doi" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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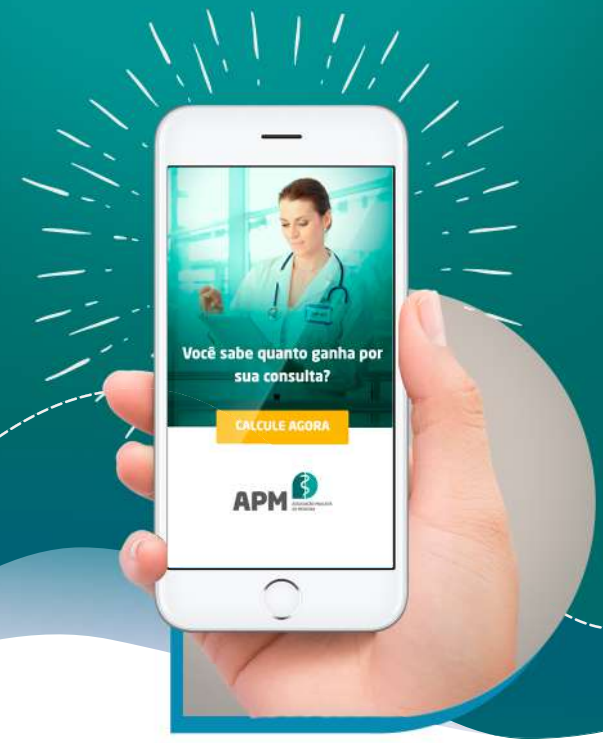

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