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Original article

Influence of dynapenic obesity on inflammation and muscle quality in oldest-old patients

Influência da obesidade dinapênica sobre a inflamação e qualidade muscular em pessoas idosas longevas

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ABSTRACT

Introduction: Aging is associated with a decrease in strength (dynapenia) and an increase in body fat. Both obesity and dynapenia negatively influence health in the oldest old. When these two variables coexist, called dynapenic obesity (DO), these further harms the older adult's health. **Objective:** To verify the influence of dynapenic obesity on inflammation, physical performance, and muscle quality in the oldest old with and without DO. **Methods:** Forty-six oldest old participants were included in this study, and sociodemographic, muscle strength, body composition, physical performance, and cytokine data were collected. The sample was divided into DO and control groups to compare the variables. **Results:** The DO group had higher levels of inflammation, lower levels of absolute handgrip strength, and field muscle quality index than the control group, but with no difference in physical performance or laboratory muscle quality index. **Conclusion:** Therefore, this study points to dynapenic obesity as an important variable that should be evaluated and considered in the oldest old to prevent possible adverse outcomes in this population.

Keywords: muscle strength; aging; obesity; inflammation.

RESUMO

Introdução: O envelhecimento está associado à diminuição da força (dinapenia) e ao aumento da gordura corporal. Tanto a obesidade quanto a dinapenia influenciam negativamente a saúde dos longevos. A coexistência dessas duas variáveis, denominada obesidade dinapênica (OD), prejudica ainda mais a saúde da pessoa idosa. **Objetivo:** Verificar a influência da obesidade dinapênica na inflamação, desempenho físico e qualidade muscular em pessoas idosas longevas com e sem OD. **Métodos:** Foram incluídos 46 idosos longevos e coletados dados sociodemográficos, de força muscular, composição corporal, desempenho físico e citocinas. A amostra foi dividida em grupos OD e controle para comparar as variáveis. **Resultados:** O grupo OD apresentou maiores níveis de inflamação, níveis inferiores de força muscular absoluta de preensão manual e índice de qualidade muscular de campo do que o grupo controle, mas sem diferença no desempenho físico ou no índice de qualidade muscular laboratorial. **Conclusão:** Portanto, este estudo aponta a obesidade dinapênica como uma variável importante que deve ser avaliada e considerada em pessoas idosas longevas para prevenir possíveis desfechos adversos nessa população.

Palavras-chave: força muscular; envelhecimento; obesidade; inflamação.

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Introduction

Most of the time, aging is linked to unfavorable changes in body composition, with increased body fat up to a certain age and a constant decline in lean muscle mass [1,2]. This accumulation of body fat can lead to obesity, an inflammatory disease with an increased risk for chronic diseases, including type 2 diabetes, hypertension, coronary heart disease, heart disease, and osteoarthritis [3]. Also, the decrease in lean mass, which is associated with several factors such as changes in the nervous system, the size and percentage of type II fibers [4], and fat infiltration into the muscle [5,6] contribute to lower muscle strength (dynapenia) [7-9] and sarcopenia [10]. Both obesity and dynapenia negatively affect the health and physical performance of older adults [3], and the coexistence of these two factors is called dynapenic obesity (OD) [11].

Another common characteristic of aging is a dysregulation of the immune system; this system typically increases inflammation when needed and decreases it when it is no longer. However, when this inflammation is not removed and remains in the long term, it can result in pathologies [12,13]. The breakdown of homeostasis of the immune system, which is usually intrinsic to aging, causes chronic low-grade inflammation where levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and IL6, are constantly increased [14].

Both obesity and dynapenia are also linked to chronic low-grade inflammation [15,16], where adipose tissue releases pro-inflammatory cytokines. These cytokines cause several negative changes, such as increased expression of proteins that contribute to atrophy of the skeletal muscle [16,17] and decreased glucose uptake in this tissue favoring the uptake of this substrate in the adipose tissue, thus creating a vicious cycle of muscle catabolism and increased body fat [15,18]. In addition, dynapenia and obesity are factors associated with adverse health prognoses, such as frailty, all-cause mortality [19,20], inability to perform activities of daily living [11], and lower physical performance [21,22].

The presence of DO can be even more harmful to the health of older adults; this is confirmed by studies that show that DO affects more than obesity or dynapenia alone; several variables such as physical performance [8], increased risk of falls [23], mortality, hospitalization, and disability [24]. In the oldest old patients, there is difficulty in diagnosing DO because often, the term DO is not known and little explored [7]. Thus, patients with low handgrip strength may be an indication that should be considered [7]. Moreover, deficits in the structure and function of the intrinsic force-generating properties of skeletal muscle are potential antecedents of dynapenia [7]. Thus, screening to clarify this decline becomes an essential geriatric clinical parameter [8]

Furthermore, studies showed an association between a pro-inflammatory condition and DO in the youngest-old and middle-old [25,26]. However, the literature still lacks data on the oldest old with and without DO and its relationship with

inflammation and muscle quality. Therefore, this study aims to verify the influence of DO on inflammation and muscle quality in the oldest old participants.

Methods

Study design and participants

This observational, descriptive, cross-sectional investigation was part of a multicenter study by the National Academic Cooperation Program (PROCAD). Only data referring to the region of Distrito Federal were subject to statistical tests. Data were considered if the participant was considered an older adult without hearing and/or visual impairment who was able to understand and respond to the instruments applied. Those with orthostatic intolerance or those with physical disabilities that prevented independent walking were excluded.

After applying the inclusion and exclusion criteria, 227 older adults were eligible for evaluation. However, for cytokines analysis (the main variables of this study), financial support was only provided for 46 participants. The variables analyzed in this study included cytokines, gender, handgrip strength (HGS), physical performance, anthropometric measurements (height and body weight), body composition, muscle quality index (MQI), dynapenia, number of medications, diagnosis of systemic arterial hypertension, and diabetes mellitus (DM). This study was approved by the local Institutional Research Ethics Committee (approval number: 50075215.2.0000.0029). The design and procedures were in accordance with ethical standards and the Declaration of Helsinki. Each subject was fully informed about the risks associated with study participation and gave their written informed consent.

Sociodemographic variables

For the adequate analysis of the sociodemographic variables, specific forms were used. The older adult or his companion filled out the identification form containing basic information such as full name, individual Taxpayer Registration Number, address, and telephone contacts. The second part of the form contained questions related to diagnosing pre-existing diseases. The answers were filled out during the consultation with the geriatrician and medical students, according to the information provided on the referral sent by a specialist doctor (e.g., cardiologist, pulmonologist, oncologist, endocrinologist, rheumatologist). This information enabled the analysis of the population's age range and the identification of the most prevalent diseases.

Handgrip strength measurement

Handgrip strength was recorded in kilograms/force (kg) using a duly calibrated hydraulic dynamometer (Lafayette Hydraulic Grip Dynamometer, Lafayette Instruments Inc.) [27]. The participants were instructed to sit in a chair with arms, keeping the dominant arm at a 90° angle with the contralateral limb relaxed on the thigh. During the measurements, the evaluator provided verbal stimuli to encourage

participants to give their best effort. Three consecutive measurements were performed with a one-minute rest interval interspersed. Also, the best of the three measurements was used in statistical analysis to encourage the participants to get as high a score as possible [27].

Body composition

Body composition was analyzed using Dual Energy X-ray Absorptiometry (DXA) (Lunar, model DPX-IQ, GE Lunar Corporation, pencil beam type, software version 4.7), which was properly calibrated and operated by a trained professional. Participants were instructed to remove metal any accessories before lying in the supine position (feet together, arms slightly away from the trunk and with the wrists in a prone position). The values for body composition outcomes were determined from the ratio of soft tissue attenuation of two X-ray energy beams for each pixel containing a minimal amount of soft tissue but no significant bone [28]. Data collected from this assessment included information regarding total body fat and appendicular skeletal muscle mass (kg).

Appendicular skeletal muscle mass was stratified into upper limb (UL-ASMM), lower limb (LL-ASMM), and total appendicular skeletal muscle mass (ASMM), which is defined by the sum between upper and lower limbs. Body fat is reported as total body fat percentage (%BF).

Muscle quality index

Laboratory MQI was determined by calculating the ratio between HGS (kgf) and UL-ASMM (kg) [29]. Field MQI was determined by calculating the ratio between HGS and BMI. The validity, reliability, and convenience of the MQI measures (field and laboratory) have been pre¬viously reported [30-32].

Dynapenic obesity criteria

Prevalence of dynapenia was defined by the handgrip strength ≤ 27 kg, and ≤ 16 kg [33,34], for men and women, respectively. Obesity was considered a body fat percentage of ≥ 27% and ≥ 38% [34], for men and women, respectively. DO was determined if participants fulfilled the criteria for both dynapenia and obesity using these definitions. The control group was considered participants who did not fulfill the criteria cited above.

Physical performance test

To assess functional performance, the short physical performance battery (SPPB) was used. The battery is composed of three tests: static balance, in three different standing positions, with increasing levels of difficulty; walking speed, on a 3-meter course with the usual walking speed; and strength of lower limbs, through the test of sitting and getting up from the chair five times, as quickly as possible. Each subtest is scored on a scale from zero to four points, with twelve being the total score [35].

Cytokines

Inflammatory profile was assessed using high-throughput flow cytometry (FACS Verse model; BD Biosciences, San Jose, CA, USA) with the serum previously collected and the Human Th1/Th2 cytokine kit as reagent (BD Biosciences) to assess six mediators: IFNc, IL-2, IL-4, IL-6, IL-10, and TNF-α. The reactions were performed following the manufacturer's protocol, producing a titration curve with standards provided by the kit. All scores were estimated by interpolation of the respective curve. Whenever a given sample yielded out of range of outlying readings, the assay was repeated with an original or diluted sample (as necessary) until a minimum of three hundred events were acquired for each type of cytokine bead used. All data were analyzed using FCAP software, version 3.0 (BD Biosciences).

Statistical analysis

Data are mean ± standard deviation, unless otherwise stated. Normality was assessed by Shapiro-Wilk's test. However, for cytokines variables, non-normality was observed, and a logarithmic transformation was applied. An independent-samples t-test was run to determine if there were differences in DO and control group in body composition, functional performance, and muscle quality index. For cytokines a Mann-Whitney U test was applied. A chi-square test (x^2) was also performed to determine if an association between groups, and diseases exists and to analyze the baseline characteristics of the participants. When expected cell frequencies were lower than five, the Fisher's Exact test was used. For power analysis, considering a mean difference of 10 pg/ml between groups for IL-6, and an effect size of 0.63. A power of 0.50 was observed for 44 participants (t-tests – Means: difference between two independent means). An alpha level of $\alpha \leq 0.05$ was considered significant. For data analysis, SPSS (version 20.00) and G*Power 3.1.6 [36] were used.

Results

Considering the financial support for cytokine analysis, the final sample included 46 octogenarians. Baseline characteristics of the 46 participants are shown in Table I.

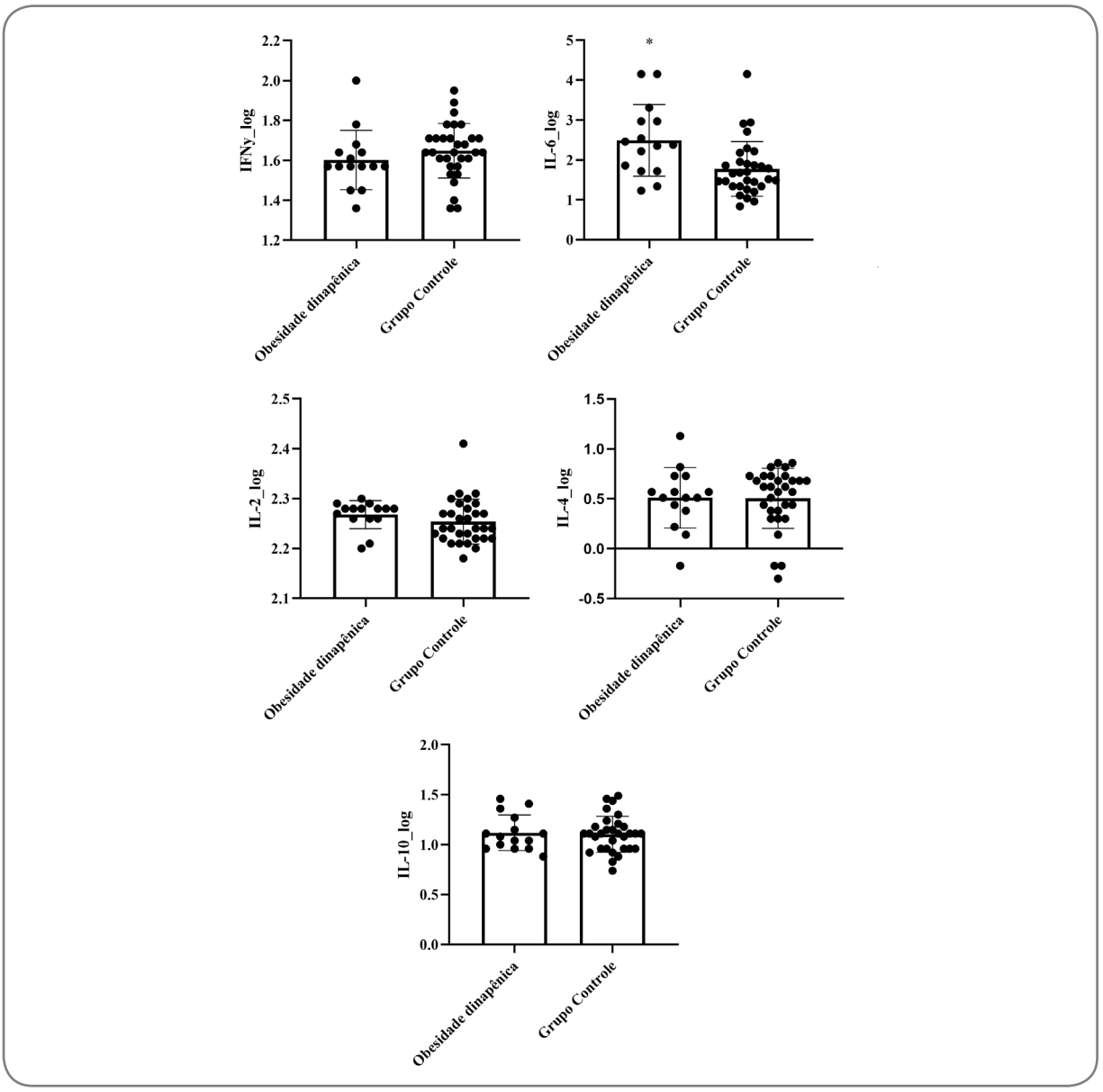
Table I shows that control group displayed a lower body fat ($p = 0.04$), higher absolute hand-grip strength ($p = 0.04$), and a higher field MQI ($p = 0.007$) compared to the DO group. For other variables, no differences were observed ($p > 0.05$).

Table I - Participant's characteristics with and without dynapenic obesity

	Dynapenic-Obesity (n = 15)	Control group (n = 31)	*P*
Sex			0.10
Male	8 (53.3)	8 (25.8)	
Female	7 (46.7)	23 (74.2)	
Age, years	84.60 ± 3.56	83.00 ± 2.82	0.17
Height, m	1.54 ± 0.05	1.56 ± 0.06	0.66
Body weight, kg	65.90 ± 8.56	65.28 ± 10.94	0.26
BMI, kg/m²	27.79 ± 3.52	26.52 ± 3.89	0.13
Body fat, %	38.19 ± 5.45	33.62 ± 10.07*	0.04
UL body fat, kg	3.02 ± 2.57	2.66 ± 2.97	0.69
LL body fat, kg	8.95 ± 5.72	7.94 ± 5.29	0.55
UL ASMM, kg	4.52 ± 0.86	4.77 ± 1.26	0.93
LL ASMM, kg	13.21 ± 2.46	14.12 ± 2.97	0.67
ASMM, kg	17.74 ± 3.27	18.89 ± 4.20	0.90
Laboratory MQI, kg/kg	3.69 ± 0.76	4.92 ± 1.29	0.06
Absolute HGS, kg	17.73 ± 4.68	21.55 ± 6.42*	0.04
Field MQI, kg/BMI	0.63 ± 0.17	0.84 ± 0.25*	0.007
SPPB	6.69 ± 2.72	7.87 ± 2.47	0.17
Number of medications	5.80 ± 2.86	5.56 ± 3.68	0.82
	Yes	**No**	**Yes**	**No**	*P*
Hypertension†	5 (35.7)	9 (64.3)	4 (13.8)	25 (86.2)	0.12
Diabetes	7 (58.3)	5 (41.7)	17 (68)	8 (32)	0.71

Result is presented by mean and standard deviation; * significantly different between groups ($p < 0.05$); BMI = body mass index; UL = upper limbs; LL = lower limbs; ASMM = appendicular skeletal muscle mass; MQI = muscle quality index; HGS = handgrip strength; For chi-square test, data is presented as frequency and percentage values; †Fisher exact test

For cytokines, significant differences between groups were observed for IL-6 levels ($p = 0.005$). The DO group displayed a higher IL-6 levels when compared to control group. For other variables no differences were observed ($p > 0.05$). Figure 1.



IL = interleukin, IFNy = Interferon gamma
Figure I - Data expressed as mean and standard deviation (SD). *significant difference between groups ($p < 0.05$)

Discussion

This was the first research to compare the oldest old participants with and without dynapenic obesity. The result of this study shows that the group oldest old with DO had significantly higher levels of inflammation (only for IL-6), lower levels of absolute handgrip strength, and field MQI compared to the control group. However, no difference was found between groups for physical performance measurement. Also, a tendency for a significantly lower laboratory MQI for the DO group was verified. However, no difference was found between groups for physical performance measurement (Figure 2).

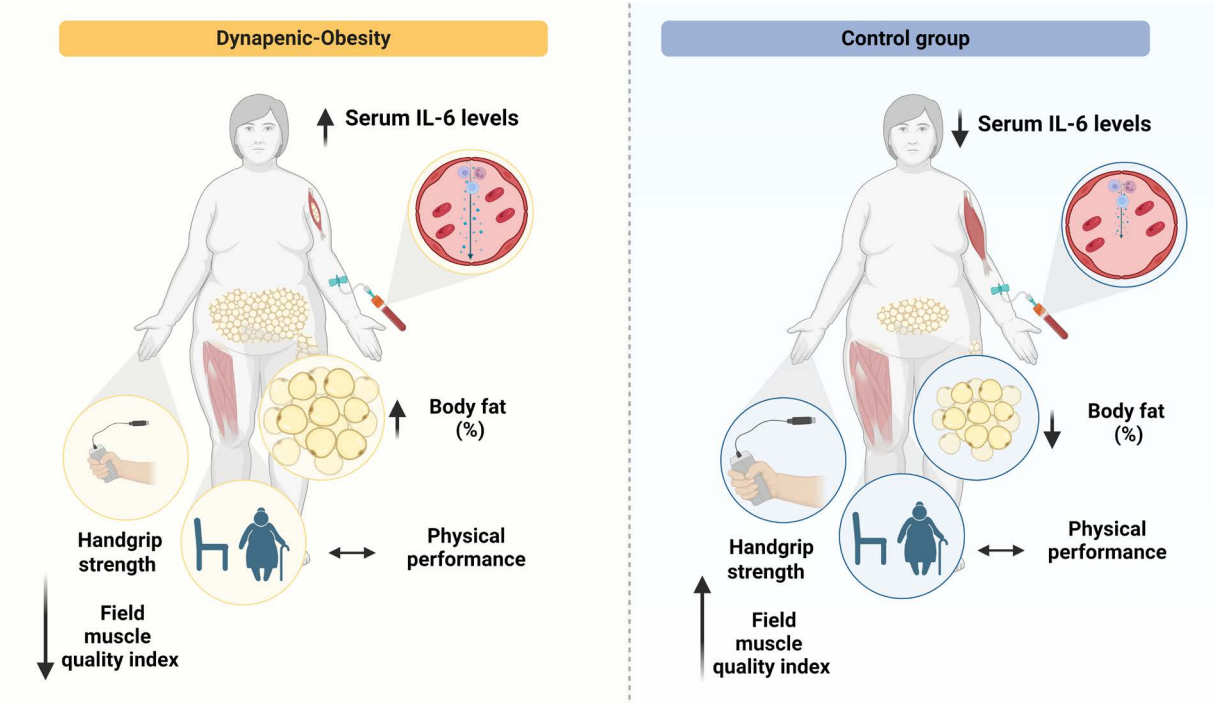


Figure 2 - Overview of comparison between dynapenic-obesity and control group. increase (↑), decrease (↓) and no changes (↔)

The data on cytokines from this research show that only IL-6 had higher levels in the DO group, suggesting that this group might display higher levels of inflammation compared to the control group. In another study with the oldest old, IL-6 was the cytokine best associated, among several cytokines, with a higher metabolic risk, low muscle strength, and gait speed [37]. This may demonstrate the crucial role of IL-6 during aging. However, one study found no difference in IL-6, IL-10, TNF-α, TNF-β, and IL-1β between older adults with DO or older adults with only dynapenia [25] and another study showed that between IL-6, IL-10, and TNF-α, only the last two had lower and higher levels, respectively, in the DO group compared to the obese, non-obese, or low-strength group [26]. Similar previous research only examined the role of the association of inflammatory markers in the youngest-old [25]. However, differences in results may be related to differences in obesity assessment methods, such as the use of BMI or differences in the research population [25,26].

Another finding of this study was a lower field MQI in the DO, but with no difference between groups for the laboratory MQI, despite a tendency towards statistical significance. The literature points out that obese people have a lower MQI compared to non-obese people [38]. In this sense, there are mechanisms that are linked to the pathogenesis of DO, such as adipose tissue dysfunction (e.g., adipocyte hyperplasia and hypertrophy) [7]. In this condition, when fat is accumulated in the form of intermuscular adipose tissue and intramyocellular lipids, it can cause a lipotoxic effect, impairing the contractility of muscle fibers and generating lower strength and potency in the elderly [5,7] In addition, the infiltration of adipocytes in muscle fibers implies a lower neuromuscular activation with low recruitment of motor units, reduction in the intrinsic contractile capacity to generate force, and changes

in actomyosin structure and function [9]. But the data on the relationship between MQI with DO is limited. However, as the MQI is derived from a measure of strength divided by a variable related to body mass [39], DO individuals are expected to present lower values of muscle quality.

Another point is that, despite the higher absolute value of the SPPB test for the control group, we did not find a significant difference between groups for performance in this research. These results do not corroborate with other studies that showed lower performance on the SPBB test in dynapenic abdominal obesity older adults [8,40]. This difference between results may be due to the reduced sample in our study or to the use of abdominal circumference measurement in other studies [8,40]. This measurement of central obesity may better reflect the distribution of fat in aging, as at this stage, there is an accumulation of visceral fat with a drop in overall fat percentage, especially in the oldest old [2,12].

Finally, we address some limitations and future directions to improve the diagnosis of DO. The main limitation of this study was the small sample size due to financial restrictions for cytokine analysis in a more significant population. Furthermore, the cross-sectional design feature of this study allows for only limited conclusions. Thus, more research is needed to understand DO's inflammatory profile and neuromuscular components.

Conclusion

In conclusion, DO oldest old displays a higher value of IL-6 and lower values for MQI compared to oldest old without DO.

Conflicts of interest
The authors declare that they have no conflict of interest.

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The authors did not receive any direct or indirect funding for their research.

Authors' contribution
Research conception and design: Nascimento DC, Abreu FMC, Neto IVS, Alves VPA; **Obtaining data:** Rosa BV, Garcia D, Paiva LRFO, Silva KHCV, Neto IVS; **Data analysis and interpretation:** Rosa BV, Garcia D, Neto IVS; **Statistical analysis:** Nascimento DC; **Writing of the manuscript:** Rosa BV, Garcia D, Paiva LRFO, Silva KHCV; **Critical review of the manuscript for important intellectual content:** Alves VPA; Nascimento DC.

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