

ORIGINAL ARTICLE

## Effects of omega-3 supplementation with or without physical activity in obese patients with type 2 diabetes mellitus: Study protocol.

*Efeitos da suplementação de ômega-3 associado à atividade física em pacientes obesos portadores de diabetes mellitus do tipo 2: protocolo de estudo.*

Mário Flávio Cardoso de Lima<sup>1</sup> , Marina Guedes Fraga Lopes<sup>1</sup> , Wellington Henrique Justo Neto<sup>1</sup> , Cláudio Teodoro de Souza<sup>2,\*</sup> 

<sup>1</sup>Postgraduate Program in Health, Universidade Federal de Juiz de Fora. Juiz de Fora, Minas Gerais, Brazil.

<sup>2</sup>Study Group of Nutrition and Physical Exercise Applied to Metabolic Syndrome - NEFASM. Department of Internal Medicine. School of Medicine. Universidade Federal de Juiz de Fora. Juiz de Fora, Minas Gerais, Brazil.

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### KEYWORDS

Diabetes Mellitus Type 2  
Exercise  
Fatty Acids Omega-3  
Obesity

### ABSTRACT

**Objective:** This study aims to evaluate the effects of omega-3-rich fish oil supplementation with or without physical activity on anti-inflammatory and insulin resistance parameters in obese and type 2 diabetic individuals.

**Methods:** Randomized, double-blind intervention study of omega-3. Adults with obesity and type 2 diabetes mellitus on exclusive use of metformin as a drug to control blood glucose will be included. The Protocol will be based on clinical and nutritional follow-up (supplementation with omega-3) and remote physical activity for eight weeks. Individuals selected for the study will be randomly assigned to one of the following groups: i) omega-3; ii) omega-3 + physical activity; iii) physical activity + placebo; iv) placebo. To analyze the results, biochemical parameters (fasting glucose and insulin, glycosylated hemoglobin, liver enzymes, urea, creatinine, total cholesterol and fractions, triglycerides, CRP, and ferritin) and inflammatory parameters (TNF alpha, IL-1 beta, IL- 6 and IL-10). At the end of the study, it is expected that the intervention associated with omega-3 in the physical activity protocol will promote a reduction in parameters related to insulin resistance, levels of inflammatory cytokines, and anthropometric parameters.

\*Corresponding author:

Programa de Pós-graduação em Saúde, Departamento de Clínica Médica, Faculdade de Medicina da Universidade Federal de Juiz de Fora.

Addr.: Av. Eugênio do Nascimento, s/n° - Dom Bosco, Juiz de Fora, MG, Brasil | CEP: 36.038-330.

Pone: +55 (32) 2102-3848

E-mail: [claudio.t.desouza@gmail.com](mailto:claudio.t.desouza@gmail.com) (Souza CT)

This study was conducted at the Universidade Federal de Juiz de Fora.

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**PALAVRAS-CHAVE**

Obesidade  
Diabetes Mellitus Tipo 2  
Ácidos Graxos Ômega-3  
Exercício Físico

**RESUMO**

**Objetivo:** O objetivo deste estudo será avaliar os efeitos de uma suplementação com óleo de peixe rico em ômega-3 associada ou não à atividade física sobre parâmetros anti-inflamatórios e de resistência à insulina em indivíduos obesos e diabéticos tipo 2.

**Métodos:** Estudo randomizado, duplamente cegado para intervenção de ômega-3. Serão incluídos indivíduos adultos com obesidade, portadores de diabetes mellitus tipo 2 em uso exclusivo de metformina, como medicamento para controle da glicemia. O Protocolo será baseado em acompanhamento clínico, nutricional (suplementação com ômega-3) e atividade física remota por período de oito semanas. Os indivíduos selecionados para o estudo serão aleatoriamente encaminhados para um dos grupos: *i)* ômega-3; *ii)* ômega-3 + atividade física; *iii)* atividade física + placebo; *iv)* placebo. Para a análise dos resultados serão avaliados parâmetros bioquímicos (glicemia e insulina de jejum, hemoglobina glicosilada, enzimas hepáticas, ureia, creatinina, colesterol total e frações, triglicerídeos, PCR e ferritina) e inflamatórios (TNF alfa, IL-1 beta, IL-6 e IL-10). Ao final do estudo, espera-se que a intervenção associada de ômega-3 ao protocolo de atividade física promova redução de parâmetros relacionados à resistência insulínica, aos níveis de citocinas inflamatórias e aos parâmetros antropométricos.

**INTRODUCTION**

In recent decades, obesity has increased worldwide, regardless of social, economic, and regional factors<sup>1</sup>. In Brazil, the Surveillance of Risk and Protective Factors for Chronic Diseases by Telephone Survey (*Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico - VIGITEL*) in 2018 revealed that 55.7% of the population over 18 years of age was overweight<sup>2</sup>. The increase in the incidence of obesity is due to the set of environmental changes that drive an individual to gain weight through an inadequate dietary pattern and level of physical activity, associated or not with genetic factors<sup>3,4</sup>.

Profound changes in physiological functions accompany an increase in body fat. The deposition of visceral adipose tissue is a major contributor to the development of hypertension, a high plasma insulin concentration, insulin resistance (IR), *diabetes mellitus*, hyperlipidemia, and low-grade chronic inflammation<sup>4</sup>. This inflammation is marked by the increased secretion of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin 1 beta (IL-1B)<sup>5</sup>. Additionally, the adipose tissue of obese individuals exhibits a marked increase in macrophage infiltration, leading to the excessive release of proinflammatory cytokines and perpetuating the inflammatory condition. In summary, obese individuals develop low-grade chronic inflammation that causes IR and progress to type 2 diabetes mellitus (T2DM)<sup>6</sup>. IR is described as the main link between obesity and T2DM; it is a condition in which the peripheral target tissue has a subnormal response to insulin levels, resulting in lower glucose uptake and a reduction in other physiological effects of insulin<sup>5</sup>.

Given the inflammation/IR ratio, it seems plausible that anti-inflammatory agents would be of great therapeutic value for patients with obesity and T2DM. Studies have shown that the consumption of omega-3 fatty acids, especially  $\alpha$ -linolenic acids, eicosapentaenoic (EPA), and docosahexaenoic (DHA)<sup>7</sup>, have anti-inflammatory potential. Additionally, omega-3 fatty acids have been shown to reduce TNF $\alpha$ , IL-1B, and IL-6 gene expression<sup>7</sup>. However, despite the proven anti-inflammatory effects of omega-3 fatty acids, few controversial human studies have analyzed their impacts on IR. Another intervention with great anti-inflammatory

potential and a significant effect on IR is physical exercise<sup>8</sup>. Thus, it would be of great value to test whether the effects of omega-3 fatty acids are potentiated when combined with physical exercise.

The existing therapeutic strategies for treating patients with obesity and T2DM are insufficient and ineffective, and there are few viable and low-cost alternatives to the morbidity of obesity. Given this scenario, the combination of nonpharmacological therapies involving physical exercise and the consumption of foods with an anti-inflammatory profile is of great value. However, the current scientific knowledge about such interventions lacks robust and reliable results for humans. Thus, the present study aims not only to demonstrate the efficacy of omega-3 fatty acids and physical exercise in isolation but also to determine whether there is an additive effect on biochemical and inflammatory parameters when both are applied simultaneously for subjects with obesity and T2DM.

**METHODS****Study design**

This protocol proposes a single-center, longitudinal, randomized clinical study to be conducted at the *Universidade Federal de Juiz de Fora (UFJF)* to treat IR. Thus, it is expected that the proposed interventions will reduce IR-related parameters (blood glucose, insulin, glycated hemoglobin, HOMA-IR index, and triglycerides) and improve inflammatory (cytokine) and anthropometric parameters (weight, body composition, circumferences, and skinfolds). The entire study will be performed in the laboratories and offices of UFJF University Hospital (HU-UFJF, for its acronym in Portuguese). One hundred volunteers who meet the inclusion criteria and agree to participate in the study will be recruited from the HU-UFJF outpatient clinics. Those who sign an informed consent form will be included in the study. After agreeing to participate in the study, each volunteer will be allocated to one of the proposed treatment groups. For the allocation of volunteers into the treatment groups, randomization will be performed using Microsoft Excel 365<sup>®</sup> software.

All possible groups will be allocated to a spreadsheet cell with a random number assigned to each group. Subsequently, the treatments will be distributed in numerical order, and the order will be established from 1 to 100. After a volunteer is recruited, their treatment will be randomly selected with the Random UX® application. The researcher responsible for the exercise protocol application will be partially blinded, i.e., not knowing which individuals receive omega-3 supplementation or placebo. The other researchers will be blinded to the exercise intervention and supplementation (omega-3 or placebo). Blinding will only be broken if there is a risk to the volunteer's health.

Throughout the study, the volunteers will be instructed to maintain their dietary habits and lifestyle regularly. The volunteers who participate in the study will have peripheral blood samples collected before and after the intervention. Blood collection will be performed at the Clinical Analysis Laboratory of HU-UFJF. Blood will be collected from the veins on the forearm. A portion of the sample will be used for laboratory analyses, and the other will be appropriately stored in a vacuum tube with heparin without separating the gel for subsequent analysis in a research laboratory at UFJF. A duly trained technical professional will perform all collections at the study site. The portion stored in a heparin tube will be centrifuged at 3,000 rpm for 10 min at 4 °C to obtain plasma. The collected plasma will be portioned and stored in an ultra-freezer at -80 °C for further analysis. Collections will occur after fasting for 12 h, with no alcohol consumption in the previous 72 h. The individuals selected for the study will be randomly assigned to one of the following groups: I) omega-3; II) omega-3 + physical activity (PA); III) PA + placebo; and IV) placebo (Figure 1). The dosage used for the omega-3 capsules will be 2,400 mg (1,440-mg EPA and 960-mg DHA), and the placebo will contain 2,400 mg of soybean oil.

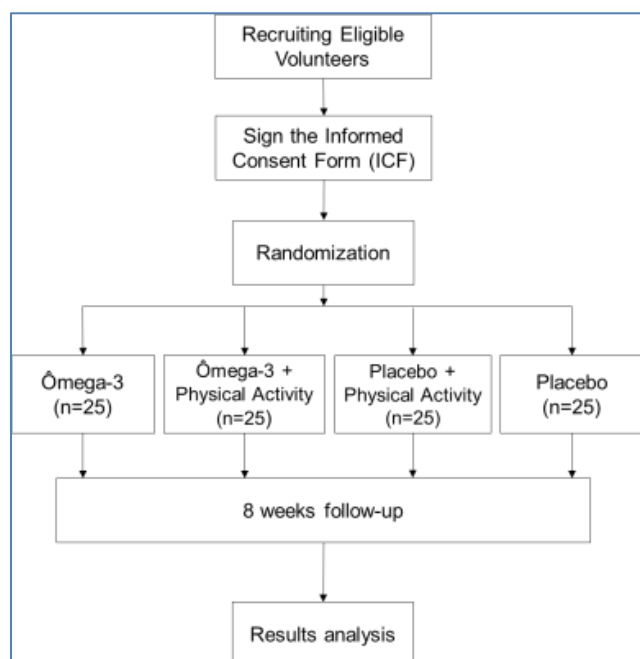


Figure 1 – Intervention protocol flowchart.

The proposed physical activity protocol will be

explained and demonstrated to each volunteer, in person, after enrollment; physical activity will be performed at home and monitored online by the project team. A weekly follow-up will be performed individually via telephone or messaging application to verify each volunteer's adherence to the protocol and, eventually, to collect reports on circumstantial adversities in the execution of the protocol and provide necessary adjustments. Participants will be asked to respond to a perceived exertion ranging (PER) scale from 0 to 10 (adapted from Borg), aiming to monitor the relative intensity of exercise<sup>9</sup>.

The individuals and the researchers involved will be blinded to the supplementation (omega-3 or placebo). The omega-3-rich fish oil capsules and placebo (soybean oil) will be purchased from Essential Nutrition®, São José, SC, Brazil. The placebo capsules will have the same appearance and odor as the fish oil capsules. Weekly, the patients will be contacted by messaging applications and asked about possible adverse effects related to using the capsules.

The study will be conducted following the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of UFJF under protocol number 4.731.228 and registered in the Brazilian Registry of Clinical Trials (ReBEC) under nr. RBR-8cb536 g.

The protocol is based on clinical and nutritional monitoring (omega-3 supplementation) and physical activity for 8 weeks. All tests and analyses used in the study will be performed before (pretest) and after the specific intervention period (post-test) and be conducted by adequately trained professionals responsible for the project (nutritionists and physical education professionals). Food consumption will be monitored during the first, fourth, and eighth weeks of treatment through a 24-hour food record. The physical activity protocol will be performed remotely at home 3 days (non-consecutive) per week. The study participants will be evaluated during visits to the outpatient clinic (Figure 2).

#### ▪ Initial moment (T<sub>0</sub>):

An initial interview will be conducted to collect socioeconomic and clinical data and to apply a physical activity questionnaire (short form IPAQ) and food frequency questionnaire (FFQ). Additionally, blood pressure (BP) at rest will be measured, the 6-minute walk test (6MWT) will be conducted, and strength will be measured by manual dynamometry. Heart rate (HR), respiratory rate, and pulse oximetry will be evaluated during and at the end of the 6MWT. Notably, the volunteers allocated to the physical activity intervention groups will be trained to perform the physical activity protocol at home properly. The individuals will be instructed to return the next day to provide blood for biochemical evaluations and, later, undergo anthropometric and body composition evaluations. After the assessments, the volunteers will be given capsules (placebo or omega-3) sufficient for 30 days and additional guidance regarding the consumption of the capsules.

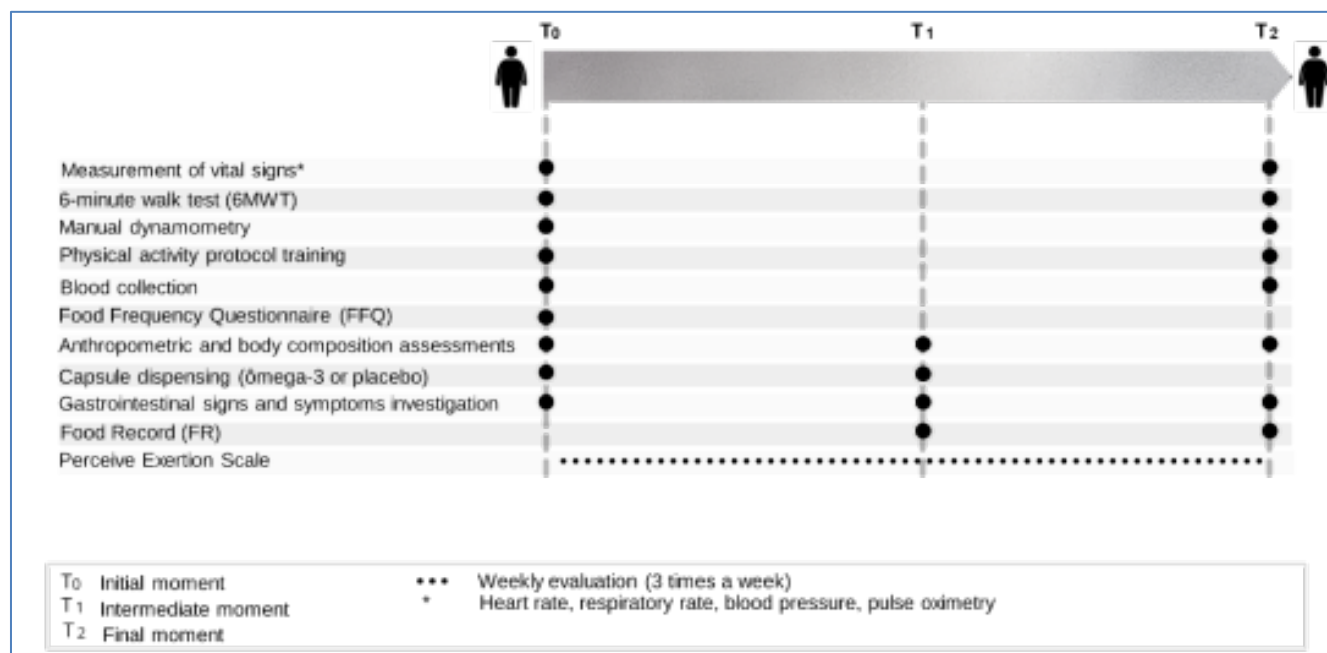


Figure 2 – Follow-up protocol.

#### Intermediate moment (T<sub>1</sub>):

The individuals will return to the outpatient clinic after 30 days and will again undergo anthropometric and body composition assessments. They will also be asked about gastrointestinal signs and symptoms related to supplementation and questions related to physical fitness. After the evaluations, the subjects will receive another 30 capsules (placebo or omega-3) to complete the study.

#### Final moment (T<sub>2</sub>):

Sixty days after the beginning of the intervention, the individuals will again undergo anthropometric and body composition assessments and be asked about adverse signs and symptoms of supplementation and questions related to physical activity. Subsequently, blood pressure at rest will be evaluated, and the volunteer will again undergo the 6MWT (with heart rate monitoring) and manual dynamometry. After this last visit, the volunteer will be instructed to report to the clinical analysis laboratory after fasting for 12 h to provide a blood sample (post-test).

#### Study subjects

The following individuals will be included:

1. Those aged between 20 and 60 years, irrespective of gender;
2. Those with a diagnosis of grade I obesity (body mass index [BMI] between 30.0 and 34.9 kg/m<sup>2</sup>) and T2DM who exclusively use metformin;
3. Those who do not present any evidence of coronary artery disease, intestinal diseases (short bowel syndrome, irritable bowel syndrome, Crohn's disease,

ulcerative colitis, celiac disease, and colorectal cancer), or diseases related to the central nervous system (Alzheimer's, Parkinson's, hepatic encephalopathy, and autism spectrum disorders);

4. Those who present physical inactivity according to the IPAQ questionnaire (short version)<sup>10</sup>; and
5. Those who sign the informed consent form (ICF).

The following individuals will be excluded:

1. Those with musculoskeletal or cardiovascular limitations that preclude the practice of physical exercise;
2. Those with fasting glucose greater than 300 mg/dL;
3. Those who have taken antibiotics, nonsteroidal anti-inflammatory drugs, or corticosteroids in the last month;
4. Those who take vitamin/food supplements containing omega-3;
5. Those with genetic- and hormonal-limiting diseases;
6. Those with alcohol and drug abuse;
7. Those with retinopathy or other vision disorders that prevent the correct execution of the study protocol;
8. Those who are pregnant or in the lactation stage;
9. Those with a life expectancy of fewer than 6 months;
10. Those with kidney failure or congestive heart failure;
11. Those with transplants;
12. Those who use wheelchairs;
13. Those who report weight loss in the previous 3 months (voluntary or involuntary);
14. Those without access to the internet;
15. Those who discontinue the use of omega-3/placebo for 3 consecutive days; and
16. Those who do not comply with the physical activity protocol for 2 consecutive sessions.

An individual may be removed from the study if he (or a legal representative) expresses interest in doing



so, is pregnant, or has any other clinical reason (discretion of the research team).

### Anthropometric assessment and body composition

The anthropometric assessment will be performed at the first visit and will include the measurement of current body weight, height, BMI, and waist circumference. The values obtained for BMI will be classified following the reference values provided by the World Health Organization for adults<sup>11</sup>. Body composition will be assessed using tetrapolar bioelectrical impedance under the following conditions: fasting for at least 4 h before the test, no exercise in the previous 24 h, and "empty bladder".

### Dietary evaluation

Dietary evaluations will be used to control for possible biases and confounding factors affecting the results. A food frequency questionnaire (FFQ) and food record (FR) will be used for dietary assessment.

A quantitative FFQ will be applied at first contact to characterize the volunteers' usual diet. Different food groups will be listed, and the frequency of consumption (day/week/month/year) will be recorded.

A FR will be used to monitor the current diet of the volunteers and will be completed for 3 nonconsecutive days, including a weekend day, during the first, fourth, and eighth weeks of the study. The volunteers will be instructed to record all food and drink ingested at the end of the days chosen, including quantity/volume in-home measurements and times/place of meals. After the information has been recorded for each day, the volunteers will send the data application to the study researchers to correct possible completion errors and clarify doubts.

### Protocol for and evaluation of physical activity

During the initial evaluation process, the volunteers will undergo indirect assessments of maximum oxygen consumption via the 6MWT under the protocol indicated by the American Thoracic Society<sup>12</sup>. The test will be performed at least 2 h after a meal. Immediately before the test, the participants will rest for 10 min. During this period, BP, pulse oximetry, PER, HR, and respiratory rate (RR) will be measured. The 6MWT will be applied in a 30-m long flat corridor marked with cones. The participants will receive instructions before the test and will perform 2 tests with a minimum interval of 15 min between them. If there is a difference greater than 10% in the distance walked between the 2 tests, a third attempt will be performed. During the tests, verbal stimuli will be provided every minute in a standardized manner. At the end of the test, the participants will sit exactly where they finished, and the variables measured before the test will be measured again. At the end of the test, oxygen consumption will be estimated using the following equation<sup>13</sup>:

$$VO_2 \text{ peak} = 0.02 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} = (0.02 \times \text{distance [m]}) - (0.191 \times \text{age [years]}) - (0.07 \times \text{weight [kg]}) + (0.09 \times \text{height [cm]}) + (0.26 \times \text{PTP} [\times 10^{-3}]) + 2.45$$

During this visit, the volunteers will be familiarized with the RPE scales (OMNI-RES scale from 0 to 10 for strength exercises and Borg scale from 6 to 20 for aerobic exercises) that will be used later to rate the intensity of the proposed physical activities<sup>9</sup>. Also, handgrip strength (HGS) will be evaluated through the maximum isometric force exerted, measured using a Jamar handheld hydraulic dynamometer. After this process, the exercise protocol will be explained and demonstrated by a certified physical education professional.

The physical activity protocol used in the present study was designed in 2013 by the *American College of Sports Medicine (ACSM)* and adapted for the study population, as suggested by the ACSM<sup>14</sup>. This program includes strength exercises that aim to work the largest and main muscle groups and aerobic and central stability exercises that aim to work core muscles. There are 12 exercises included:

1. Jumping jacks
2. Isometric squats
3. Push-ups on the ground
4. Sit-ups on the ground
5. Step up and down from a chair
6. Dynamic squats
7. Triceps dip on a chair
8. Isometric plank
9. Running in place
10. Unilateral squat
11. Push-up with rotation
12. Isometric side plank

A physical education professional will perform all exercise sessions under remote supervision. The physical activity program will begin with 1 set for each exercise, with a 30-s stimulus followed by a 1-min interval in passive recovery. Starting from the second week, there will be an increase to 2 to 3 sets, and the interval may be adjusted to 45 or 30 s to increase the intensity of the session, maintaining the parameters previously stipulated throughout the intervention.

### Biochemical parameters

Individuals who participate in the study will have peripheral blood samples collected before and 8 weeks after the intervention. The collections will be made after fasting for 12 h, with no alcohol consumption in the previous 72 h. The following laboratory parameters will be evaluated at the beginning of the study and after the intervention: fasting glucose, fasting insulin, HbA1c, glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), urea, creatinine, total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglycerides (TGs), CRP and ferritin. LDL-C will be calculated using the Friedewald equation ( $LDL-C = CT - HDL-C - (TG / 5)$ ). The atherogenic

index of plasma will be calculated using the following equation:  $\text{Log (TG/HDL-C)}$ . The Castelli I and II indices will be determined by the  $\text{TC/HDL-C}$  and  $\text{LDL-C/HDL-C}$  ratios, respectively. The homeostatic model assessment (HOMA-IR) index will be calculated using the following formula:

$$(\text{fasting insulin } [\mu\text{U/mL}] \times \text{fasting glucose } [\text{mmol/L}]) / 22.5$$

### Enzyme-linked immunosorbent assay - ELISA

To measure the cytokines TNF alpha, IL-1 beta, IL-6, and IL-10 (Thermo Fisher, Waltham, Massachusetts, USA), ELISAs will be used following the manufacturer's protocols.

### Sample size calculation

The sample size calculation for the study was obtained using GPower software (version 3.1.9.4), considering an  $\alpha$  value of 0.05 and a power of 95%. A 43% reduction in serum triglycerides was considered the primary outcome for the effect size. The effect size was defined based on previous studies by authors<sup>15</sup>. Thus,

100 individuals will be enrolled, divided among the 4 treatment groups (25 individuals in each group).

### Statistical analysis

The data will be grouped and presented in graphs and tables. The pre- and postintervention results for each group will be tested for normality using the Shapiro–Wilk test and homogeneity of variances using the Levene test. If the results indicate normality and equality of variance, the mean values will be compared by Student's t-test for paired samples. Comparative analyses among different groups will be performed by one-way ANOVA after confirmation of normality (by Shapiro–Wilk) and equality of variance (by Levene), followed by Tukey's *post hoc* test. Pearson's correlation coefficient will be used for the correlation analysis using the Statistical Package for the Social Science® (SPSS®) version 27.0.1.0.

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**Author contributions:**

Conception and design: MFCL, MGFL, WHJN, CTS

Data collection: MFCL, MGFL, WHJN

Writing of the manuscript: MFCL, MGFL, WHJN

Critical revision of the article: CTS

Final approval of the manuscript\*: MFCL, MGFL, WHJN, CTS

Statistical analysis: Not applicable

Overall responsibility: CTS

\*All authors have read and approved of the final version of the article submitted to Rev Cienc Saude.

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