Methods & Protocols

Effects of physical exercise on the lipid and inflammatory profile of young women using combined oral contraceptives: protocol of a cross-sectional study

Efeitos do exercício físico sobre o perfil lipídico e inflamatório de mulheres jovens em uso de contraceptivo oral combinado: protocolo de um estudo sequencial cruzado

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ABSTRACT | INTRODUCTION: The use of combined oral contraceptives (COC) is a risk factor for atherosclerotic disease because it compromises the lipid and inflammatory profile, and physical exercise can minimize these conditions. **OBJECTIVE:** To test the hypothesis that high intensity interval physical exercise promotes changes in the lipid and inflammatory profile of women who are irregularly active using COC. **METHODS:** Protocol of a cross-sectional study with women of 20 and 30 years, irregularly active, using COC for at least 6 months. A physicalclinical assessment (AFC) was performed on the participants with anthropometric measurements, VO2max. analysis and analysis of the lipid and inflammatory profile. Afterwards, the participants were divided into 2 groups: the initial intervention group (GII) that started practicing high intensity interval exercises for 2 months, and the posterior intervention group (GIP), which remained irregularly active for the same period. Then the GII and GIP would alternate their conditions for another 2 months, totaling 4 months of follow-up and 3 AFC, performed at the beginning, after 2 months and at the end of the study. The information collected was divided into 3 moments: Initial moment (MI), post-exercise moment (MPE) and post-inactivity (MPI).

KEYWORDS: Combined oral contraceptives. High intensity interval exercise.

RESUMO | INTRODUÇÃO: O uso de contraceptivos orais combinados (COC) trata-se de um fator de risco para a doença aterosclerótica por comprometer o perfil lipídico e inflamatório, podendo o exercício físico minimizar essas condições. **OBJETIVO:** Testar a hipótese de que exercício físico pode modificar o perfil lipídico e inflamatório de mulheres em uso COC. **MÉTODOS:** Protocolo de um estudo sequencial cruzado com mulheres de 20 e 30 anos, irregularmente ativas, em uso de COC há pelo menos 6 meses. Realizou-se uma avaliação físico-clínica (AFC) nas participantes com medidas antropométricas, VO2máx. indireto e análise do perfil lipídico e inflamatório. Na sequência separou-se as participantes em 2 grupos: O grupo intervenção inicial (GII) que iniciou praticando exercícios intervalados de alta intensidade por 2 meses, e o grupo intervenção posterior (GIP), que seguiu irregularmente ativo pelo mesmo período. Em seguida o GII e o GIP alternariam suas condições por mais 2 meses, totalizando 4 meses de acompanhamento e 3 AFC, realizadas no início, após 2 meses e ao final do estudo. As informações colhidas foram divididas em 3 momentos: Momento inicial (MI), momento pós exercício (MPE) e pós inatividade (MPI).

PALAVRAS-CHAVE: Contraceptivos orais combinados. Exercício físico.

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Introduction

Historical reports claim that women across the planet began using rudimentary contraceptive methods at least 4,000 years ago. Over time, these methods improved, until between the 1950s and 1960s, the first oral contraceptives appeared in the United States of America[1,2]. Mostly made up of an estrogenic and a progestogenic component, in a short time they started to be commercialized worldwide due to their effectiveness, low cost, and viability of use[2].

Among the possible side effects, the use of oral contraceptives, we can highlight the increase in endothelin, peroxynitric, angiotensin 2, oxidative stress, and insulin resistance[3,4]. As well as the reduction of nitric oxide, prostacyclin, and alteration of hepatocytes can also occur[3-6].

All of these new conditions favor thrombolytic, vasoconstrictive, inflammatory, and lipid changes, which in combination can promote a series of cardiovascular injuries that are determinant for atherosclerotic disease[3,7,8].

In 2013, a cross-sectional study.[9] demonstrated that the inflammatory profile, assessed by the levels of C-reactive protein (CRP), was significantly higher in users of combined oral contraceptives (COC).

Another study was able to verify a lower magnitude of postprandial lipemia (LPP) in women who did not use COC, making it clear in these two cases that contraceptive therapy influences the inflammatory and lipid profile[10].

As a means of attenuating or even reversing these conditions, physical exercise has been widely used in several populations around the world[11].

It was with this in mind that Petto et al.[12] evaluated both postprandial lipemia and the inflammatory profile of women who declared themselves "irregularly active" and "active" using COC. It was observed that the participants in the "active" group had lower levels of subclinical inflammation and that although both groups had normal levels of triglycerides, the "irregularly active group" showed 56% higher values, thus being closer to the abnormality threshold[12].

It is known that the inflammatory and lipid profile is higher in COC users[9,10,12], especially in those who have lower levels of physical activity[12]. With this in mind, physical exercise has been used to mitigate or even reverse these conditions in some populations[11].

However, in our previous studies, there were no studies that verified the cause-effect relationship of physical exercise in women who use COC continuously.

Objective

Test the hypothesis that physical exercise can modify the lipid and inflammatory profile of women using combined oral contraceptives.

Hypotheses

H0 - A high-intensity interval exercise program does not reduce the lipid and inflammatory profile of young women, irregularly active using combined oral contraceptives.

H1 - A high-intensity interval exercise program reduces the lipid and inflammatory profile of young women, irregularly active using combined oral contraceptives.

Methods

Study design

The research is characterized as a protocol of a sequential crossover study registered in the Brazilian Registry of Clinical Trials (ReBEC), with the number: RBR-4jm343.

Study population

Normolipidic young women irregularly active in continuous use of combined oral contraceptives.

Inclusion criteria

Irregularly active women in categories A and B, aged between 20 and 30 years, nulliparous, in continuous use of COC for at least 6 months. The COCs to be used should be the fourth generation and have an estrogen dosage between 15 and 35 micrograms. To prove the level of physical activity and category of study participants, the International Physical Activity Questionnaire (IPAQ)[18], in the short version, was used. This questionnaire was used because it has the following advantages: it can be carried out in two forms (short and long), it allows to estimate caloric expenditure and has a more detailed classification in sedentary, irregularly active, active, and very active, in addition to allowing a greater chance of comparisons and being adapted to the Brazilian reality[13].

Exclusion criteria

Women who refer and present physical and clinical conditions incompatible with physical exercises, such as reports of hypoglycemia, muscle or joint pain in the lower limbs, postural hypotension, labyrinthitis, dyslipidemia, liver dysfunction, pre-diabetes or diabetes, hypo or hyperthyroidism, polycystic ovary syndrome, kidney disease, use of dietary or anabolic supplements and hypo or hyperlipidic diet, history of alcoholism, smoking, use of lipid-lowering drugs, corticosteroids, diuretics or beta-blockers and body mass index (BMI) above 30 kg / m^2.

Ethical aspects

Throughout the study, the guidelines on research with human beings of the Declaration of Helsinki and Resolution 466/12 of the National Health Council will be observed. This study was submitted and approved by the Research Ethics Committee of Faculdade Nobre de Feira de Santana - CAAE: 79549517.3.0000.5654. All participants will receive detailed information about the study objectives, risks, and benefits involved in the procedures and will sign the informed consent form (TCL). Two copies will be filled, one to the participants and the other to the researchers.

Sample calculation

A previous pilot study was carried out for sample calculation (n = 3), considering triglycerides outcome variable with Mean and SD = 32 ± 9, requiring 22 volunteers. Alpha = 0.05 (bidirectional) and beta = 0.80 were considered; adopting a significant difference of 20% for the triglyceride variable between the moments. Bearing in mind that the laboratory variation coefficient of the triglyceride dosage is 5% and that a difference four times greater than expected cancels the bias of this analytical variation coefficient. A crossover will be done, so 12 participants will be needed, with 6 allocated to the GII and another 6 allocated to the GIP. The sample calculation was performed using WinPepi version 11.65.

Data collect

To collect general information about the characteristics of the sample, all study participants that are selected will be subjected to a Clinical Physical Assessment (AFC) that will be based on 4 steps:

1 = Application of a standard questionnaire: In order to perform a sample screening regarding information relevant to the study protocol at a given time.

2 = Assessment of vital signs / physical examination: Composed of measures of heart rate and blood pressure at rest, total body mass, height and waist circumference. To measure the heart rate, a Polar® pulse cardiofrequency meter will be used. To measure blood pressure, the recommendations of the Brazilian Society of Hypertension[14] will be followed, using a sphygmomanometer and stethoscope from the brands WelchAllyn® and Littman® respectively. Height will be measured with total will be obtained with a Filizola® digital scale with a maximum capacity of 150 kg, verified by Inmetro, with its own certificate specifying an error margin of ± 100 g. The abdominal circumference will be obtained with a metallic and inelastic measuring tape, brand Starrett, with a definition of 0.1 cm. It will be measured in the smallest curvature located between the last rib and the iliac crest without compressing the tissues[14]. The body mass index (BMI) will be calculated with the measures of mass and height, according to the Quetelet equation: BMI = mass (kg) / height2 (m). The cutoff points adopted will be those recommended by the IV Brazilian Guideline on Dyslipidemias and Atherosclerosis Prevention of the Department of Atherosclerosis of the Brazilian Society of Cardiology[15], that is, low weight (BMI <18.5), eutrophy (18.5 < BMI <24.9), overweight (25 <BMI <29.9) and obesity (BMI

≥ of a professional Sanny® stadiometer with 0.1 cm precision, performed with the participants barefoot, with the buttocks and shoulders supported on a vertical.

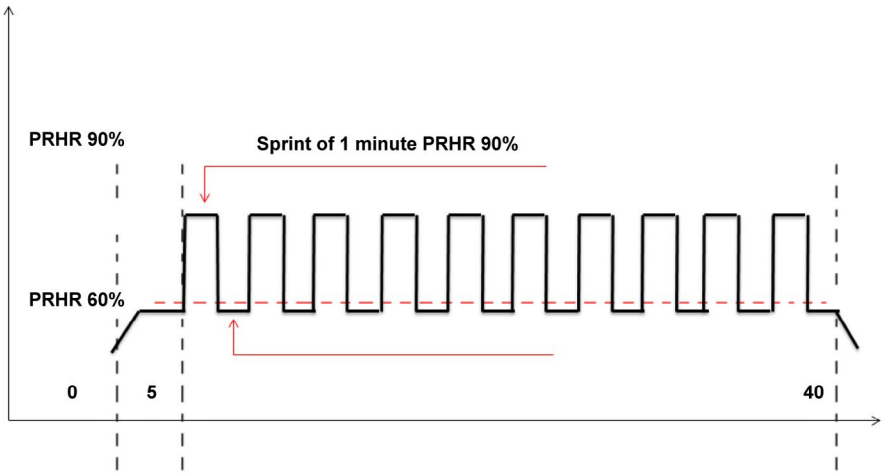
3 = Graduation test of maximum oxygen consumption (VO2 max.) Indirect emplying the Cooper protocol, performed on the treadmill[19]: In this test, the participants will initially be instructed about all stages of the test and later instructed to perform a warm-up in the form of walking at speed that represents a self-perceived effort level "easy", regulated by the person evaluated for 5 minutes on a treadmill without inclination of the Movement® brand. Immediately after the warm-up period, the treadmill will be turned off and instantly switched on again, and from that moment on, the assessment will in fact be started, and the participant will have to walk at their own pace and regulation the longest possible distance, running, walking and walking will be allowed. After the 12th minute of evaluation, the distance covered will be visualized on the treadmill odometer and recorded on the participant's record, ending at that moment, with a subsequent cooling down of the treadmill, with a gradual reduction in speed that will be performed in 2 minutes until the speed of the treadmill. mat is zeroed. If for any possible reason it is necessary to reset the treadmill speed during the 12 minutes of testing, it must be interrupted and canceled that day, with a new performance after 72 hours.

4 = Blood collection: After the minimum 72h period of the Cooper test, the study participants will be submitted to a blood sample collection for VPLI in the morning period with 12h and fasting between the fifth and tenth days of the menstrual cycle, considering the smallest hormonal fluctuations, and / or on the 28th day without medication (inactive phase) as recommended by Casazza et al.[16] So that there is no influence of the menstrual period on the value of the blood variables analyzed. The VPLI will be at the Clinical Pathology Laboratory (LPC) of the Barra unit in the city of Salvador-BA, which will provide the space, physical materials and human resources needed for collections and laboratory analysis. Total cholesterol (TC) values will be observed; Triglycerides; (LDL) -cholesterol; (HDL) -cholesterol, (VLDL) -cholesterol and high sensitivity CRP; so that according to these values, the lipid and inflammatory profiles of the sample are traced. The study participants will be instructed not to change their diet in the week of the test and not to practice any physical effort other than usual, as well as not to drink alcoholic beverages in the 24 hours preceding the test. The assessment of total cholesterol (HDL) -cholesterol and triglycerides, will be done by enzymatic method. (LDL) -cholesterol will be calculated using Friedwald's formula[17] and non-HDL-C cholesterol will be calculated by the difference between total cholesterol and (HDL) -cholesterol. The High Sensitivity PCR will be measured by turbidimetry.

Intervention Protocol

The volunteers who will be assigned to the moment of physical exercise will undergo an assessment of vital signs at the beginning, during and at the end of each session. If expected standards for age and level of effort are checked, activities will continue. The protocol consists of a high intensity interval training done by means of sprints, performed on a treadmill without inclination, with a frequency of 2 times a week and a total period of 2 months as previously described. During the exercise sessions, the warm-up phase lasts for 5 minutes with an intensity of 60% of the predicted reserve heart rate (FCRP), which will be calculated according to the following formula[20]: {[(220 - age) - Resting HR] x 0.6] + resting HR}. Then, for the conditioning phase, the belt speed will be increased until 90% of the FCRP was reached {[(220 - age) - resting FC] x 0.9] + resting FC}, maintaining this speed for 1 minute with a subsequent reduction to the heating speed for the next 2 minutes, setting active rest. Sprints will be alternated to the moments of active rest 10 times, with respective durations of 1 and 2 minutes (1 'sprint and 2' active rest), with the last 9 sprints and active rest speeds being maintained according to the speeds achieved in the first phase of each of these moments. For the cool-down phase at the end of the session, the speed identical to the heating speed will be maintained, lasting 2 minutes, until the treadmill is turned off as shown in figure 1.

Figure 1. Representation of high intensity interval training



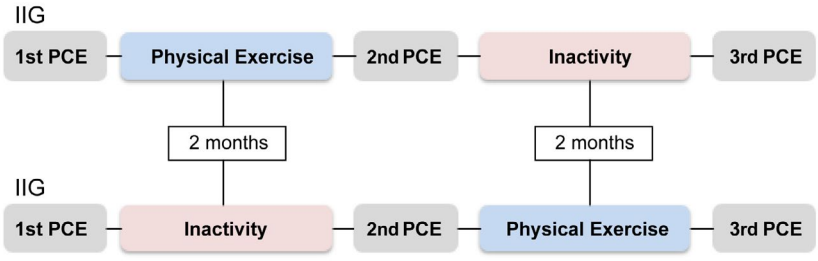
Training based on predicted reserve heart rate (PRHR). The sprints had duration of 1 minute and speed identical to the value reached in the first sprint. Periods of active rest had duration of 2 minutes and speeds identical to that achieved in the warm-up.

Participants will be monitored by the same Polar® pulse cardio frequency meter used during the Cooper protocol, that measures the caloric expenditure of the session, based on BMI, age, maximum expected HR and average HR during exercise[19].

Follow-up period

The intervention protocol, as well as the first three steps described in the physical-clinical evaluation, will take place at the Fisiocordis Clínica de Cardiovascular Rehabilitation, located in the city of Salvador-BA, which will also make available its space, physical materials and human resources. Right after the first VPLI test, those first six participants entering the study will be allocated to the GII and the last six will be directed to the later GIP intervention group. At first, only the participants of the (GII) will enter the high-intensity interval exercise program. Those participants in the (GIP) will maintain the same level of physical activities as before the beginning of the study, with a follow-up period of 2 months for each group. A second AFC will then be performed after this period, followed by alternating groups in relation to physical exercise and physical inactivity in another 2 months. Finally, a third and last AFC will be performed, totaling a follow-up of approximately 4 months, as seen in figure 2.

Figure 2. Study design



Sequential crossover study, where both groups underwent 3 physical-clinical evaluations (PCE), performed at the beginning of the study, after 2 and 4 months of follow-up. The initial intervention group (IIG) performed the high intensity interval exercise protocol right after the 1st PCE, and after the 2nd PCE, the period of inactivity began, followed by the 3rd PCE. The posterior intervention group (PIG) after the 1st PCE maintained its routine (inactive), after 2 months it underwent a new PCE and started a period of 2 months of high intensity interval physical exercise, and at the end of that period it performed the last PCE.

Data analysis

To verify the distribution of the data, the symmetry and kurtosis tests, the Shapiro-Wilk test, and the visual inspection of the histograms will be applied. Variables that present non-normal distribution will be used as a measure of central tendency and median dispersion and interquartile deviation, respectively, using the Kruskal Wallis test for comparison. For all other variables, the mean and standard deviation verified using the Anova test with repeated measures and Tukey's post-test will be used. All analyzes will be performed using the SPSS (Statistical Package for the Social Sciences) version 21.0, adopting a 5% significance level.

The results collected from the GII and GIP groups will be distributed in 3 different moments: 1 - initial moment (IM), 2 - post-exercise moment (MPE) and 3 - post-inactivity moment (MPI). To assess the data of the "initial moment" of the GII and GIP groups, they will be combined, obtaining the values of central tendency and dispersion resulting from 12 collections.

A cross will be made between the data of the MEPs and MPI of the GII and GIP, with the difference that in the GII the data of the MPE will be collected 2 months after the beginning of the study, whereas in the GIP these same data could only be collected after Four months. Likewise, MPI data may already be collected in the GIP 2 months after the beginning of the study, and can only be collected after 4 months in the GII.

After all data crossings, comparisons of the investigated variables will be performed between the three different moments, as follows: MI vs. MPE; MPE vs. MPI and MI vs. MPI. This crossing aims to make the participants control themselves, minimizing the risk of bias.

Variables

Predictor variable - High intensity interval physical exercise.
Outcome variable - Lipid and inflammatory profile.
Confounding variable - Food and lifestyle.

Primary outcomes

Lipid and inflammatory profile.

Author contributions

Gomes AF participated in the design and writing of the manuscript. Barbosa J, Sacramento MS AND Ferreira MA participated in writing the manuscript. Petto J participated in the conception, writing of the manuscript and critical review of the manuscript for intellectual content.

Competing interests

No financial, legal or political conflicts involving third parties (government, companies and private funds, etc.) have been declared for any aspect of the submitted work (including, but not limited to, grants and funding, participation in advisory council, study design, preparation of the manuscript, statistical analysis, etc.).

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