ORIGINAL MANUSCRIPT

Postprandial Lipemia and Subclinical Inflammation on Active Women Taking Oral Contraceptive

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Abstract

Background: Women taking oral contraceptives (OC) have higher fasting lipid profile, postprandial lipemia (PPL) and C-reactive protein (CRP) than women not taking OC. Exercise has shown good results in controlling lipid and inflammatory levels.
Objective: To compare fasting lipid, PPL and CRP levels among regularly active and irregularly active women taking OC.
Methods: The study evaluated forty-four women taking OC, from the city of Salvador, BA, stratified into two groups: active group (AG; n=22), composed of physically active women and irregularly active group (IAG; n=22) composed of irregularly active women. In both groups, after 12-hour fasting, fasting lipid profile and CRP were assessed. Then, the volunteers took a compound containing 25g fat and triglycerides were measured to check PPL. Mann-Whitney's test was used to compare PPL and CRP.
Results: The delta values of triglycerides representing PPL respectively for the AG and the IAG were: 93±38.4 mg/dL vs. 163±49.6 mg/dL and 89±50.9 mg/dL vs. 156±47.6 mg/dL ($p<0.01$). The CRP values respectively for the AG and the IAG were: 1.1 mg/L (0.4-2.1 mg/L) and 2.1 mg/L (0.8-3.4 mg/L) ($p=0.04$).
Conclusion: In this study, physically active women taking OC presented triglycerides and fasting LDL, PPL and CRP significantly lower than irregularly active women taking OC.

Keywords: Exercise; Basal metabolism; Hormones; Primary prevention; Dyslipidemias

Introduction

Recent studies have shown that women taking combined oral contraceptive (COC) have triglycerides, fasting low-density lipoprotein (LDL), postprandial lipemia (PPL) and C-reactive protein (CRP) greater than women that do not take COC[1-3].

Although the clinical consequences of this increase are not known, studies in healthy populations have suggested that increased LDL and CRP is a strong predictor of vascular disease[4,5]. Around 17,800 individuals of both sexes presenting low-density lipoprotein (<130 mg/dL) and CRP >2 mg/L have been evaluated in the JUPITER[5] study. The group that received no drug treatment showed higher incidence of myocardial infarction, hospitalization for unstable angina, stroke and death from cardiovascular disease[5].

Similarly, the PPL, while not deemed as a conventional risk factor for development of cardiovascular diseases, today it is considered as the best predictor of cardiovascular risk than conventional factors, even in healthy individuals[6,7]. The meta-analysis by Hokason and Austin[8] highlighted that the magnitude of PPL in women is related to the 76.0% increase in the risk of developing heart disease[8]. The

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ABBREVIATIONS AND ACRONYMS

- *BMI – body mass index*
- *COC – combined oral contraceptive*
- *CRP – C-reactive protein*
- *LDL – low-density lipoprotein*
- *PPL – postprandial lipemia*
- *UCP – uncoupling proteins*

refore, measures to minimize the effects of oral contraceptives are necessary.

Physical exercise is a non-drug therapy that has shown good results in controlling the levels of fasting triglycerides and LDL, and in lowering the levels of PPL and CRP[9-11]. Thus, this study aims to compare the values of fasting LDL and triglycerides, PPL and CRP among physically active and irregularly physically active women taking combined oral contraceptive.

Methods

Prospective longitudinal study carried out from February to December 2013, which investigated eutrophic women aged 19-30 years, physically active or irregularly physically active for at least one year, with fasting triglycerides ≤150 mg/dL, and taking low-dose combined oral contraceptive (ethinyl estradiol between 15-30 mcg) for at least one year.

This study complied with the guidelines on human research of the Declaration of Helsinki, and the Resolution of the Brazilian Health Council CNS 466/12. This study was approved by the Committee for Ethics in Research of the School of Science and Technology from Salvador, under No. 3390, and all the volunteers signed an informed consent form.

The population under study was composed according to the probability simple random sampling, comprising students of the Physiotherapy course from Faculdade Social da Bahia (Social College of Bahia), Salvador, state of Bahia - Brazil. All students received information on the study and had the same chance to take part in the research.

The sampling sufficiency calculation considered an alpha = 0.05 (bidirectional) and a beta = 0.80, adopting a significant difference of 20% between groups. As the laboratory variation coefficient for CRP and triglycerides doses is 5%, and that a difference four times greater than the expected overrules the bias of such coefficient, 44 volunteers were then required, i.e., 22 volunteers for each group. The GraphPad StatMate 2.0 for Windows performed the sampling calculation.

Women with obesity, diabetes, dyslipidemia and under drug treatment; women with kidney diseases, polycystic ovary syndrome; background of alcoholism or smoking; women in hypo or hyper caloric diet; women with CRP >10 mg/dL. Women taking corticosteroids, diuretics or beta-blockers were not included in the population under study.

The population under study was divided into two groups: the active group (AG) of physically active women taking low-dose combined oral contraceptive; and the irregularly active group (IAG) of women irregularly physically active also taking low-dose combined oral contraceptive.

The International Physical Activity Questionnaire (long version)[12], developed by the World Health Organization and the U.S. Centers for Disease Control and Prevention, was chosen to determine the physical activity level of volunteers. It allows you to specifically sort individuals (sedentary, irregularly active, active and very active), minimizing the classification bias. Besides, it provides greater chance of comparisons with other studies, since it has worldwide application and has been validated in Brazil[13]. Active volunteers were not sorted by type of exercise practiced. However, all active volunteers were engaged in running activities and/or neuromuscular exercises.

The selected volunteers answered the questionnaire and underwent physical examination; both exams aimed to gather clinical and socio-demographic information. The physical examination measured blood pressure at rest, total body weight, height and waist circumference. The eating habits of volunteers were not evaluated.

Blood pressure was measured following the recommendations of the Brazilian Society of Hypertension[14], by an average-sized BD tensiometer for adults, duly calibrated by the Brazilian Institute of Metrology, Quality and Technology (Inmetro), and by a BD Duo-Sonic stethoscope (São Paulo, SP - Brazil).

Height of participants was measured by a Sanny professional stadiometer (São Paulo, SP - Brazil) with 0.1 cm accuracy. The total body mass was measured by Filizola digital scales (São Paulo, SP - Brazil), of 150 kg maximum capacity, duly checked by Inmetro, with its own certificate specifying the margin of error of approximately 100 g.

Waist circumference was measured by a Starrett metal inelastic tape (São Paulo, SP - Brazil) with measure definition of 0.1 cm, measured at the smaller curve

between the last rib and the iliac crest without compressing the tissues[15].

The body mass index (BMI) was calculated according to the Quetelet equation: BMI = weight (kg)/height^2 (m). We adopted the cutoffs of the 4th Brazilian guideline on dyslipidemias and prevention of atherosclerosis from the Department of Atherosclerosis of the Brazilian Society of Cardiology[14], i.e., low weight (BMI <18.5 kg/m^2); eutrophia (BMI ≥18.5 kg/m^2 - <24.9 kg/m^2); overweight (BMI ≥25 kg/m^2 - <29.9 kg/m^2), and obesity (BMI ≥30 kg/m^2).

Laboratory collection procedures

5 mL of blood were collected after 12-hours fasting to assess the CRP, the total cholesterol and fractions, triglycerides, glucose, and glutamic-pyruvic transaminase.

Soon after fasting blood collections, the volunteers ingested a diet cereal bar and 25g lipid compound. Three and four hours after the intake of this compound, blood samples were collected to measure triglycerides levels and determine the PPL behavior. Lipoproteins, glutamic-pyruvic transaminase, glucose and total cholesterol were measured only in fasting. A highly trained professional in proper laboratory environment performed all blood collections. For blood collection, the antecubital vein was cannulated with a 16-mm Jelco; each sample collected was hydrolyzed with saline solution.

The lipid compound was provided by Tecnovida (São Paulo, SP - Brazil), where: 25g lipid compounds were monounsaturated, 8g lipid compounds were polyunsaturated, and 2g lipid compounds were saturated, representing 45% of the daily intake of fat recommended for a 2,000 kcal diet. The cereal bar had 0g of carbohydrates, 1.2g of protein, and 0.8g of lipids. The bar was administered to make the intake of the lipid compound more palatable, and to avoid stomach discomfort.

On the day of laboratory blood collection, volunteers were told not to change their eating habits during the week of the test, and not to practice any different physical effort than the usual; they were also asked not to drink alcohol within 24 hours prior to exams.

CRP was measured by turbidimetry with plasma serum. Glucose, triglycerides, total cholesterol and high-density lipoprotein values were obtained by Trinder's enzymatic colorimetric method[16]. Low and very low-density lipoprotein values were calculated by the Friedewald equation[1]. The glutamic-pyruvic transaminase was determined by the Reitman-Frankel's colorimetric method[18].

Statistical analysis

Symmetry and kurtosis tests and the Shapiro-Wilk test were used to verify data distribution. CRP values were non-parametric distributed and were described in medians and interquartile ranges. The bidirectional Mann-Whitney test to compare the medians was applied for within-group comparisons of CRP values. Other fasting variables presented parametric distribution, being described in medians and standard deviations; the bidirectional unpaired Student t test was applied to compare such variables.

The delta (Δ) reflecting the PPL, i.e., the variation of triglycerides between the fasting collection and the 180 min (Δ1) and 240 min (Δ2) points showed no parametric distribution, and was described in medians and interquartile ranges. Therefore, the bidirectional, independent-sample Mann-Whitney test was applied to compare Δ1 and Δ2. The values for triglycerides at collection points on the lipid curve (180 min and 240 min) presented normal distribution, being described in medians and standard deviations. The bidirectional unpaired Student t test was applied to compare the values between these points.

All analyzes were performed in the SPSS (Statistical Package for Social Sciences) software, version 13.0, adopting a 5% significance level.

Results

We evaluated 46 women, two of which were excluded from the IAG due to their triglycerides of >150 mg / dL. Therefore, the sample comprised 44 women, 22 in each group.

Table 1 shows the clinical and anthropometric variables of the two groups. The sample homogeneity is noticeable, with no significant difference between variables. About the oral contraceptives taken by the volunteers, 100.0% contained ethinyl estradiol, 52.0% had gestodene, 29.0% had levonorgestrel, 7.0% had chlormadinone acetate, 8.0% had drospirenone, and 4.0% had desogestrel.

Table 2 shows the fasting lipid profile between groups. As provided in the table, only the high-density lipoprotein showed no significant difference (p>0.05).

Table 1
Clinical and anthropometric variables of the population under study

Variables	AG (mean ± SD)	IAG (mean ± SD)	p* value
Age (years)	26 ± 2.1	25 ± 3.1	0.42
Body mass index (kg/m²)	20 ± 1.2	21 ± 1.2	0.65
Waist circumference (cm)	69 ± 4.2	70 ± 6.4	0.97
Systolic blood pressure (mmHg)	100 ± 7.3	107 ± 9.7	0.67
Diastolic blood pressure (mmHg)	65 ± 6.5	68 ± 8.2	0.12
Glycemia (mg/dL)	77 ± 5.9	85 ± 3.2	0.54
Glutamic-pyruvic transaminase (U/L)	14 ± 5.2	15 ± 3.4	0.14
Contraceptive usage time (years)	5.8 ± 1.4	4.7 ± 2.2	0.14

AG – active group; IAG – irregularly active group; SD – standard deviation
*Bidirectional Student t test for independent samples

Table 2
Fasting lipid profile (md/dL) of the study population, by groups

Variables	AG (mean ± SD)	IAG (mean ± SD)	p* value
Fasting triglyceride	60 ± 12.4	106 ± 22.7	< 0.01
Fasting total cholesterol	169 ± 16.3	208 ± 43.6	< 0.01
Fasting HDL	55 ± 11.7	55 ± 9.9	0.18
Fasting LDL	96 ± 39.8	131 ± 10.7	0.01
Fasting VLDL	12 ± 4.2	21 ± 9.7	< 0.01

AG – active group; IAG – irregularly active group; HDL – high density lipoprotein; VLDL – very low density lipoprotein; LDL – low density lipoprotein; SD – standard deviation
* Bidirectional Student t test for independent samples

Figure 1 shows the value of CRP in the groups evaluated. The median and the interquartile deviation of CRP in AG and IAG groups were 1.1 mg/L (0.4-2.1 mg/L), and 2.1 mg/L (0.8-3.4 mg/L) respectively, with statistical significance (p=0.04).

The values of triglycerides medians and standard deviations at the points on the lipid curve (180 min and 240 min) for AG and IAG were, respectively: 93±38.4 mg/dL vs. 163±49.6 mg/dL, and 89±50.9 mg/dL vs. 156±47.6 mg/dL, with significant difference (p<0.01).

Figure 2 shows that the behavior of the lipid curve was similar between groups, with the peak of the curve at 180 min stable until 240 min. Table 3 shows the comparison between the postprandial lipemia of groups under study. There was a significant difference in the first and second delta (p<0.01).

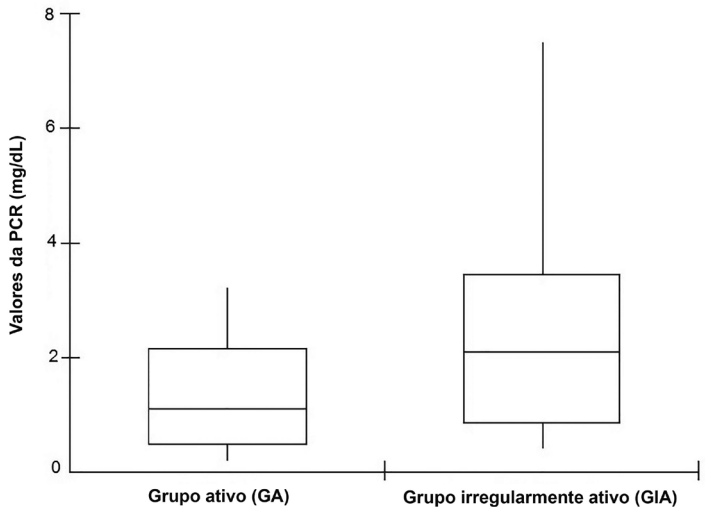

Figure 1
C-reactive protein values (median and quartiles) of the study population, by groups
CRP – C-reactive protein

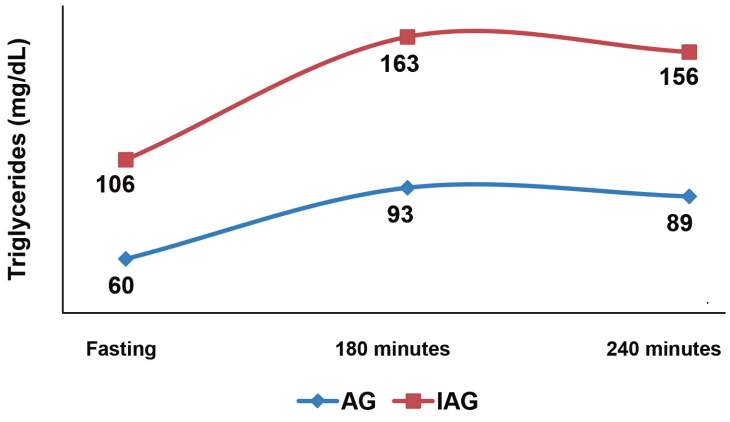

Figure 2
Postprandial lipid curve of the study population, by groups
AG – active group; IAG – irregularly active group

Table 3
Postprandial lipemia (md/dL) of the study population, by groups

Variables	AG median (IQD)	IAG median (IQD)	p* value
Δ1 (TG0 - TG180)	13 (7–20)	47 (38–56)	< 0.01
Δ2 (TG0 - TG240)	20 (18–27)	47 (17–70)	< 0.01

AG – active group; IAG – irregularly active group; IQD – interquartile deviation; TG – triglycerides
*Bidirectional Mann-Whitney t test for independent samples

Discussion

The findings suggest that the values of fasting LDL and triglycerides, PPL and CRP among physically active women are smaller than that of irregularly physically active women taking combined oral contraceptive. Although the results of this study are not conclusive and do not establish a perfect relationship of cause and effect, they are reinforced by the homogeneity of the sample. Factors that notably interfere with variables under study: BMI, waist circumference, blood pressure, glucose, time of use of the oral contraceptive, metabolic disorders and use of drugs were minimized in the groups (Table 1).

The mechanisms by which physical exercise improves fasting lipid profile, decreases the LPP and attenuates subclinical inflammation have not been studied in this population. However, we can go beyond the results of studies in other populations, and use them as a basis to raise some inferences.

It is a known fact that obesity is directly associated with increased levels of fasting low-density lipoprotein and triglycerides[6], but also with increased levels of PPL[19] and CRP[20]. Regular physical activity chronically increases the basal metabolic rate, reducing the BMI and decreasing all these variables directly related to obesity[20]. However, this study included only eutrophic women without difference in BMI between the groups evaluated (Table 1). It is understood, therefore, that the differences between the lipid and inflammatory profiles cannot be explained by the reduction of body mass caused by physical exercises.

However, studies suggest that weight improvement, which specifies the relationship between lean and fat mass caused by physical exercise, stimulates the use of lipids in energy production. The increase in lean body mass raises the basal metabolic rate, regardless of the reduction in the BMI[21], and triggers the consumption of fatty acids. This is due to stimulation of proteins located inside the mitochondrial membrane, called uncoupling proteins (UCP). Five UCPs are known so far, where UCP3, discovered in 1997[22], manifests itself mainly on the skeletal muscle. It increases the thermogenesis by stimulating the consumption of fatty acids[21].

When it comes to the ability of physical exercises reducing subclinical inflammation, the study of Panagiotakos et al.[23] examined 1,524 men and 1,518 women, observing that individuals who practice large-volume physical activities have 29.0% lower plasma levels of CRP than those individuals classified as sedentary in leisure time. The researchers came to such conclusion even after arranging the population under study by age, smoking habits, total cholesterol, glucose, systolic and diastolic blood pressure[23].

In agreement with these data, Viana et al.[24] published a randomized clinical testing that evaluated two groups of patients with coronary artery disease and associated cardiovascular risk factors. One group undertook a physical exercise program for three months associated with drug treatment; the other group underwent drug treatment only. CRP values were checked before the test and three months after it in both groups. The only significant difference was an increase in CRP levels in the group that did not undertake physical exercises. This result suggests that physical exercise can control blood vascular inflammation also in people with coronary artery disease[24].

The recent characterization of skeletal muscle as an endocrine organ that produces and secretes bioactive substances, including interleukin-6, seems to be the main mechanism stimulated by physical exercise, which inhibits subclinical inflammation[25]. Although known to be a pro-inflammatory molecule, when produced in the muscle, the interleukin-6 prevents the increase of TNF-α and interleukin-1β, unlike what occurs in inflammations[25]. Another known fact is that the transient increase of muscle interleukin-6 promotes, after exercise, the production of anti-inflammatory cytokines, such as interleukin-1 receptor antagonist, interleukin-10, and soluble TNF-α-receptors, thus contributing to the control and prevention of chronic diseases triggered by low-level inflammation[26].

However, the mechanism that best explains the results of this study possibly is the lipoprotein lipase action. The lipoprotein lipase is produced mainly in skeletal and heart striated muscles, and in the adipose tissue. It is responsible for the lysis of chylomicron-triglycerides and very low-density lipoproteins. Both aerobic[27,28] and anaerobic[29] exercise stimulate the production and activation of lipoprotein lipase in muscles and adipose tissue. This increases lipolysis in these tissues, which represent more than 50% of body mass, reducing plasma levels of chylomicrons and very low-density lipoproteins. As a result, LDL and PPL levels decrease. This lipid control cascade causes a decrease of subclinical inflammation, as fastening lipid levels[30] and PPL[31] are directly associated with vascular inflammation.

Extending the discussion on the action of lipoprotein lipase, the study showed that progestins, synthetic

hormones that mimic the effects of progesterone found in COC, promote decreased sensitivity to insulin[32]. This effect therefore promotes increased insulin production. The increased level of circulating insulin decreases the activity of lipoprotein lipase, reducing the uptake and usage of triglycerides by the muscle tissue[32]. Another known fact is that the decrease in insulin sensitivity triggers metabolic changes ranging from increased fasting triglycerides to increased vascular inflammation[33].

Unlike this physiological cascade, physical exercises promote increased sensitivity of muscle receptors to insulin, thus stimulating the decrease in insulin resistance, improving glucose influx into the muscle cell[34]. With the decreased insulin resistance, insulin production also goes down, increasing the production and activity of the protein lipase[32]. Thus, physical exercise can reverse the process that leads to increased triglycerides and fasting LDL, as well as increased PPL, in physically active women taking COC.

Kannt et al.[35] found that women with insulin resistance or type II diabetes have a higher expression of nicotinamide N-methyltransferase, protein expressed by the white adipose tissue, showing that this molecule not only can control the basal metabolic rate, but is also directly related to insulin resistance. In this study, however, it was observed that, after 12 weeks of aerobic exercising, women reduced both the expression of nicotinamide-N-methyltransferase and insulin resistance, a fact that proves that physical exercise can reduce the expression of this protein, hence increasing insulin sensitivity[35].

In light of this work and the results of this study, the hypothesis proposed is that physical exercise, by reducing insulin resistance, leads to decreased insulin production and the resulting increase in lipoprotein lipase action. This reverses the cascade caused by the use of COC, thus lowering triglycerides and fasting LDL, PPL and CRP in physically active women taking COC. No manuscripts on lipoprotein lipase in this population were found; therefore, future studies should seek to demonstrate this hypothesis, opening new perspectives to understand the effects of COC and physical exercise in this population.

In addition to the factors discussed herein, physical exercise promotes increased blood flow in active tissues, increasing the interaction between triglycerides and lipoprotein lipase; it also changes the hepatic fat metabolism by reducing blood triglyceride release and synthesis of very low density lipoproteins; and finally, it decreases the release of dietary lipids in the circulation, possibly due to a drop in bowel activity, which reduces the release of chylomicrons in the blood stream[36].

Limitations of this study: lack of control over eating habits and no stratification of oral contraceptives; lack of a method for directly assessing the functional capacity (cardiopulmonary test), specification and quantification of physical exercise undertaken by active women. Thus, we could not quantify the influence of these factors on the results.

Physically active women tend to have healthier living habits. Following a diet with the lowest consumption of saturated fats and alcohol decreases the risk of cardiovascular diseases. Studies have shown that these eating habits interfere directly both in lipid and inflammatory profiles by increasing or decreasing the risk of cardiovascular diseases[37]. Thus, it is paramount for future works to seek to better monitor the influences of these factors.

Conclusion

In this study, physically active women taking oral contraceptive presented fasting serum levels of triglyceride and low density lipoprotein, postprandial lipemia and CRP values significantly smaller than that of irregularly physically active women taking oral contraceptive. This suggests that regular physical activity reduces the risk of cardiovascular diseases in this population.

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Potential Conflicts of Interest
No relevant potential conflicts of interest.

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