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RESEARCH ARTICLE

IS THE USE OF COMBINED ORAL CONTRACEPTIVE ABLE TO CHANGE THE INSULIN SENSITIVITY?

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ABSTRACT

Introduction: Women using low-dose of combined oral contraceptive (COC) present fasting triglycerides, postprandial lipemia, and higher C-reactive protein. This condition seems to be related to the decrease in the action of the lipoprotein lipase enzyme due to decreased insulin sensitivity. ***Objective:*** To test whether there is a difference between the function of beta-pancreatic cells of women using or not COC and to verify the association between these indexes and the fasting lipid profile in this population. ***Methods:*** The sample was divided into two groups: COC group (COCG) composed of 22 women using low dose COC and without COC group (WCOCG). The correlation between the values of Homa-IR (HIR) and Homa-Beta (Hβ), which respectively evaluated insulin resistance and pancreatic beta cell function- were verified with all variables of the lipid profile - triglycerides, total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein (LDL). For the intergroup comparison of the parametric variables, we used the unpaired bidirectional Student t test and non-parametric variables the Mann-Whitney test. ***Results:*** Highest HIR (0.03%) and Hβ (< 0.01 #) were observed for COCG. There was a moderate and positive linear correlation between HIR and total cholesterol (r=0.34 and p=0.02) and Hβ with triglycerides (r=0.41 and p<0.01), TC (r=0.40 and p<0.01) and LDL (r=0.30 and p=0.04).

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INTRODUCTION

Recent studies have pointed out that women on combined oral contraceptive (COC) of low dosage have fast triglycerides, postprandial lipemia and C-reactive protein (CRP), higher than women who do not use this drug (Petto *et al.,* 2015; Josse *et al.,* 2012; Petto *et al.,* 2014). According to Petto *et al.* (2015) this is possibly due to the lower production and activity of the lipoprotein lipase enzyme responsible for cleaving the triglycerides molecules of the lipoproteins (chylomicrons and VLDLs) in the blood so that they are later absorbed by the muscles and used as a substrate for energy production. According to these authors, what triggers this mechanism is the decrease of the insulin sensitivity caused by the progestin's found in COCs. Decreased insulin sensitivity in muscle cells inhibits the production and action of lipoprotein lipase which consequently raises triglycerides and postprandial lipemia, which cause subclinical inflammation, characterized by elevation of CRP (Petto *et al.,* 2015; Petto *et al.,* 2014; Stern *et al.,* 2005). Although little discussed, there is difference between reduced insulin sensitivity or insulin resistance. Decreased insulin sensitivity occurs when insulin cell membrane receptors have difficulty recognizing insulin. This decrease in insulin sensitivity decreases the absorption of glucose by adipose and muscle cells. Increased circulating plasma glucose values stimulate β-pancreatic cells to produce more insulin in an attempt to correct glucose uptake, especially by muscle tissue. In these cases, it is observed that, although there is a decrease in insulin sensitivity, plasma levels of fasting and postprandial glucose levels are within limits considered normal. As for insulin resistance, the compensatory mechanism is not enough. It is then observed, abnormal glucose metabolism mainly evidenced by elevated postprandial glucose which can progress to Diabetes Mellitus Type II (DM2) (Stern *et al.,* 2005). One of the main ways to measure insulin sensitivity or resistance is through the HOMAIR (HIR) and HOMA-beta *cell* (Hβ) indices. These are indices calculated from fasting insulin and blood glucose dosages. Because of their reproducibility and high sensitivity and specificity (Stern *et al.,* 2005; Otten *et al.,* 2014), they are among the most commonly used markers in clinical practice to assess insulin sensitivity and beta-pancreatic cell function (Matsudo *et al.,* 2001). In the decrease of the insulin sensitivity it is noticed Hβ, thereby increasing the function of beta-pancreatic cells. In insulin resistance both HIR and Hβ are altered. In Josse's study *et al.* (2002) HIR and Hβ were

compared among women who used and did not use a hormone-based contraceptive. The authors found that the use of hormonal contraceptives causes elevation of Hβ but not HIR. However, in this study, the groups were composed of women using different hormonal contraceptives (oral, injectable and intrauterine contraceptives) and the presence of polycystic ovarian syndrome and Body Mass Index (BMI) was not used as exclusion criterion) (Josse *et al.,* 2002). Therefore, the present study was designed to test the hypothesis that there is a difference between the function of beta-pancreatic cells in women who use and do not use COC. This hypothesis will be tested by measuring the HIR and Hβ indices. We also intend to test the hypothesis that there is an association between these indices and the fasting lipid profile in this population.

METHODOLOGICAL ASPECTS

Sample: The research is described as a comparative observational cross-sectional study. The present study has as predictor variable the use of COC and as outcome variable the HIR and Hβ indices. The population consisted of 44 eutrophic women, irregularly active, aged between 19 and 30 years, nulliparous, with fasting triglycerides below 150mg/dL and fasting glycemia below 100mg/dL, who used and did not use COC. All the participants were students of Faculdade Social da Bahia, Salvador, BA - Brazil. The sample was divided into two groups: COC group (COCG) consisting of 2 2 women using low dose COC of ethinylestradiol (15-30 mcg) for at least one year; and Without COC group (WCOCG), consisting of 22 women who had not used any type of hormone-based contraceptive for at least one year. To determine if participants were irregularly active, the International Physical Activity Questionnaire - a long version, developed by the World Health Organization and the North American Center for Disease Control and Prevention (Matsudo *et al.,* 2001). Women were excluded if they reported family dyslipidemia, hypo- or hyperthyroidism, history of alcoholism or smoking, polycystic ovary syndrome, be in hypo- or fat diet, make use of dietary supplements or anabolic, and star in in use of lipid - lowering drugs, steroids, diuretics or beta-blockers. Excluded also women who had reviewed the physical systemic blood pressure (BP) values of 140/90mm Hg, waist circumference ≥ 80cm or changes in laboratory test pyruvic glutamic transaminase (PGT), oxidative (PGO) and creatinine. PGT and PGO were evaluated in order to identify pancreatic and hepatic diseases and creatinine to identify the presence of renal dysfunction. All the participants answered the semi-structured questionnaire, elaborated by the authors of the research, and underwent a physical examination. Physical examination consisted of resting BP, total body mass, height and waist circumference.

The Body Mass Index (BMI) was calculated with mass and height measurements, according to the Quetelet equation: BMI = mass (kg)/height ^{2} (cm). The BMI cutoff points adopted were those recommended by the IV Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis Department of Atherosclerosis of the Brazilian Society of Cardiology (Sposito *et al.,* 2007), that is, low weight (BMI < 18.5); normal weight (BMI 18.5-24.9); overweight (BMI 25-29.9) and obesity (BMI ≥ 30). The abdominal circumference was obtained with metric and inelastic tape, brand Starrett ®, with definition of measurement of 0,1cm. It was measured in the lowest curvature located between the last rib and the iliac crest without compressing the tissues and adopting as reference the values recommended by the Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis Department of Atherosclerosis of the Brazilian Society of Cardiology (Xavier *et al.,* 2013).

Laboratory Data Collection Protocol: All participants were referred to the Laboratory of Clinical Pathology in the city of Salvador, BA - Brazil, to perform blood collections. After puncturing the antecubital vein were collected 10 ml of blood for determination of triglycerides, high density lipoprotein (HDL) cholesterol, total cholesterol, insulin, blood glucose and transaminase and glutamic pyruvic oxidative s. Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated by the Friedewald equation (Friedewald *et al.,* 2019).The samples were collected with the volunteers fasting for 12 hours. They were instructed not to modify their diet during the week of the test, not to perform any physical exertion other than usual and not to drink alcoholic drinks 24 hours before the laboratory examination. The blood was collected by a trained professional and in a laboratory environment appropriate for this type of procedure. The values of triglycerides, HDL, total cholesterol and glycemia were obtained by the enzymatic colorimetric method of Trinder (Casella *et al.,* 2005). PGT and PGO were measured by the Reitman-Frankel colorimetric method (Friedewald *et al.,* 2019). The HIR and Hβ respectively to evaluate the insulin resistance and the function of pancreatic beta cells, they were calculated by equations Matheus (9): HIR = fasting glycemia x 0.0555 x fasting insulin / 22.5 and Hβ = (20 x fasting insulin) / (fasting blood glucose x 0.0555) - 3.5. The sample calculation was performed in the program Graph Pad Stat Mate 2.0 for Windows. Adopted 5% alpha and 80% beta and considering as significant a 20% difference between the values of H β between the groups, 36 women were needed, that is, 18 for each group.

Statistic: Initially, to verify the distribution of the data, symmetry and kurtosis tests and the Shapiro- Wilk test was applied. The values of the variables with normal behavior were described in mean and standard deviation and the values of the non-parametric variables, in median and interquartile range. For the intergroup comparison of the parametric variables, we used the unpaired bidirectional Student t test and the non-parametric variables the Mann-Whitney test. The correlation between values of HIR and Hβ with all the variables of the lipid profile - triglycerides, total cholesterol, HDL and LDL. To verify the association between the HIR and Hβ and the variables of the lipid profile, the *Sperman* correlation coefficient was used. Variables that presented the statistical significance of correlation with HIR (total cholesterol) and Hβ (triglycerides, total cholesterol and LDL) were included in the logistic regression model, along with the use of COC. The cut-off point used in the logistic regression for the HIR was 1.2 and for the Hβ was 167. These points were adopted by the characteristics of the sample as recommended by Ghiringhello *et al.* (2006). The calibration of the model was tested by the *Homer and Lemershow* test and the calibration was calibrated (p = 0.07). All analyzes were performed in the statistical package SPSS version 13.0, adopting a significance level of 5%.

Ethical aspects: Throughout the study the guidelines on human research in the Declaration of Helsinki and Resolution

466/12 of the National Health Council were observed. This study was submitted and approved by the Research Ethics Committee of the Faculdadede Ciências e Tecnologia de Salvador - BA under number 3390/2010. All participants received detailed information about the study objectives, risks and benefits involved in the procedures and signed the informed consent form. Two routes were completed, one being in the possession of the participant and the other in the researcher's possession.

RESULTS

Table 1 shows the clinical and anthropometric characteristics of the sample. Note the uniformity among the groups and highlights the difference between systolic BP (p <0.02), which is the greater the COCG. To compare the lipid parameters of fasting and the TG / HDL (Table 2) it is clear that the COCG shows plasma triglyceride levels (P <0.01), total cholesterol (p = 0,02), VLDL (p < 0 01) and the TG / HDL (p <0.01) greater than the G SCO C.

In Table 3, there is shown the comparison between the values of fasting glucose (p = 0.50), fasting insulin (p = 0.01), HIR (p = 0.03) and Hβ (p < 0.01) between COCG and WCOCG. It is noteworthy that although the glycemia was equal between the groups, the COCG presented higher insulin, HIR and Hß values. The same is shown in Figures 1, 2 and 3.

Table 4 exhibited the correlation analysis between Hβ and HIR and the variables of the fasting lipid profile. Positive and moderate linear correlation was observed between HIR and total cholesterol (r = 0.34 and p = 0.02). In the HSS correlation analysis we found the correlation linear with moderate positive and triglycerides (r = 0.41 and p <0.01), with total cholesterol (r = 0.40 and p <0.01) and with LDL (r = 0.30 and p = 0.04). However, as seen in Table 5 when the multivariate linear association analysis was performed, it was verified significance of independent association only between the use of COC and Hß with an odds ratio of 8.15 for a confidence interval of (1.02 - 64.94) with p <0.01.

Table 1. Clinical and anthropometric characteristics of women using and not using combined oral contraceptives (n=44)

Variables	WCOCG (n = 22)	COCG (n = 22)	p-value
Age (years)	23 ± 3.1	23 ± 3.4	0.98
Body Mass Index (kg/m^2)	20 ± 2.1	19 ± 2.8	0.07
Waist Circumference (cm)	73 ± 7.8	70 ± 5.9	0.32
Systolic Blood Pressure (mmHg)	118 ± 8.8	111 ± 9.7	0.02*
DiastolicBloodPressure (mmHg)	77 (74 – 80)	70 (70 – 80)	0.18
PyruvicGlutamicTransaminase (U/L)	15 ± 4.2	14 ± 3.4	0.16
Time of use of COC (anos)	3,7 ± 2.3		-

COCG - Combined Oral Contraceptive Group; WCOCG - Without Combined oral contraceptive Group; COC - Combined Oral Contraceptive. * Two-way Student's t test for independent samples; # Bi-directional Mann-Whitney Test.

Table 2. Comparison of fasting lipids (mg/dL) between the groups studied

Variables	WCOCG (n = 22)	COCG (n =22)	p-value
Triglycerides (mg/dL)	88 (72 – 111)	49 (40 – 64)	< 0.01#
Total Cholesterol (mg/dL)	207 ± 38.2	183 ± 29.7	0.02*
HDL (mg/dL)	54 ± 13.0	48 ± 11.2	0.10
LDL (mg/dL)	134 ± 36.4	125 ± 27.2	0.34
VLDL (mg/dL)	18 (14 – 22)	10 (8 – 13)	< 0.01#
Ratio TG/HDL	1.1±0.5	1,7±0.5	< 0.01*

COCG - Combined Oral Contraceptive Group; WCOCG - Without Combined oral contraceptive Group; HDL - High Density Lipoprotein; LDL - Low Density Lipoprotein; VLDL - Very Low Density Lipoprotein. * Two-way Student's t test for independent samples; # Bi-directional Mann-Whitney Test.

Table 3. Comparison of HOMA-IR E HOMA-beta (n=44)

Variables	WCOCG (n = 22)	COCG (n =22)	p-value
Glicemia (mg/dL)	83 ± 5.7	82 ± 7.1	0.50
Insulina (uM/L)	6 (5 – 7)	8 (6 – 12)	0.01#
HOMA-IR	1,2 (0.9 – 1.5)	1.6 (1.1 – 2.5)	0.03#
HOMA-beta	101 (86 – 132)	207 (116 – 241)	< 0.01#

COCG - Combined Oral Contraceptive Group; WCOCG - Without Combined oral contraceptive Group; #Two-way Mann-Whitney test.

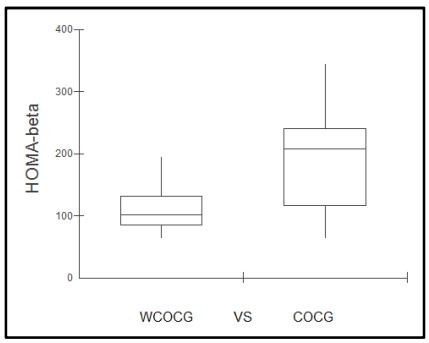

Figure 1.Medians and HOMA-beta quartiles of the groups studied.

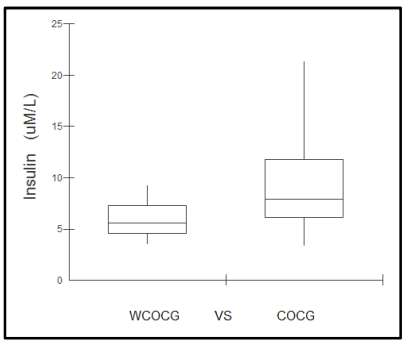

Figure 2.Medians and Insulin quartiles of the groups studied.

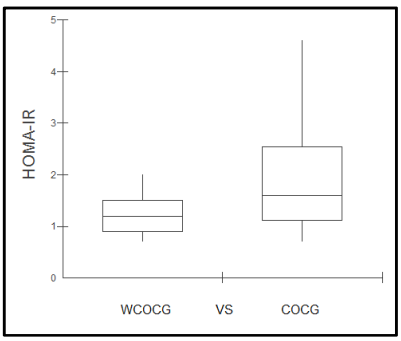

Figure 3.Medium and Intervals quarters of the HOMA-beta of the studied groups.

Table 4. Correlation between the variables of the lipid profile and the HOMA-IR and HOMA-beta indices

Crossings	CorrelationStrength	p-value
HIR vs TG	0.24	0.11
HIR vsTC	0.34	0.02*
HIR vs HDL	0.07	0.65
HIR vs LDL	0.25	0.10
HIR vsCRP	0.04	0.79
Hßvs TG	0.41	< 0.01*
HßvsTC	0.40	< 0.01*
Hßvs HDL	0.07	0.66
Hßvs LDL	0.30	0.04*
Hßvs PCR	0.24	0.11

TC - Total Cholesterol; HDL - High Density Lipoprotein; LDL - Low Density Lipoprotein; Hβ-HOMA-beta; HIR-HOMA-IR; TG - Triglycerides. * Spearman Correlation Test.

Table 5. Results of HOMA-IR and HOMA-beta multivariate linear regression

Crossings	*OR*	IC	p-value
HIR vs CT	1.00	0.96 – 66.87	0.63
HIR vs COC	1.00	0.94 - 1.05	0.85
HB vs TG	1.01	0.97 - 1.05	0.56
HB vs CT	1.00	0.95 - 1.04	0.74
HB vs LDL	1.00	0.95 - 1.05	0.32
HB vs COC	8.15	1.02 - 64.94	< 0.01*

TC - Total Cholesterol; HDL - High density lipoprotein; Hβ-HOMA-beta; HIR-HOMA-IR; CI–Confidence interval; LDL - Low density lipoprotein; OR - Odds Ration; TG - Triglycerides. * Independent Association Test by Multivariate Linear Regression.

DISCUSSION

In this study, we aimed to test the hypothesis that there is a difference in the Hß values of women who use and do not use COCs. In addition, we also verified if there is a correlation between the HIR and Hβ indices and the fasting lipid profile in this population. Although it is not possible, due to the study design, to establish a causal relationship, the results indicate that women who use COC present decreased insulin sensitivity compensated with increased beta-pancreatic cell activity. This was confirmed by linear regression, identifying an independent association between Hβ and COC use, with an eightfold increase in COC women. The results are reinforced by the characteristics of the sample. Although not selected in a probabilistic way, factors that could directly interfere in the results such as overweight and obesity, smoking, age, metabolic diseases and drugs were excluded in the group's formation. It was not possible to define only one type of COC (formulation and label), such as controlling the diet of the volunteers, but even so, the sample was constituted in a characteristically homogeneous way. Since the 70's, studies show that progestins influence on lipid metabolism and induce hyperinsulinemia, as well as in studies in 2003 Diamanti *et al.* (2003) a review paper that also raised the hypothesis that the use of COC could aggravate insulin resistance and exert other undesirable metabolic actions in women with polycystic ovary syndrome. Possibly the use of COC could increase the long-term risk of developing DM2 and cardiovascular disease (Diamanti *et al.,* 2003), since it is known that insulin resistance is considered an independent risk factor for ischemic heart disease (Diamanti *et al.,* 2003). At the time, the authors said that the challenge was to critically explore the immediate and long-term metabolic effects of COCs so that physicians could treat polycystic ovary syndrome safer (Després *et al.,* 1996). However, these authors did not describe the pathophysiological mechanism that causes the decrease of insulin sensitivity in this population. According Beck (1977) progestins, synthetic hormones that mimic the effects of progesterone promote decreased insulin sensitivity. In an attempt to decrease the dosages of ethinylestradiol in oral contraceptives, new formulas were created by introducing into their compositions of progestins such as gestodene and levonorgestrel (Giribela *et al.,* 2007). These new formulations gave rise to the third and fourth generation low-dose pills currently being marketed, called COCs.

The decrease in insulin sensitivity causes an increase in blood glucose. In an attempt to compensate for this increase, beta-pancreatic cells increase their action by producing larger amounts of insulin. In order to verify the decrease in insulin sensitivity, it is necessary to observe the values of IR and Hβ. Since insulin receptors are less sensitive, plasma glucose levels remain higher, which results in positive β-pancreatic cell feedback, releasing larger doses of insulin into the bloodstream to correct circulating glucose values. Soon, the HIR this ha within normal range, but the Hβ will be increased. This is due to the fact that insulin sensitivity is reduced by some authors, since it is not characterized as insulin resistance since HIR values are within normal values (Quintão *et al.,* 2011). In this study, the same was observed. Although both HIR values as those of women in use Hβ COC were higher than those from the group of women without COC only Hβ values will COC group is above normal values. This corroborates the idea that these women have decreased sensitivity of the insulin receptors, which cause an increase in the activity of beta-pancreatic cells.

In the continuity of this pathophysiological cascade, the decrease in insulin sensitivity causes a decrease in lipoprotein lipase activity and a consequent decrease in the uptake and use of triglycerides by muscle tissue (Chapman and Sposito, 2007). This raises the amount of plasma triglycerides and consequently of circulating VLDL and LDL and postprandial lipemia (Lin *et al.,* 2008). Both the increase in circulating insulin and lipids promotes endothelial dysfunction and inflammation in healthy individuals (Orio *et al.,* 2005; Kadowaki *et al.,* 2005; Arcaro *et al.,* 2002). Steinberg *et al.* in 1996 have already shown that normoglycemic obese patients with insulin resistance (IR) present endothelial dysfunction similar to DM2 compared to lean control. Insulin resistance causes endothelial dysfunction through the induction of disturbances in the activation of the phosphatidylinositol 3-kinase pathway, which regulates the expression of nitric oxide in endothelial cells, in addition to increasing oxidative stress, endothelin-1 (ET-1), the activity of the renin-angiotensin system, aggravating the vascular relaxation dependent on the endothelium (Orio *et al.,* 2005; Kadowaki *et al.,* 2000; Kuboki *et al.,* 2000; Galvão *et al.,* 2012). This, again corroborates with data from the literature. In another study by Petto *et al.* (2015) it was found that women taking COC had higher plasma renin levels than women who did not use COC. Conversely endothelial dysfunction may increase insulin resistance, reducing blood flow in the tissue caused by an imbalance between the nitrous oxide and (Kim *et al.,* 2006) ET -1 expression. In addition associated alteration of endothelium-dependent vasodilation, insulin resistance contributes to a decrease inarterial compliance, and both changes contribute to the development of arterial hypertension (Kelly *et al.,* 2002). It is emphasized that the increase in triglycerides, total cholesterol and TG / HDL ratio in the COCG, is not associated with a decrease in insulin sensitivity. Only the use of COC is that in the multivariate analysis it remained as an independent

predictor .Ratifying, that the progestins possibly are the key that triggers the whole cascade of insulin sensitivity decrease that consequently causes changes in lipid metabolism (decreased lipolysis) and a consequent increase in subclinical inflation, as observed in other studies (Santos *et al.,* 2016). CRP is an inflammatory marker found to be elevated in people with insulin resistance and DM2. It is also a possible cause of endothelial dysfunction (Pickup, 2004). It is observed in individuals with insulin resistance increased production byadipocytes cytokines as the adiponectin, leptin, resistin, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Possibly not only the insulin resistance but also the decrease in the insulin sensitivity caused by the use of COCs is the link between the proinflammatory state which, associated with altered lipid metabolism may increase the risk of cardiovascular diseases in women who use COC3,28. Therefore, monitoring of the insulin, HIR and Hβ values of this population should be performed before and during COC administration, especially in women who have other risk factors such as obesity, sedentarism and polycystic ovary.

Conclusion

According to the results obtained in the present study, women who use COC present Hβ and HIR above that of women who do not use COC. Also, women in COC useHβ above normal values, which characterize decreased insulin sensitivity. This may be the beginning of the different metabolic disorders, especially lipid, found s in this population.

Abbreviations

BP	Blood Pressure
BMI	Body Mass Index
COC	Combined Oral Contraceptive
CRP	C-Reactive Protein
DM II	Diabetes Mellitus Type Ii
HDL	High Density Lipoprotein
Hβ	HOMA-BETA *CELL*
HIR	HOMA-IR
LDL	Low Density Lipoprotein
PGO	Pyruvic Glutamic Oxidative
PGT	Pyruvic Glutamic Transaminase
TG	Triglycerides
TNF-α	Tumor Necrosis Factor-A

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