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USE OF ORAL CONTRACEPTIVE DECREASE ADIPONECTIN PLASMA LEVELS?

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ABSTRACT

Adiponectin (APN) is the most abundant polypeptide produced by adipose tissue in humans. It has an important anti-atherogenic role, suppresses the expression of proinflammatory substances and increases the production of nitric oxide, protecting against most diseases related to the inflammatory process, such as atherosclerosis. On the other hand, observational studies indicate that the use of low-dose combined oral contraceptives (COC) is associated with increased subclinical inflammation. Based on the above, it is plausible to think that there is also an association between COC use and decreased APN levels. Objective: To test the hypothesis that oral contraception has an influence on plasma APN levels in women using low-dose COC. Method: Included 44 eutrophic women, aged 19-30 years, irregularly active for at least one year, with fasting triglycerides ≤150mg/dL and using or not COC (ethinyl estradiol between 15-30mcg) for at least one year. The population was stratified into two groups: COCG (22), made up of women using COC and GWCOC (22), made up of women who did not use COC. After 5 hours of fasting, 5 ml of blood were collected for the measurement of APN, C-Reactive Protein (CRP), blood glucose, cholesterol and triglycerides. APN was measured by the plasma radioimmunoassay method. Results: To verify the distribution of data, symmetry and kurtosis tests and the Shapiro-Wilk test were applied. For intergroup comparison of APN values, the two-way Student t-test for independent samples was used. Correlation analyzes between APN and lipid profile values were performed using Pearson's test and CRP by Sperman's test, adopting a significance level of 5%. APN values respectively for COCG and GWCOC were 7.6 ± 1.5 vs 6.0 ± 2.4 ($p = 0.37$). No significant correlations were observed between APN and lipid profile or CRP. Conclusion: The use of low dose combined oral contraceptive does not cause changes in APN plasma values in eutrophic women.

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INTRODUCTION

Adiponectin (APN) is the most abundant polypeptide produced by adipose tissue in humans and there is strong evidence that it is also produced by cadiomyocytes and skeletal striated muscle (Silva, 2012 and Junqueira, 2009).

Opposing other cytokines secreted by adipocytes, APN has decreased expression as adipose tissue undergoes hypertrophy or hyperplasia. Studies also indicate that it is less abundant in individuals with cardiovascular diseases, type II diabetes, systemic arterial hypertension, insulin resistance (IR) or stroke (Raitakari, 2005;Santos, 2016; Petto, 2013 and Nazmi, 2008).

It has an important anti-atherogenic role demonstrating the ability to inhibit monocyte adhesion to vascular endothelium and the transformation of macrophages into foam cells (Nazmi, 2008).

APN also suppresses the expression of proinflammatory substances such as tumor necrosis factor alpha (TNF-α), a C-reactive protein (CRP), interleukin-6 (IL-6), and increases

nitric oxide production, protecting against most disease-related diseases. inflammatory process (Raitakari, 2005; Josse, 2012; Petto, 2015).

On the other hand, observational studies indicate that the use of low-dose combined oral contraceptives (COC) is associated with increased subclinical inflammation, increased risk of venous thrombosis and cardiovascular disease (Santos, 2016 and Petto, 2013). The process of vascular inflammation is still difficult to measure directly. CRP is the most studied indirect inflammatory biomarker and considered the most sensitive in the prognosis of cardiovascular diseases (Petto, 2013 and Nazmi, 2008).

Given the above, it is plausible to think that there is also an association between COC use and decreased APN levels. However, few studies have tried to test this hypothesis. In the study by Josse et al, no difference was observed between the COC group APN and the group of women who did not use COC (Josse, 2012). However, the study population was composed of characteristics that are known to interfere with APN values, especially overweight and obesity. In addition, women using both oral and injectable contraceptives and patches were included in the study.

Considering that APN has anti-inflammatory characteristics and that women using COC have higher elevation of subclinical inflammation, this study aims to test the hypothesis that eutrophic and irregularly active young women using COC present different plasma APN values than women that don't use it.

MATERIALS AND METHODS

The method described here has already been used in other studies previously developed by our group (Petto 2013). Cross-sectional study, where the studied population was composed in a probabilistic (simple random) manner by students of the Physiotherapy course of the Social College of Bahia, Salvador, BA - Brazil.All students were informed about the study and had the same chances to participate in the work. The population was stratified into two groups: group 1 (COCG), consisting of women who were irregularly active on low-dose oral contraceptives; and group 2 (GWCOC) formed by irregularly active women who do not use low dose oral contraceptives.

To calculate the sample sufficiency, an alpha = 0.05 (bidirectional) and a beta = 0.80 were considered, adopting a significant difference of 20% between the groups. Considering that the coefficient of laboratory variation of APN dosage is 3.1%, CRP and triglycerides is 5% and that a difference four times greater than expected nullifies the bias of this coefficient, then 44 volunteers were necessary, that is, 22 volunteers in each group. The sample calculation was performed in GraphPad Stat Mate 2.0 for Windows.

This study followed the guidelines on research with human beings of the Declaration of Helsinki and Resolution CNS 466/12. This study was submitted and approved by the Research Ethics Committee of the FaculdadeNobrede Santana, under CAAE No. 79549517.3.0000.5654 and all participants signed the Informed Consent Form.

Inclusion criteria: Eutrophic women, aged 19-30 years, irregularly active for at least one year, with fasting triglycerides ≤150mg/dL and using a low-dose combined oral contraceptive (ethinyl estradiol 15-30mcg) for at least one year.

Exclusion Criteria: Diabetic, dyslipidemic women undergoing drug treatment, with kidney disease, with polycystic ovary syndrome, with a history of alcoholism or smoking, on a hypo or hypercaloric diet, with CRP> 10mg/dL and using corticosteroids, diuretics or beta blockers.

Data collect: The International Physical Activity Questionnaire (long version), developed by the World Health Organization and the US Centers for Disease Control and Prevention, was chosen to determine the degree of physical activity of volunteers. It allows to classify the individual in a specific way (sedentary, irregularly active, active and very active), minimizing the classification bias. In addition, it allows a greater chance of comparisons with other studies, as it has worldwide application and has been validated in Brazil (US, 1996 and Matsudo, 2001).

The selected volunteers answered the questionnaire and underwent physical examination, both with the function of collecting clinical and sociodemographic information. Physical examination included measurements of resting blood pressure, total body mass, height and waist circumference. The eating habits of the volunteers were not evaluated.

Waist circumference was obtained with Starrett metallic and inelastic tape measure (São Paulo, SP - Brazil) with a definition of 0.1cm, measured at the smallest curvature located between the last rib and the iliac crest without compressing the tissues (WHO, 2000). Body mass index (BMI) was calculated according to the Quetelet equation: BMI = mass (kg) / height^2(m).

The cutoff points adopted were those recommended by the IV Brazilian Guideline on dyslipidemia and prevention of atherosclerosis of the Atherosclerosis Department of the Brazilian Society of Cardiology(SociedadeBrasileira de Cardiologia, 2010), that is, low weight (BMI <18.5kg/m^2); eutrophy (BMI ≥18.5kg/m^2- <24.9kg/m^2); overweight (BMI ≥25kg/m^2 - <29.9kg/m^2) and obesity (BMI ≥30kg/m^2).

Laboratory collection procedure

Five mL of blood were collected after a 12-hour fasting for APN, CRP, total cholesterol, and triglyceride fractions. All collections were performed by a qualified professional and in his own laboratory environment.

The volunteers were instructed not to change their diet during the week of the test and not to exercise any physical effort different of usual, as well as not to drink alcohol in the 24 hours prior to the laboratory collection.

APN levels were obtained by the competitive assay for quantitative APN Human ELISA Kit (ADIPOQ Human ELISA Kit, 2010). CRP was measured by the plasma serum turbidimetry method.

The triglycerides, total cholesterol and high density lipoprotein values were obtained by the Trinder (Casella, 2003)

colorimetric enzymatic method. The values of low density and very low density lipoprotein were calculated by Friedewald's equation (Friedewald, 1972).

Statistical analysis: To verify the distribution of the data were applied symmetry and kurtosis tests and the Shapiro-Wilk test. The APN and CRP, values were nonparametric and weredescribed as medians and interquartile ranges. For intergroup comparison of APN and CRP values, the bidirectional Mann-Whitney test wasused to compare the medians.

The other fasting variables presented parametric distribution being described as means and standard deviations and for their comparison the two-way unpaired Student's t-test was applied.All analyzes were performed using the SPSS (Statistical Package for Social Sciences) version 13.0 program, adopting a significance level of 5%.

RESULTS

Forty-four women were equally divided between two groups. Table 1 presents the clinical data and anthropometric characteristics of the sample. It is observed that the groups were homogeneous, with no differences in age, BMI, waist circumference.

Table 1. Clinical and anthropometric characteristics of women who use and do not use combined oral contraceptive (n = 44)

Variables	GWCOC (n = 22)	COCG (n = 22)	p Value*
Age (years)	23 ± 1.9	22 ± 2.0	0.90
Body mass index (kg/m^2)	21 ± 2.5	20 ± 2.1	0.12
Waistcircumference (cm)	72 ± 5.9	73 ± 7.6	0.31
COC use time (years)	-	4.2 ± 2.6	-

* Bidirectional Student t test for independent samples; GWCOC: group without combined oral contraceptive; COCG: combined oral contraceptive group.

Table 2 describes the comparison of lipid profile and CRP of the intragroup sample. It can be observed that the values of the triglycerides, total cholesterol and CRP variables were significant showing an unfavorable lipid and inflammatory profile.

Table 2. Comparison of lipid profile, C-Reactive Protein, and Adiponectin values (n = 44)

Variables	GWCOC (n=22)	COCG (n=22)	pValue*
Triglycerides (mg/dL)	48 (44 – 64)	92 (76 – 111)	< 0.01$^{\#}$
Total Cholesterol (mg/dL)	188 ± 29.7	210 ± 32.2	0.02*
HDL (mg/dL)	50 ± 11.2	54 ± 13.0	0.10
LDL (mg/dL)	131 ± 24,2	138 ± 38.2	0.34
C-Reactive Protein (mg/L)	1.0 (0.5 – 1.1)	2.3 (1.9 – 5.8)	< 0.01$^{\#}$
Adiponectin (µg/dL)	7.6 ± 1.5	6.0 ± 2.4	0.37

GWCOC: group without combined oral contraceptive;COCG: combined oral contraceptive group.
* Bidirectional Student t test for independent samples; # Bidirectional Mann-Whitney test.

Table 3 shows the individual correlations of CRP and lipid profile variables with APN. The variables did not present significant correlations.

Table 3. Correlations between APN and lipid profile variables and CRP. (n = 44)

Crossings	Correlation Force	p Value*
CRPvs APN	0.28	0.46
TPG vs APN	0.34	0.37
LDL vs APN	0.10	0.10
HDL vs APN	0.25	0.78
CT vs APN	0.04	0.88

TC - total cholesterol; HDL - High Density Lipoprotein; HB - HOMA-beta; HIR - HOMA-IR; LDL - Low Density Lipoprotein; CRP - C-Reactive Protein; TG - triglycerides. * Spearman correlation test.

DISCUSSION

Although studies indicate metabolic changes resulting from the use of COC, such as elevation of total cholesterol (TC), triglyceride (TG) levels, as well as alteration of high CRP values, increasing risk factors for cardiovascular diseases, unlike what we thought, they were not Significant results were found between the use of COC and the decrease in plasma APN levels (Ouchi, 1999). Several factors may be related to this clinical finding.

Tilgand Moschen(Tilg and Moschen, 2006), describes in his review that more than fifty products derived from adipocytes have already been cataloged. Unlike most of the proteins secreted by adipose tissue cells, the APN concentration decreases as the adipose tissue increases and its plasma concentration is reduced in obese or insulin-resistant rodents and individuals. Bearing in mind that obesity is considered an inflammatory disease and physical exercise directly modulates these processes, it is essential that one of the main objectives in rehabilitation programs is physical exercises to improve the inflammatory response of obese people.

Due to the concentrations of androgens that inhibit APN, females have 40% more adiponectinemia than males, which represents a cardioprotective factor for women (Nishizawa, 2002). APN also increases insulin sensitivity and inhibits vascular inflammation, including the ability to stimulate beta-oxidation of fatty acids in skeletal muscle. Anti-atherogenic effects have also been observed. In this sense, circulating APN appears to protect the vascular endothelium against most of the processes involved in the etiopathogenesis of atherosclerosis (Funahashi, 2004).

For there to be a decrease in the levels of APN, there must be an increase in the production of other adipokines. This increase is triggered by an inflammatory process generated by the hypertrophy of adipose tissue and is ultimately characterized by obesity (Gregor, 2011). The expansion of adipose tissue occurs through adipocyte hyperplasia, hypertrophy or a combination of both, and the hypertrophy and hyperplasia of the tissue in question are directly related to the development of disorders resulting from overweight. Hyperplasia is nothing more than an increase in the number of cells, unlike hypertrophy, which is an increase in cell size. It is important to note that the hypertrophied adipocyte has a limited capacity for growth, and when this limit is reached, cracks in the cell walls appear favoring the production and release of pro-inflammatory cytokines, while considerably decreasing the ability to produce APN (anti-inflammatory), secreted largely by young cells (Lessard, 2014).

Hypertrophy or hyperplasia of adipocytes in adipose tissue also causes a reduction in blood flow with consequent hypoxia and infiltration of macrophages, which amplifies the inflammatory cascade. The cytokines produced by macrophages (such as TNFα, IL-6) inhibit adipogenesis, feeding back inflammation. Among these, TNF-α is highlighted for cyclically stimulating the secretion of other cytokines and chemokines, in addition to directly activating the kappa transcription factor B (NF-kB), which further compromises glucose uptake, promotes IR and maintains chronic hyperglycemia (Lessard, 2014).

In an attempt to resume homeostasis, glucose inflows into cells that are not dependent on glucose transporter (GLUT)-4 and, therefore, not dependent on insulin, such as kidney cells, which have types GLUT-1 and GLUT-2, unable to regulate the entry of glucose into cells, which induces intracellular glycotoxicity (Volp, 2008).The location of this fat will also be important with regard to its behavior, since it is possible to observe that the metabolic profile of intra-abdominal fat differs from peripheral subcutaneous adipose tissue, the former being, among other factors, more subject to lipolysis and also presenting lower expression of Insulin receptor substrate 1 (IRS-1) (Volp, 2008).

It is clear that women participating in the COCG have unfavorable lipid and inflammatory profiles; this second, appearing more significantly. However, we face the limitation of not having other inflammation markers that would bring more specificity to the work. However, with the APN values within the normal range, the question arises about the real impact of this adipokine in delaying negative morphological changes in adipose tissue.

Conclusion

The present study suggests that the use of low dose combined oral contraceptive does not cause changes in adiponectin plasma values in young and eutrophic women.

REFERENCES

Silva D, Lacerda AP. Proteína C reativa de alta sensibilidade como biomarcador de risco na doença coronária. RevPortCardiol. 2012;31(11):733-745. doi: 10.1016/j.repc.2012.02.018

Junqueira ASM, Filho LJMR, Junqueira CLC. Evaluation of the Degree of Vascular Inflammation in Patients with Metabolic Syndrome. *Arq.Bras.Cardiol*. 2009;93(4):360-6. doi: 10.1590/S0066-782X2009001000008

Raitakari M, Mansikkaniemi K, Marniemi J, Viikari JSA, Raitakari OT. Distribution and determinants of serum high-sensitive C-reactive protein in a population of young adults.The Cardiovascular Risk in Young Finns Study.J. Intern. Med. 2005;258:428-434. doi: 10.1111/j.1365-2796.2005.01563.x

Santos ACN, Petto J, Oliveira FTO, Diogo DP, Ladeia ANM. C-Reactive Protein in Oral Contraceptive Users: Related Factors and Cardiovascular Risk. Int J CardiovascSci. 2016;29(4):320-325. doi: 10.5935/2359-4802.20160051

Petto J, Pereira LS, Santos ACN, Giesta BA, Melo TA, Ladeia AMT. Inflamação Subclínica em Mulheres que Utilizam Contraceptivo Oral. RevBrasCardiol. 2013;26(6):465-71.

Nazmi A, Oliveira IO, Victora CG. Correlates of C-reactive protein levels in young adults: a population-based cohort study of 3827 subjects in Brazil.Braz J Med Biol Res. 2008;(5):357-67.doi: 10.1590/S0100-879X2008000500003

Josse AR, Garcia-Bailo B, Fischer K, El-Sohemy A. Novel Effects of Hormonal Contraceptive Use on the Plasma Proteome.PLoS ONE. 2012;7(9):e45162. doi:10.1371/journal.pone.0045162.

Petto J, Silveira DW, Santos ACN, Seixas CR, Espirito Santo DGC, Oliveira FTO, Luz CS, Ladeia AMT. Lipemia Pós-Prandial e Inflamação Subclínica em Mulheres Ativas que Utilizam Contraceptivo Oral. Int J Cardiovasc Sci. 2015; 28(3).doi: 10.5935/2359-4802.20150031

US Department of Health and Human Services.Centers for Disease Control and Prevention.National Center for Chronic Disease Prevention and Health Promotion.Division of Nutrition and Physical Activity.[Internet]. Physical activity and health: a report of the Surgeon General. Executive Summary. 1996. [cited 2014 Dec 20]. Available from: http://www.cdc.gov/nccdphp/sgr/summary.htm

Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al. Questionário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Rev Bras AtivFísSaúde. 2001;6(2):5-18.

World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation.World Health Organ Tech Rep Ser. 2000;894:i-xii,1-253.

Sociedade Brasileira de Cardiologia; Sociedade Brasileira de Hipertensão; Sociedade Brasileira de Nefrologia. VI Diretrizes brasileiras de hipertensão. ArqBrasCardiol. 2010;95(supl.1):1-51. Erratum in: ArqBrasCardiol. 2010;95(4):553.

ADIPOQ Human ELISA Kit. Abnova. 96 (7) KA0016: 3-20. Disponível em: http://www.abnova.com/protocol_pdf/KA0016.pdf)

Casella M. Home monitoring of blood glucose by owners of diabetic cats and dogs: technical problems and evaluation of differences between home and hospital blood glucose curves. [Doctoral Thesis in Veterinary Sciences]. Zurich: University of Zurich; 2003.

Friedewald WT, Levy RI, Fredrickson DS.Estimation of the concentration of low-density lipoproteincholesterol in plasma, without use of the preparative ultracentrifuge.Clin Chem. 1972;18(6):499-502.

Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation. 1999;100(25):2473-6. doi: 10.1161/01.cir.100.25.2473

Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat RevImmunol, 2006;6(10):772-83. doi: 10.1038/nri1937

Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocity-

derived protein. Diabetes, 2002;51:2734-41. doi: 10.2337/diabetes.51.9.2734

Funahashi T, Matsuzawa Y, Kihara S. Adiponectin as a potential key player in metabolic syndrome Insights into atherosclerosis, diabetes and cancer.Int Congress Series. 2004; 1262:368-71. doi:10.1016/j.ics.2004.01.091

Gregor MF, Hotamisligil GS.Inflammatory Mechanisms in Obesity.Annu Rev Immunol. 2011;29:415-45. doi: 10.1146/annurev-immunol-031210-101322

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