

C-reactive protein is inversely and independently associated with maximal oxygen uptake in adolescents with obesity

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Abstract

The purposes of this study were: 1) investigate whether different markers of inflammation (CRP and TNF- α) are correlated to cardiorespiratory fitness in adolescents with obesity; 2) examine the association of these variables when adjusted by parameters of body composition. Were selected 57 individuals, 34 girls and 23 boys, with 16.4 ± 1.56 years and body mass index 36.0 ± 4.3 kg/m². Anthropometric measurements (weight, height and abdominal circumference) and body composition (BMI, visceral fat, body fat) were assessment. Body composition was estimated by analyzer of tetrapolar bioelectrical impedance. Obesity was defined as BMI > 95th percentile of the curve proposed by the Center for Diseases Control. Plasma TNF- α was measured by a quantitative two-site high-sensitivity enzyme immunoassay and CRP was measured by high-sensitivity immunoturbidimetric assay. Graded maximal exercise testing was performed to obtain the maximum oxygen consumption (VO_{2max}) and velocity associated with the VO_{2max} (vVO_{2max}). Significant correlations of CRP with VO_{2max} and vVO_{2max} were found ($r = -0.40$ and $r = -0.36$, respectively). No correlations were observed between TNF- α and VO_{2max} e vVO_{2max} . CRP was associated to the VO_{2max} and vVO_{2max} independently of measurements of body composition. The CRP was independently and inversely associated with direct measurement of VO_{2max} and the indirect variable of cardiorespiratory fitness vVO_{2max} in obese adolescents, even after adjustments in body composition, a potential confounding factor. No association was found between TNF- α and the parameters of cardiorespiratory fitness.

KEYWORDS: Ecytokines; Oxygen consumption; Treadmill test and exercise therapy.

Introduction

The increased prevalence of obesity in adolescence has become a public health problem¹, because obesity in childhood and adolescence is strongly correlated with adult obesity, which reduces the quality of life of individuals and increases the economic costs of health care².

Recent studies have demonstrated a systemic inflammation in obese children and adolescents, characterized by high level of pro-inflammatory cytokines and chemokines^{3,4}. Another studies show a mediator role of systemic inflammation in the development of chronic diseases such as cardiovascular diseases and type 2 diabetes⁵⁻⁷. Therefore, adolescents with obesity are more

exposed to possible comorbid conditions.

A high cardiorespiratory fitness is associated with a reduced systemic inflammation⁸. Previous studies have shown an inverse association between the C-reactive protein (CRP) and cardiorespiratory fitness⁹⁻¹¹. However, research on the association between markers of inflammation and cardiorespiratory fitness were not performed with the obese adolescent, which would be important due to potential future prevention of comorbidities in this population.

In addition, the association between inflammatory markers and a practical parameter of prescription of training, which can be used in the

field, as the velocity associated with maximum oxygen consumption (vVO_{2max}), has not yet been studied. The vVO_{2max} is defined as the speed which elicited the highest oxygen consumption, and was first examined by COOPER¹², as an alternative method for predicting VO_{2max} in the effort to simplify the procedures of the tests and

reduce costs.

Thus, the purposes of this study were: 1) investigate whether different markers of inflammation (CRP and TNF- α) are correlated to vVO_{2max} and VO_{2max} in adolescents with obesity; 2) examine the association of these variables when adjusted by parameters of body composition.

Methods

One hundred and seventy-five participants were initially recruited for participation in this study which were medically screened, their pubertal stage was assessed, and their anthropometric measures were recorded (ie, height, weight and BMI). The endocrinologist completed a clinical interview including questions to determine eligibility based on inclusion criteria: being post-pubescent, according to the classification of TANNER and WHITEHOUSE¹³ and obese, BMI > 95th percentile of the curve proposed by the Center for Diseases Control (CDC); and exclusion criteria: identification of genetic, metabolic or endocrine diseases, and previous use of drugs. At the end of this screening were selected 57 individuals, 34 girls and 23 boys (TABLE 1). This study was approved by the Ethics Committee and Research in Human Beings of the Federal University of Uberlândia-Brazil and all the participants and their parents have signed a consent form.

Weight was measured by an electronic balance and height by a stadiometer. Body mass index (BMI) was calculated as kilograms per square meter. The abdominal circumference (AC) was assessed by perimeter of the abdomen at the height of the navel with a anthropometric tape (Sanny, SN-4010, Brasil). Body composition was estimated by analyzer of tetrapolar bioelectrical impedance (Biodynamics, BIA310e, USA). Visceral fat (VF) was estimated by ultrasonography (Mindray, DC-6, China), defined as the distance between the internal surface of the abdominal rectus muscle and the anterior wall of the aorta¹⁴. All abdominal ultrasonographic (US) procedures and the measurements of visceral fat tissue were performed by the same physician. The intraexamination coefficient of variation for US was 2.6%.

Blood samples were obtained by venipuncture after an overnight fast. Plasma TNF- α was measured

by a quantitative two-site high-sensitivity enzyme immunoassay (DRG Diagnostics, Germany), CRP by a polystyrene particle enhanced high-sensitivity immunoturbidimetric assay (Aptec Diagnostics, Belgium)

Graded maximal exercise testing (2min by stage, initial speed - 3km.h⁻¹, increase of 1km.h⁻¹ by stage and treadmill inclination fixed at 1%) was performed on a motor-driven treadmill (Movement, RT 250pro, Brasil). A ergospirometer (Cosmed, FitMatePro, Italy) was used for analysis of the consumption of oxygen breathing by breathing. The maximum oxygen consumption (VO_{2max}) was defined as the highest 30-s average during exercise. The velocity associated with the VO_{2max} (vVO_{2max}) was obtained by the following formula: vVO_{2max} (km.h⁻¹) = $v + 1.0 \times (t/120)$. Where v is the last velocity completed for 120 seconds; t the number of seconds the final not completed velocity was sustained; 1.0 is the value of the increase in velocity in km.h⁻¹ from the last stage and 120 is the number of seconds in the stage¹⁵.

Initially, we tested the normality of all variables (Shapiro Wilk's test). CRP, TNF- α , relative VO_{2max} and vVO_{2max} were logarithmically transformed [$\log(x+1)$] to reduce skewness. Descriptive statistics are given as mean (SD) (as well as range). The correlation between the parameters of cardiorespiratory fitness (VO_{2max} , vVO_{2max}) and the markers of systemic inflammation (CPR and TNF- α) was performed by Pearson's correlation coefficient. To assess whether inflammatory markers were independently associated with cardiorespiratory fitness after adjustment for potential confounders (body composition), was performed multivariable regression analyses. Predictive variables were included in models with a significance level of $p \leq 0,10$. Statistical significance was inferred at $p \leq 0,05$. Statistical analyses were performed with Statistica version 7.0.

Results

The participants characteristics are shown in TABLE 1. Significant correlations of CRP with VO_{2max} and vVO_{2max} are shown in FIGURE 1A and B.

The relationship between the CRP and the VO_{2max} was reduced when adjusted for three variables of body composition, $r=-0,40$ for $\beta=-0,28$ (BMI), $\beta=-0,34$ (AC) and $\beta=-0,35$ (VF), as well as, two parameters have reduced the association between

CRP and vVO_{2max}, $r=-0,36$ for $\beta=-0,29$ (AC) and $\beta=-0,31$ (VF), however these associations remained significant. No relationship was found between the CRP and the parameters of cardiorespiratory fitness when adjusted by BF (TABLE 2).

No correlations were observed between TNF- α and VO_{2max} e vVO_{2max} (figure 1C and D), the association of these factors adjusted for body composition did not change the results (TABLE 2).

TABLE 1 - Participants characteristics.

	Mean (SD)	Range
Age, years	16.4 (1.56)	13.0 - 20.0
Body Composition		
Body mass index, kg/m ²	36.0 (4.3)	29.1 - 49.2
Abdominal circumference, cm	114.6 (10.5)	93.0 - 142.0
Body fat, %	33.5 (5.5)	20.0 - 44.4
Visceral fat, cm	3.7 (1.1)	1.5 - 6.5
Cardiorespiratory Fitness		
VO _{2max} , ml.kg ⁻¹ .min ⁻¹	26.0 (4.6)	18.0 - 38.5
VO _{2max} , L.min ⁻¹	2.6 (0.6)	1.8 - 4.2
Velocity associated with VO _{2max} , km.h ⁻¹	8.3 (1.3)	6.2 - 11.8
Markers of Inflammation		
CRP, mg/dL	1.1 (0.8)	0.5 - 4.4
TNF- α , pg/mL	5.0 (4.2)	0.0 - 18.0

TABLE 2 - Association between markers of inflammation and cardiorespiratory fitness adjusted by parameters of body composition.

	CRP		TNF- α	
	β	p	β	p
BMI/ vVO _{2max}	0,31 ^a /-0,22	0,03/0,11	-0,27/0,08	0,07/0,59
BMI/ VO _{2max}	0,29 ^a /-0,28 ^a	0,03/0,03	-0,25/0,14	0,08/0,34
AC/ vVO _{2max}	0,26 ^a /-0,29 ^a	0,05/0,03	-0,04/0,19	0,79/0,18
AC/ VO _{2max}	0,24 ^a /-0,34 ^a	0,05/0,01	-0,03/0,23	0,85/0,10
BF/ vVO _{2max}	0,25/-0,22	0,09/0,13	-0,12/0,13	0,44/0,34
BF/ VO _{2max}	0,23/-0,27 ^a	0,10/0,03	-0,10/0,19	0,48/0,21
VF/ vVO _{2max}	0,30 ^a /-0,31 ^a	0,02/0,01	0,06/0,21	0,67/0,13
VF/ VO _{2max}	0,28 ^a /-0,35 ^a	0,03/0,01	0,08/0,25	0,57/0,06

Regression coefficient β and p values of multiple linear regression analysis; AC: abdominal circumference; BF: body fat; BMI: body mass index; CRP: C-reactive protein; TNF- α : tumor necrose factor alpha; VF: visceral fat; VO_{2max}: maximum oxygen consumption; vVO_{2max}: velocity associated with VO_{2max}; ^a: significant association.

Scatter plots depicting correlation between log (x+1) C-reactive protein (CRP), and log (x+1) tumor necrose factor alpha (TNF- α) with log (x+1) maximal O_2 consumption (VO_{2max}) and log (x+1) velocity associated with VO_{2max} (vVO_{2max}). Bold: significant association.

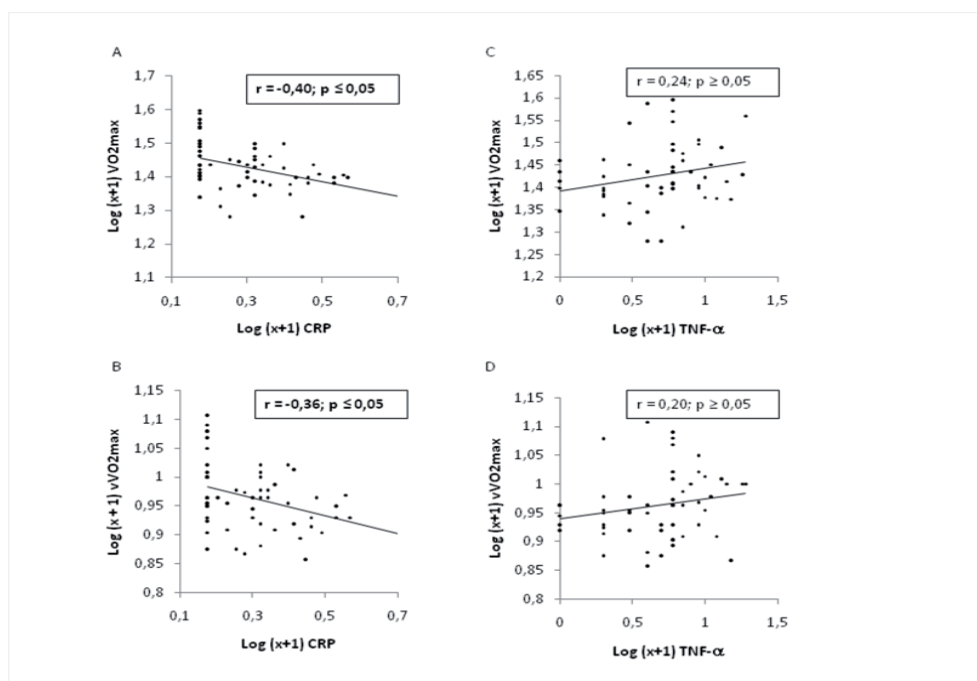


FIGURE 1 - Correlations between markers of inflammation and cardiorespiratory fitness.

Discussion

The main finding of the present study was that, CRP was inversely related to VO_{2max} and vVO_{2max} (FIGURE 1A and B), even after adjustment for potential confounders such as BMI, AC and VF (TABLE 2), in adolescents with obesity. Although other studies have demonstrated the inverse correlation between inflammatory markers and cardiorespiratory fitness⁹⁻¹¹, this is the first study to demonstrate: 1) this association in obese adolescents and 2) a significant correlation between the CRP and vVO_{2max} .

It has been recommended for subjects with chronic diseases, including obese, exercise of moderate and vigorous intensities¹⁶⁻¹⁸. In this sense, the vVO_{2max} can be used as a reference for prescription of training, as shown in some studies^{19,20}. It is a parameter which can be obtained in practice: it is viable and not requiring equipment of high cost and specialized personnel. Adding to this, the findings of this study, it becomes clear the usefulness of vVO_{2max} as a tool in the exercise evaluation for obese adolescents.

As vVO_{2max} and the VO_{2max} show similar correlations with inflammatory markers (FIGURE 1) and indicators of body composition (TABLE 3), we can infer that it can be reliably used for prescription of

training in obese adolescents. The parameter most scientifically studied, VO_{2max} , is not commonly available at training centers, gyms, parks and schools, and thus rarely used in the training prescription. In addition, the exercise based on vVO_{2max} , reduces the empiricism and generalization, because suits the intensity to biological individuality of obese adolescents.

The levels of CRP were associated to the VO_{2max} and vVO_{2max} independently of measurements of body composition (TABLE 2). One study with 172 subjects aged 26-84 years also found a significant correlation ($r = -0.40$) between CRP and VO_{2max} , which is in accordance with the data found in this study¹¹. This finding is also consistent with the results of previous studies^{10,21}, however more studies are needed to clarify the reasons for this association.

The motives for the correlation between cardiorespiratory fitness and levels of CRP are not well elucidated. However, hepatic CRP production is stimulated by interleukin-6 (IL-6) and, to a lesser extent, by interleukin-1 (IL-1) and TNF- α ²². Individuals who are obese and/or hyperinsulinemic have increased adipocyte production of inflammatory markers, including IL-6 and TNF- α ²³⁻²⁵. Several studies

suggested a close relationship between cardiorespiratory fitness and inflammatory status^{26,27}. Although we have not examined the concentrations of IL-6 and IL-1, our study demonstrated a production of TNF- α in obese adolescents (TABLE 1), similarly to other studies²⁸. Whereas, the inverse correlation between the accumulation of body fat and cardiorespiratory fitness is well established, therefore, the relationship between, CRP, VO_{2max} and vVO_{2max} should be mediated by the adipose tissue.

Association between the VO_{2max}, vVO_{2max} and the TNF- α was not found (FIGURE 1C and D). The reason for increased circulating TNF- α levels observed in obese people is not thought to be associated with over-production in the adipose tissue. It is hypothesized that systemic effects of leptin or other adipokines may induce TNF- α secretion from macrophages

and lymphocytes²⁹. However, TNF- α is involved in the pathophysiology of obesity-associated insulin resistance and atherosclerosis^{30,31}, therefore, the study of its association with the variables related to obesity still deserves attention.

Limitations of the present study include the relatively small sample size and cross-sectional design. Future studies are needed to identify which inflammatory pathway is associated with cardiorespiratory fitness and determine the pathophysiological mechanisms involved in this association.

In conclusion, the CRP was inversely associated with direct measurement of VO_{2max} and the indirect variable of cardiorespiratory fitness vVO_{2max}, in obese adolescents, even after adjustments in body composition. No association was found between TNF- α and the parameters of cardiorespiratory fitness.

Resumo

Proteína C reativa é inversamente e independentemente associada com o consumo máximo de oxigênio em adolescentes com obesidade

Os objetivos deste estudo foram: 1) investigar se diferentes marcadores da inflamação (PCR e TNF- α) são correlacionados com a aptidão cardiorrespiratória em adolescentes com obesidade; 2) examinar a associação dessas variáveis quando ajustadas por parâmetros da composição corporal. Foram selecionados 57 indivíduos, 34 garotas e 23 garotos, com 16.4 \pm 1.56 anos e índice de massa corporal de 36.0 \pm 4.3 kg/m². Mensurações antropométricas (massa corporal, estatura e circunferência abdominal) e de composição corporal (IMC, gordura visceral e massa gorda) foram realizadas. A composição corporal foi estimada por impedância bioelétrica tetrapolar. A obesidade foi definida como IMC acima do percentil 95 da curva do CDC. O TNF- α plasmático foi mensurado por imunoenensaio de alta sensibilidade e a PCR foi determinada por ensaio imunoturbidimétrico de alta sensibilidade. Teste incremental máximo foi realizado para obter o consumo máximo de oxigênio (VO_{2max}) e a velocidade associada ao VO_{2max} (vVO_{2max}). Correlações significativas foram encontradas da PCR com o VO_{2max} e a vVO_{2max} (r=-0.40 e r=-0,36, respectivamente). Não foram observadas associações entre o TNF- α , VO_{2max} e a vVO_{2max}. A PCR foi associada com o VO_{2max} e a vVO_{2max} independentemente dos parâmetros da composição corporal.

PALAVRAS-CHAVE: Citocinas; Consumo de oxigênio; Teste incremental; Terapia e exercício.

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