Influence of Nutritional Status and VO_{2max} on Adiponectin Levels in Men Older than 35 Years

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Abstract

Background: Adiponectin is considered an important factor in the pathogenesis of cardiovascular and metabolic diseases, due to its anti-atherogenic and anti-inflammatory properties. Few studies, however, have suggested the existence of a direct association between adiponectin levels and cardiorespiratory fitness and physical activity levels.

Objective: To verify the influence of the nutritional status and cardiorespiratory fitness on plasma adiponectin levels in adult men.

Methods: A total of 250 subjects, all in active duty in the Brazilian Army (BA), with a mean age of 42,6 ± 4,8 years volunteered to participate in the study. Plasma levels of adiponectin were measured, as well as body mass, height, waist circumference (WC), fat percentage by hydrostatic weighing and VO_{2max} by ergospirometry. A questionnaire was used to obtain the characteristics of the physical training performed by the individuals.

Results: The sample showed that 121 (48%) individuals were overweight and 36 (14%) were obese. Moreover, 66 individuals (27%) had a body fat percentage > 25% and 26,7% had a WC ≥ 94 cm. Overweight and obese individuals had significantly lower adiponectin levels than those with an adequate nutritional status. Individuals at the highest tertile of VO_{2max} had higher adiponectin levels than the others. The adiponectin levels were positively correlated with the total weekly physical training time and VO_{2max} and inversely correlated with body mass, BMI and WC. The correlation between adiponectin levels and VO_{2max} did not remain significant after being adjusted for BMI and WC.

Conclusion: Individuals with better cardiorespiratory fitness and normal nutritional status seem to present healthier levels of adiponectin. (Arq Bras Cardiol. 2011; [online].ahead print, PP.0-0)

Keywords: Adiponectin; obesity; nutritional states; physical fitness; military personnel.

Introduction

Recent advances in the biomedical sciences are continuously modifying concepts regarding the role of different tissues and organs in the physiology of the human body. In addition to its classic function of storing energy, adipose tissue (AT) is now recognized as an important and very active endocrine gland[1]. According to Hauner[2], AT produces and secretes a wide variety of peptides and bioactive proteins, called adipocytokines, especially adiponectin, which is a potent modulator of glucose and lipid metabolism, as well as an indicator of metabolic disorders[3]. This hormone is produced exclusively by the adipocytes and differs from the others by its reduced plasma concentration in obese subjects[4].

Adiponectin is considered an important factor in the pathogenesis of metabolic diseases[5] due to its anti-atherogenic, anti-diabetic and anti-inflammatory effects[6]. Subjects with higher plasma concentrations of adiponectin have lower risk for cardiovascular and metabolic diseases[7].

It has been suggested that physical exercise, enhanced physical fitness and obesity reduction are associated with improvements in the metabolic state, although concentrations of adiponectin have not changed after some experimental studies[8,9]. Although controversial, few studies[10-12] have suggested a direct relationship between the levels of adiponectin and physical activity and, as pointed out by Blüher et al[13], physical training appears to increase the number of adiponectin receptors in subcutaneous fat. However, only a few studies have associated adiponectin plasma levels with objective measures of cardiorespiratory fitness. Thus, the objective of this study was to verify the association of anthropometric measurements, an estimation of nutritional status, and cardiorespiratory fitness with adiponectin plasma levels in subjects over 35 years of age.

Methods

The subjects for this study were recruited via printed flyers in Military Organizations of the Brazilian Army (BA) in the city

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of Rio de Janeiro, Brazil. A total of 250 subjects, all in active duty in the BA, volunteered to participate in the study.

On a pre-scheduled day the subjects came to the laboratory in the morning (between 7:00-8:00 a.m.) having fasted for 12 hours. All procedures were explained in depth to the subjects who signed an informed consent form before data collection. One test tube of 4.5 ml of blood was drawn and kept frozen until adiponectin levels were measured (ADIP - enzyme immunoassay).

Immediately thereafter, body mass (BM) and stature were measured using a Filizola digital scale to the closest 50 g and a Sanny wall mounted stadiometer with accuracy of 1 mm, respectively. Body mass index (BMI) was calculated as BM (kg) divided by squared stature (m) and used to established the nutritional status as adequate ($18.5 \leq BMI < 25\ kg.m^{-2}$), overweight ($25 \leq BMI < 30\ kg.m^{-2}$), and obesity ($BMI \geq 30\ kg.m^{-2}$) according to WHO[14]. Waist circumference (WC) was measured at the mid-point between the lower border of the rib cage and the iliac crest. The WC cut-off point of 94 cm was used to assess the increased risk of metabolic complications associated with obesity[14]. These measures were followed by hydrostatic weighing, when body density was obtained, and percentage body fat (%BF) was calculated. Total body fat (TBF) was computed (BM x %BF) and used in the analysis. After underwater weighing, the subjects had breakfast and answered a questionnaire about their physical training routines, followed by a resting electrocardiogram and a maximal cardiopulmonary treadmill exercise test (CPET). The total time spent on physical training (PT), in minutes per week, was calculated by multiplying the weekly frequency of physical activity by the average duration of the sessions. The cut-off value of 150 $min.wk^{-1}$ of physical activity at moderate to high intensity was considered as the minimum recommended amount of physical activity[15].

A ramp protocol was used in the CPET which consisted of a 3 minute warm-up at a fast walking pace followed by running flat on a treadmill (Inbrasport Super ATL - Porto Alegre - Brazil) with constant increases in speed for 8 minutes, after which the speed was kept constant and the grade was increased until volitional exhaustion. All tests lasted between 8 and 12 minutes. Oxygen consumption and carbon dioxide production were measured using a CPX-D metabolic cart (Medical Graphics - St Paul Minnesota) during the CPET. Before the first test of each day, the equipment was calibrated manually after which it self-calibrated before each test. VO_{2max} was measured at maximal effort defined as the inability to continue exercise despite vigorous encouragement and confirmed by respiratory exchange ratio (R) ≥ 1.1, $VE/VO_2 \geq 35$, heart rate $\geq 95\%$ of age-predicted maximum and respiratory rate ≥ 30[16].

Statistical analysis included descriptive characteristics of the subjects (average, standard deviation, maximum and minimum values). Pearson correlation coefficients were calculated to verify the association among variables. ANOVA was used to test the significance of the main effect of cardiorespiratory fitness (tertiles of VO_{2max}: < 36.43; 36.43-42.45 and ≥ 42.45 ml $O_2.kg^{-1}.min^{-1}$) and nutritional status on the plasma levels of adiponectin. The same analyses were performed controlling for WC, VO_{2max} or both (ANCOVA). Tukey post hoc tests were used to test the significance among means. Statistical significance was set at a probability of 5%.

The biochemical measurements were conducted by the NKB Medicina Diagnóstica (Rio de Janeiro, Brazil) and Roche Diagnóstica (Rio de Janeiro, Brazil).

All research procedures were approved by the Institutional Review board of the Sergio Arouca National Public Health School, *Fundação Oswaldo Cruz* and all subjects signed an informed consent form.

Results

The average (± sd) age of the subjects was 42.6 ± 4.8 years with BMI of 26.5 ± 3.8 $kg.m^{-2}$ and adiponectin serum levels of 15.1 ± 9.9 $\mu g.ml^{-1}$ (Table 1). The sample included 121 overweight subjects (48%) and 36 were obese (14%). A total of 66 subjects (27%) had %BF greater than 25% and 26.7% had waist circumference ≥ 94 cm.

Overweight (13.9 ± 8.88 $\mu g.ml^{-1}$) and obese (12.0 ± 7.5 $\mu g.ml^{-1}$) subjects had significantly lower values of adiponectin in comparison to subjects with adequate BMI (18.1±11.3 $\mu g.ml^{-1}$). These differences were maintained even when the analysis was controlled by waist circumference, VO_{2max} or both. Subjects in the lowest tertile of VO_{2max} had significantly lower adiponectin level (Figure 1). Subjects with high %BF (≥ 25%) had significantly lower values of adiponectin (12.7 ± 7.4 $\mu g.ml^{-1}$) than subjects with %BF < 15% (18.7 ± 11.4 $\mu g.ml^{-1}$).

Adiponectin serum levels showed a weak and positive correlation with PT and VO_{2max} and an inverse correlation with body mass, BMI, %BF, total body fat (TBF) and WC (Table 2). The correlation between adiponectin and VO_{2max} ($r = 0.07$) was not significant ($p = 0.29$) after controlling for BMI and WC. The correlation with PT remained significant after controlling for age, BMI and WC ($r = 0.14$). Subjects who engaged in at least 150 $min.wk^{-1}$ of moderate to high-intensity training had higher levels of adiponectin (16.9 ± 10.4 $\mu g.ml^{-1}$), compared to those who did not reach this volume of training (14.3 ± 10.1 $\mu g.ml^{-1}$).

Discussion

In general, the results of the present study agree with the literature, which has shown that circulating levels of

Table 1 - Physical, physiological and biochemical profile of the subjects

	Mean	SD	Min	Max
Age (years)	42.6	4.8	35.0	57.4
Body mass (kg)	82.0	13.8	53.8	142.0
Stature (cm)	175.7	6.5	162.1	192.8
BMI ($kg.m^{-2}$)	26.5	3.8	19.2	41.0
Body fat (%)	20.9	6.5	5.1	39.0
Waist circumference (cm)	90.9	9.9	68.3	128.0
Adiponectin ($\mu g.ml^{-1}$)	15.1	9.9	2.0	56.0
VO_{2max} (ml $O_2.kg^{-1}.min^{-1}$)*	38,1	7.3	17,9	62.1
PT ($min.wk^{-1}$)	188.3	126.9	0.0	770

**n = 249. BMI - body mass index; PT - total physical training time.*

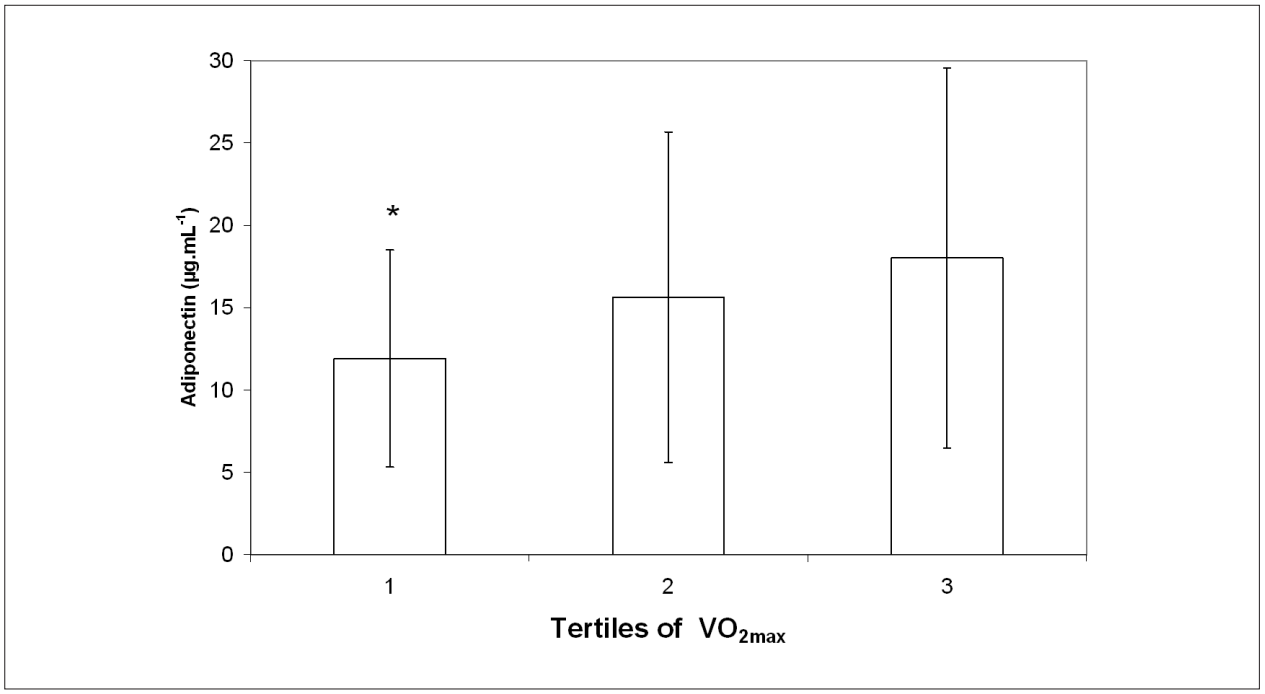

*Figure 1 - Adiponectin levels (µg.ml-1) according to tertiles of cardiorespiratory fitness (VO_{2max}). * Significantly different from the third tertile ($p < 0.05$).*

Table 2 - Pearson correlation coefficients (r) between adiponectin and physical and physiological variables (VO_{2max}) and total physical training time (PT) of the subjects

		BM (kg)	BMI ($kg.m^{-2}$)	%BF	TBF (kg)	WC (cm)	VO_{2max} ($ml.kg^{-1}.min^{-1}$)	PT (min)
Adiponectin ($\mu g.ml^{-1}$)	r	-0.224	-0.237	-0.180	-0.197	-0.226	0.192	0.178
	p	0.000	0.000	0.005	0.002	0.001	0.002	0.006

p - probability value; BM - body mass; BMI - body mass index; %BF - percentage body fat; TBF - total body fat; WC - waist circumference; VO_{2max} - cardiorespiratory fitness; PT - total physical training time.

adiponectin are higher in non-obese in comparison to obese subjects and that adiponectin levels were negatively correlated with anthropometric measures (BMI and WC), even after adjusting for age and total body fat[7,17]. Kantartzis et al[18] did not find any difference in adiponectin levels among overweight and obese subjects, even after controlling for abdominal fat. In the current study, adiponectin was also not different between overweight and obese subjects, but subjects with adequate nutritional status had significantly higher levels of adiponectin.

The inverse relationship between adiponectin and BMI or %BF found in the present study agrees with several other studies[7,12,18]. Gavrila et al[19] suggested that obesity and central fat distribution are independent negative predictors of serum adiponectin and that adiponectin could represent a link between core obesity and metabolic diseases, probably due to the increase in the expression of TNF-α, which reduces the expression of adiponectin and *in vitro* secretion of adipocytes[20,21]. Esposito et al[22] found a 48% increase in adiponectin levels after 2 years of a combined low-energy Mediterranean diet and increased physical activity for 8 weeks in women. After the intervention, the subjects presented lower BMI, %BF, body mass and WC and higher adiponectin serum levels than the pre-intervention period.

According to Tsukinoki et al[12], subjects with adiponectin levels < 4 $\mu g.dl^{-1}$ presented higher BMI than subjects with levels above > 4 $\mu g.dl^{-1}$. Men with BMI higher than 30 $kg.m^{-2}$ and more than 25% of body fat were found to have lower values of adiponectin that those with less BMI and %BF[23]. The change in body mass and body fat mass after training was significantly and negatively correlated with changes in adiponectin levels. Hulver et al[8] concluded that the body mass loss after one year of gastric bypass surgery caused significant decreases in BMI, fasting insulin and glucose and significant increases in adiponectin levels. Moreover, a reduction in subcutaneous adipose tissue (AT) mass alone, after abdominal liposuction, does not lead to a similar decrease in low-grade inflammation[24], indicating that the visceral AT depot is more closely associated with the inflammatory state in obesity than the subcutaneous AT depot.

Although obese subjects have more body fat, they also exhibit higher levels of pro-inflammatory cytokines IL-6 and TNF-α. This can cause a reduction in the expression of adiponectin mRNA and adiponectin release from adipocytes.

Adiponectin and TNF-α inhibit each other. Adiponectin expression is suppressed by IL-6[25]. This may explain why obese people have lower circulating levels of adiponectin.

In obese individuals, plasma adiponectin levels were lower although adipose tissue is the only tissue in its synthesis, suggesting a negative feedback in its production brought on by the development of obesity. So, body weight reduction would result in an at least transient loss of inhibition and, therefore, an elevation in plasma adiponectin. Nadler et al[26] showed by microarray that the expression of adipogenic genes was suppressed by the development of obesity in mice, suggesting the existence of a feedback inhibitory pathway. In ob/ob obese mice, the expression of adipoQ was down-regulated. The fact that the steady state mRNA of adipoQ decreased in ob/ob mice compared with those of wild type indicates that the level of regulation is related, in part, to the transcript or mRNA stability. Moreover, the steady state mRNA of adiponectin in adipose tissue seems to be reduced in obese humans[27]. However, the biological mechanisms that modulate the expression of adiponectin during reduction weight need further studies to be better understood.

Although the literature is still inconsistent in relation to the acute and chronic effects of aerobic training and the role of the intensity of exercise on adiponectin levels[28], St-Pierre et al[11] suggested a positive correlation between adiponectin and physical activity. Kraemer et al[29] have suggested that the effect was more frequently observed with vigorous physical activity. However, Blüher et al[10] and Oberbach et al[30] have shown significant increases in adiponectin levels in obese and insulin-resistant subjects who exercised moderately. It has been estimated[31] that vigorous aerobic exercise (80 to 90% of maximal heart rate) can represent an increase in adiponectin levels of 0.9 $\mu g.ml^{-1}$, while moderately intense exercise can lead to an increase of 0.7 $\mu g.ml^{-1}$.

Exercise increases the release of interleukin-6 from active muscles, which can in turn suppress other pro-inflammatory markers, such as TNF-α and may be associated with the increase in the adiponectin levels[32]. Effects of resistance training include an up-regulation of GLUT4 expression, chronic activation of AMPK, facilitation of insulin signal transduction, as well as increases in the expression of several proteins involved in glucose and lipid utilization and their turnover may be associated with adiponectin. Moreover, exercise training could modulate cytokine production at the levels of gene expression, protein ligand and receptor binding[33].

Esposito et al[22] and Hulver et al[8] suggest that physical exercise alone is not enough to increase adiponectin levels. They concluded that some body mass loss is necessary to increase adiponectin levels in sedentary individuals or those with physical activity patterns. After 6 weeks of aerobic training 5 times per week, Yatagai et al[34] found no change in adiponectin levels. The changes in VO_{2max}, %BF and TBF after training were not associated with changes in adiponectin levels, contrary to the findings of Bruun et al[35] that showed increases of about 29% in circulating adiponectin levels after 15 weeks of hypocaloric diet plus exercise in severely obese men, which was associated with reduction in BMI and WC and increase in VO_{2max}.

Kim et al[36] showed an increase of 10% in the adiponectin levels after training (supervised jump roping) five times per week, 40 min per day for 6 weeks in obese Korean youths. Adiponectin levels increased by 81% after strenuous exercise during 2 weeks (skiing expedition in the Swedish mountains), but returned to baseline values after 6 weeks in 20 males[37]. After 24 months of physical training (cycling, ≥ three times per week, ≥ 45 min per session at 50-65% of VO_{2peak}) in adults with predisposition to metabolic syndrome, Ring-Dimitriou et al[28] found that an improvement of 4.7 ml $O_2.kg^{-1}.min^{-1}$ in VO_{2peak} was associated with an increase of 1.6 $\mu g.ml^{-1}$ in adiponectin levels in males. After one year of training, adiponectin levels significantly increased in men (1.7 $\mu g.ml^{-1}$), but no change was found in VO_{2peak}, BMI and %BF in obese men. In the present study, VO_{2max} was directly (but weakly) associated with serum adiponectin levels. Subjects with the highest VO_{2max} had significantly higher values of adiponectin in accordance with data from Kumagai et al[38] who also found a direct association between adiponectin levels and VO_{2max}.

In relation to the acute effect of exercise, a study by Jürimäe et al[39] have not found changes in the levels of adiponectin immediately after aerobic exercises lasting approximately 1 hour in healthy subjects. However, adiponectin levels were altered in the highly-trained athletes after high intensity exercise involving several muscular groups and significantly increased above the resting value after the first 30 min of recovery[39].

Recent advances in adiponectin biochemistry have indicated that adiponectin receptor expression also increases after exercise training. AdipoR2 mRNA expression in both visceral and subcutaneous fat is positively associated with circulating adiponectin levels, but negatively associated with obesity even after adjusting for fat mass[10]. Four weeks of intensive physical training resulted in increases in skeletal muscle AdipoR1/R2 mRNA expression. The same intervention led to increases in AdipoR1 and AdipoR2 mRNA expression in subcutaneous fat and it was significantly and positively correlated with the increases of AdipoR2 in skeletal muscle[13].

Despite the increase in VO_{2max} and decreases in body mass, BMI, fat mass and WC, Polak et al[40] showed no significant difference in adiponectin levels after 12 weeks of aerobic training. The authors speculated that the maintenance of mRNA levels for adiponectin in subcutaneous adipose tissue would be the reason for these findings. Adiponectin can activate AMP-activated protein kinase and increase fatty acid oxidation in skeletal muscle. While total AMP-activated protein kinase activity is related to muscle mass, it can be postulated that athletes who use greater muscle mass during exercise need more adiponectin in order to regulate metabolic fluxes.

In conclusion, although the association between adiponectin levels and %BF and BMI was weak, this is in accordance with some studies. It seems that the increase in adiponectin levels is not caused by exercise itself, but is modulated by changes in body composition. However, it is still necessary to clarify how much of body fat reduction is necessary for adiponectin levels to increase. Conversely, although the results suggest that having adequate body mass carries the most benefit, it is important to promote physical activity for the dual benefits of maintaining healthier BMI and cardiorespiratory fitness.

Contributors

EC Martinez and LA Anjos planned the research and conducted data analyses. EC Martinez and MSR Fortes supervised field data collection. EC Martinez wrote the first draft of the paper, which was revised and approved by the other authors.

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