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ORIGINAL PAPER

Interleukin-6 is a better metabolic biomarker than interleukin-18 in young healthy adults

Júlia Cristina Cardoso Carraro · Helen Hermana M. Hermsdorff · Blanca Puchau · M. Ángeles Zulet · Fermín I. Milagro · Josefina Bressan · J. Alfredo Martínez

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Introduction

Inflammation is a physiological defense response to injury and foreign substances, in order to maintain body homeostasis [27]. However, it can also be triggered by disorders, such as obesity or diabetes, in metabolically active tissues [4].

Obesity and excessive body fat content are associated with increased circulating levels of proinflammatory cytokines [47, 18], supporting a link between chronic low-grade inflammation and diseases such as diabetes and insulin resistance [41], dyslipidemia [18], and, consequently, metabolic syndrome (MetS) features [36]. In addition, previous studies have reported that weight loss leads to a reduction of these proinflammatory molecules [17], making the cytokines an interesting biomarker to follow changes associated to cardiometabolic risk and obesity management. On the other hand, it has been postulated that inflammation could trigger obesity [28]. Thaler and Schwartz (2010) proposed that inflammation in hypothalamic cells, caused by excess of nutrients (mainly fatty acids), can promote resistance to insulin or leptin actions, driving to excessive weight gain [38].

Therefore, the identification of early biomarkers to metabolic disturbances with diagnostic value, including inflammatory markers, in order to prevent future damages and facilitate early treatments is still a great challenge, mainly in young subjects.

In this context, interleukin 6 (IL-6) is a proinflammatory cytokine whose levels have been reported to increase in proportion to the degree of obesity, particularly central adiposity, and to insulin resistance [23]. The levels of IL-6 are often increased in obese subjects, both in adipose tissue and in the blood [11], decreasing in patients undergoing exercise and after caloric restriction [13]. IL-6 levels have been associated with the percentage of total body fat, waist circumference (WC), waist-hip ratio (WHR), and total cholesterol:HDL ratio (TC:HDL ratio), [18] as well as the development of chronic disorders, such as cardiovascular diseases [44].

Another cytokine associated with obesity is interleukin 18 (IL-18). IL-18 is produced by macrophages and Kupffer cells, and was first described as an interferon-γ-inducer factor (IGIF) in T and natural killer cells from mice infected with *Propionibacterium acnes* [10]. The secondary structure of IL-18 in the form of β-sheet folded makes it more closely related to IL-1β than any other cytokine [10]. Increased levels of this cytokine have been related to obesity, type 2 diabetes [45], insulin resistance [1], and atherogenesis [12].

J. C. C. Carraro · H. H. M. Hermsdorff · J. Bressan
Department of Nutrition and Health, Universidade Federal de Viçosa, Viçosa, Minas Gerais, Brazil

B. Puchau · M. Á. Zulet · F. I. Milagro · J. A. Martínez (✉)
Department of Nutrition, Food Science and Physiology, Centre for Nutrition Research, University of Navarra, C/ Irunlarrea 1, 31008 Pamplona, Navarra, Spain
e-mail: jalfmtz@unav.es

M. Á. Zulet · F. I. Milagro · J. A. Martínez
CIBERobn, Centro de Investigación Biomédica en Red-Fisiopatología de la Obesidad y la Nutrición, Carlos III Institute of Health, Madrid, Spain

In turn, it is recognized that lifestyle factors, such as dietary pattern, physical activity, and smoking, can interfere with inflammatory marker concentrations [24, 16, 21, 14]. However, little is known about the relationships between inflammatory markers and metabolic traits in young healthy subjects.

The hypothesis of the present study is that subtle changes may occur in healthy people long time before the onset of the disorders, and may increase the risk to develop metabolic complications. Therefore, we aimed to assess the potential value of IL-6 and IL-18 as early biomarkers of metabolic disorders, as well as to identify the determinants of variation in the concentrations of these cytokines in young healthy adults, with emphasis in metabolic and lifestyle variables.

Materials and methods

Subjects

In this study, 153 apparently healthy young adults (50 males, 103 females), with a mean age of 21±3 (range: 18–34 years old) and a mean body mass index (BMI) of 22.1±2.5 (range 17.4–29.3 kg/m^2), were recruited through magazines, radio, web page, and intranet tools from the Universities of Navarra (UNAV) and Public of Navarra (UPNA). In the recruitment message, the age range (18–35 years old) was mentioned, as well as relevant clinical information for those interested in participating in this nutritional survey. The enrollment questionnaire was devised to assess the nutritional status and to provide appropriate dietary advises to the participants. In addition, a phone number and an e-mail address were provided for a continuous contact. Exclusion criteria included pregnancy, inflammatory, heart and respiratory diseases, hormonal treatments, or prescribed drugs that could affect glucose metabolism, alcohol and drug dependence, recent follow-up of diets designed to weight loss, or unstable weight in the last 3 months. These exclusion criteria were screened firstly by phone, and those that passed this step were further screened by a questionnaire fulfilled by a trained physician. Each volunteer signed a written informed consent, which was previously approved by the Investigation Ethics Committee of the Clínica Universidad de Navarra (ref number 79/2005), in accordance with the principles of the Helsinki Declaration.

Anthropometry and body fat distribution

Anthropometric determinations, such as weight, height, waist and hip circumferences, and skinfold thickness, as well as calculated indexes, were taken using standard measurement procedures [20]. BMI (kg/m^2) and total BF (%) were used as indicators of total adiposity, while measurements of WC (cm) and WHR were used as indicators of central fat accumulation [20].

Blood pressure and biochemical assessments

Systolic (SBP) and diastolic blood pressures (DBP) were measured following World Health Organization guidelines [42]. Venous blood samples were drawn after a 12 h overnight fast by venipuncture. The EDTA–plasma and serum samples were obtained by centrifugation (3500 rpm×15 min at 4 °C), and frozen immediately at −80 °C until assay. Serum concentrations of triglycerides, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), Complement C3 (C3), and glucose and insulin were measured by standard methods as previously described [18]. Insulin resistance was calculated as homeostasis model assessment-estimated insulin (HOMA-IR) according to Matthews et al. [25]. Another index used to estimate insulin resistance was the triglyceride-glucose index (TyG), calculated according to Simental-Mendía et al. [37]. Plasma circulating concentrations of C-reactive protein (CRP, Immundiagnostik AG, Bensheim, Germany), high-sensitivity IL-6 (hs-IL-6; R&D Systems, Minneapolis, MN, USA), high-sensitivity tumor necrosis factor-alpha (hs-TNF-α; R&D Systems, Minneapolis, MN, USA), and IL-18 (Medical & Biological Laboratories Co., Naka-ku Nagoya, Japan) were evaluated by specific commercial enzyme-linked immunosorbent assay procedures in an automated analyzer system (Triturus, Grifols, Barcelona, Spain) as described by the manufacturer. In our laboratory, the inter- and intra-assay coefficients of variability were <10 %.

Lifestyle features

The participants were asked about smoking status (never, former, or current smokers), smoking time in life-course, and number of cigarettes per day. With respect to physical activity, the participants informed whether they performed regular physical activity (yes/no), and if so, the type and the physical activity (h/week) [16]. To

quantify the volume of activity, a metabolic equivalent index was also computed by assigning a multiple of resting metabolic rate to each activity [8].

Statistical analyses

Results are reported as mean±SEM and variable distribution was determined by the Shapiro–Wilk test. In order to analyze anthropometric, biochemical, inflammatory, and dietary pattern and lifestyle characteristics with respect to IL-6 and IL-18 concentrations, these cytokines were taken as suitable variables considering their medians as cutoff values (1.07 pg/mL and 180.0 ng/μL, respectively). Statistical comparisons between groups were performed by the parametric Student *t* test, Mann–Whitney *U* test, or χ^2 test, as appropriate. In order to analyze inflammatory marker concentrations with respect to anthropometrical and metabolic data of the study participants, BMI, WC, WHR, HOMA-IR, and TyG index were distributed into tertiles in order to assess trends. Finally, multiple linear regression models were performed to analyze the prediction of plasma IL-6 and IL-18 concentrations (outcome) for selected variables and using both cytokines as predictors of metabolic and inflammatory traits related to the MetS. Non-normally distributed variables were log-transformed prior to inclusion in linear regression analyses. Statistical analyses were performed with SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered as statistically significant.

Results

Anthropometric, metabolic, inflammatory, and lifestyle characteristics are described according to the medians of IL-6 and IL-18 (Tables 1 and 2). Gender distribution (data not shown) and age did not differ between the lower and higher IL-6 or IL-18 groups. Individuals with higher concentrations of IL-6 had higher values of BMI, WC, WHR, body fat percentage, and plasma CRP concentration, as well as higher TyG index. Those subjects with higher concentrations of IL-18, in turn, showed an increased TC:HDL ratio (Table 1).

When evaluated by lifestyle, individuals with higher concentrations of both cytokines showed higher frequency of smoking or higher daily number of cigarettes (Table 2). No significant differences were found with regard to physical activity between groups (Table 2). IL-6, but not IL-18, showed a trend to increase with the rise of WC and TyG index (Fig. 1).

When using multiple linear regression models to analyze the factors that contribute to the variations in the studied interleukins (Table 3), age, BMI, glucose, triglycerides, C3, CRP, number of cigarettes smoked per day, and physical activity level contributed with approximately 24 % to IL-6 variation. Age, BMI, triglycerides, glucose, and CRP were independent predictors (P<0.005). In turn, BMI, total cholesterol, triglyceride, C3, HOMA-IR, and number of cigarettes smoked per day contributed to a variation of 19 % in plasma IL-18. BMI, C3, HOMA-IR and smoking habits were independent predictors (P<0.005).

Furthermore, IL-6 was able to predict the concentrations of TyG index, CRP, Total cholesterol and C3. However, once have been found that IL-6 levels are correlated to number of cigarettes smoked per day, the regressions were adjusted by number of cigarettes and others confounding variables. The relationship between IL-6 levels and TyG index and CRP remained significant even after adjustment for age and BMI and number of cigarettes smoked per day (p adjusted) as shown in Fig. 2. IL-18 predicted HOMA-IR and insulin and triglyceride concentrations, even after the adjustments (data not shown), but this influence was very poor in relation to the biological effects. All models were also further adjusted by sex, daily energy intake, and physical activity level (metabolic equivalents/day) without changing the associations (data not shown).

Discussion

Inflammation appears to be a defense metabolic process that links obesity onset and the development of MetS features [47]. Inflammatory biomarker concentrations, such as those of CRP, TNF-α, IL-6, and IL-18, are often elevated in obese individuals, and associated to higher cardiovascular risks and insulin resistance [1, 2].

The expansion of adipose tissue promotes the recruitment of immune cells, enhancing the production of proinflammatory cytokines, as well as the density of macrophages in visceral adipose tissue [39]. Furthermore, hypoxia, promoted by the expansion of adipose tissue, leads to increased production of these cytokines in order to trigger angiogenesis and improve the blood flow to the tissue [34]. However, the increase in the

Table 1 Anthropometric and clinical characteristics of the participants (n=153), according to the median of plasma IL-6 (1.07 pg/mL) and IL-18 (180.0 ng/μL) concentrations

Descriptive means	All (n=153)	Lower IL-6 (n=76)	Higher IL-6 (n=77)	P value	Lower IL-18 (n=76)	Higher IL-18 (n=77)	P value
Age (years)	20.8±0.2	20.7±0.2	20.9±0.3	0.572	21.0±0.3	21.0±0.3	0.614
BMI (kg/m^2)	22.0±0.2	21.4±0.2	22.7±0.3	*0.001*	21.9±0.3	22.2±0.3	0.622
WC (cm)	72.7±0.6	70.7±0.7	74.8±0.9	*0.001*	72.8±0.9	72.7±0.8	0.957
WHR	0.74±0.00	0.73±0.00	0.75±0.01	*0.024*	0.742±0.01	0.741±0.00	0.912
Body fat (%)	20.0±0.5	18.8±0.7	21.2±0.8	*0.002*	19.6±0.8	20.4±0.7	0.956
Systolic BP (mmHg)	114.9±0.9	114.3±1.4	115.6±1.2	0.481	116±1	114±1	0.439
Diastolic BP (mmHg)	65.2±0.6	64.5±0.9	65.6±0.9	0.335	66±1	64±1	0.204
Glucose (mg/dL)	85.1±0.6	84.3±0.8	85.9±0.9	0.181	84.2±0.8	86.0±0.9	0.138
Insulin (μU/L)	7.9±0.3	7.7±0.4	8.1±0.4	0.516	7.7±0.3	8.1±0.42	0.515
HOMA-IR	1.7±0.0	1.6±0.1	1.7±0.1	0.376	1.6±0.1	1.7±0.1	0.354
TyG index	8.0±0.0	7.99±0.2	8.06±0.2	*0.004*	8.02±0.2	8.04±0.2	0.438
Total cholesterol (mg/dL)	174.8±2.2	176.1±3.2	173.5±3.1	0.566	172.1±3.2	177.5±3.1	0.228
HDL-c (mg/dL)	59.8±1.0	60.3±1.5	59.2±1.4	0.605	61.4±1.4	58.1±13.0	0.111
TC: HDL-c	3.0±0.1	3.0±0.1	3.0±0.1	0.948	2.9±0.1	3.2±1.5	0.008
Triglycerides (mg/dL)	67.9±2.1	70.3±3.3	65.6±2.6	0.267	64.0±2.8	71.9±3.2	0.066
Complement C3 (g/L)	1.1±0.0	1.0±0.0	1.1±0.0	0.082	1.1±0.2	1.1±0.2	0.179
CRP (mg/L)	1.1±0.1	0.9±0.1	1.3±0.1	*<0.001*	1.1±0.1	1.1±0.1	0.621
TNFα (pg/mL)	2.1±0.2	1.9±0.2	2.3±0.3	0.190	2.0±0.3	2.2±0.2	0.657
IL-6 (pg/mL)	1.2±0.1	0.75±0.0	1.8±0.1	N/A	1.2±0.1	1.3±0.1	0.573
IL-18 (ng/μL)	484.1±65.2	563.6±99.5	403.6±83.7	0.220	130.2±3.8	833.4±116.8	N/A

P value from Student t test or Mann–Whitney U test (to non-normally distributed variables), when groups were compared

Data are mean±SEM

BP blood pressure, *CRP* C-reactive protein, *HOMA-IR* insulin resistance index, *HDL-c* high-density lipoprotein-cholesterol, *TC* total cholesterol, *N/A* not available

In italics are p values <0.05

circulating levels of these cytokines interferes with the insulin signaling pathway, leading to resistance to the action of this hormone in target tissues [47].

IL-6 is a cytokine produced by many cell types and elicit paracrine, autocrine, and endocrine effects, acting as a mediator of the acute response and determining the

Table 2 Lifestyle features of the participants (n=153), according to the medians of plasma IL-6 (1.07 pg/mL) and IL-18 (180.0 ng/μL) concentrations

Characteristics	All (n=153)	Lower IL-6 (n=77)	Higher IL-6 (n=76)	P value	Lower IL-18 (n=76)	Higher IL-18 (n=77)	P value
Self-reported physical active practice (yes)	82 (53.6)	38 (46.3)	44 (53.7)	0.289	41 (50)	41 (50)	0.930
Metabolic equivalents (h/week)	37.6±2.3	41.5±3.4	36.6±3.0	0.213	39.8±3.3	35.4±3.2	0.188
Smokers (yes)	50 (32.7)	23 (46)	27 (54)	0.556	19 (38)	31 (62)	*0.044*
Smoking time (years)	1.3±0.2	1.2±0.3	1.4±0.2	0.497	0.8±0.2	1.8±0.3	*0.019*
Cigarettes (n/day)	2.5±0.4	1.9±0.5	3.2±0.6	*0.003*	1.6±0.5	3.5±0.7	*0.021*

P values from Mann–Whitney U test to continuous variables and χ^2 test to dichotomy variables, when groups were compared

Data are mean±SEM or n (frequency in percents) to continuous or dichotomy variables

In italics are p values <0.05

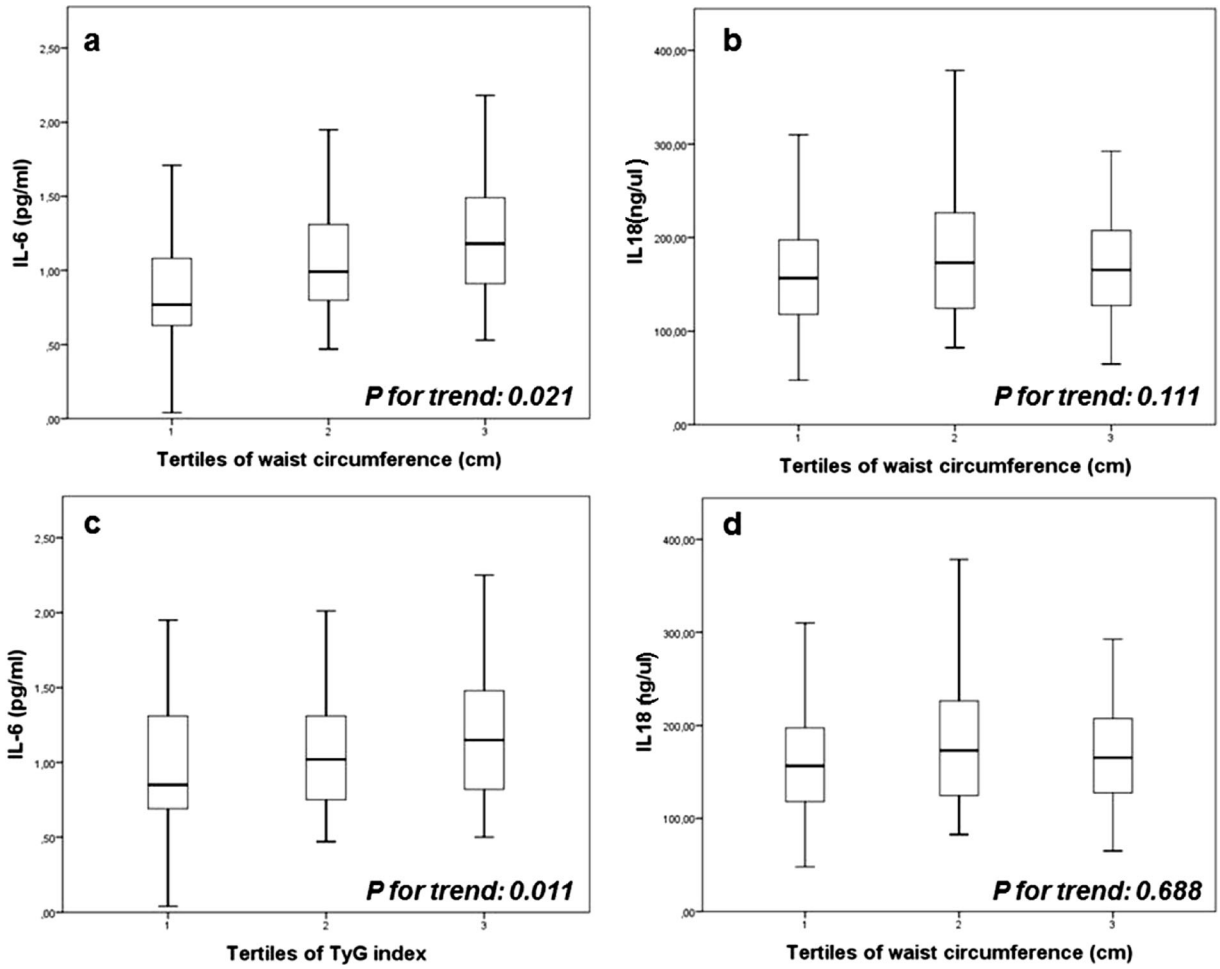

Fig. 1 Plasma IL-6 (**a**) and IL-18 (**b**) concentrations (n=153), according to the distribution of waist circumference (centimeters) into tertiles, and IL-6 (**c**) and IL-18 (**d**) according to the distribution of TyG index into tertiles. Data are expressed as median (interquartile range)

increase of plasma concentrations of acute phase proteins, such as CRP [44, 9]. As in this study, the correlation between IL-6 and abdominal adiposity has been previously documented [18, 21], and chronic elevations of IL-6 concentration have been associated with both obesity and insulin resistance [32]. IL-6, produced in large scale in adipose tissue macrophages, may have a pivotal role in obesity and insulin resistance, impairing insulin sensitivity by reducing tyrosine phosphorylation and increasing serine phosphorylation of key molecules in the insulin signaling pathway, leading to resistance to its action in target tissues, increasing lipolysis and decreasing glucose uptake in the adipose tissue [15]. Although in this study IL-6 levels were not associated with insulin resistance when measured as HOMA index, subjects with higher IL-6 concentration showed a higher TyG index. In this sense, Vasques et al. [40] suggested that the TyG index was a better predictor of insulin resistance than the HOMA-IR.

Regarding inflammatory markers, plasma concentration of IL-6 was a predictor of CRP, as has been reported in the scientific literature [43], even after adjustment for factors related to the lifestyle. Other studies have suggested that CRP concentrations were independently associated to insulin resistance [31], even in a healthy population [43], strengthening the relationship between IL-6 concentrations and insulin resistance. However, the predictive power of IL-6 in relation to C3 and total cholesterol was not significant after adjusting for the daily number of cigarettes smoked. In fact, it has been reported that smoking is associated with elevated levels of plasma IL-6 [16], and high concentrations of IL-6 may be a central mediator of the association between

Table 3 Multiple linear regression analyses showing the independent contributions of variables of studied domains to the variation of the plasma IL-6 and IL-18 concentrations

Variables	B coefficient	95 % Confidence interval	*P* value
Plasma IL-6 as dependent			
Age (years)	−0.015	(−0.030; 0.000)	*0.043*
BMI (kg/m^2)	0.025	(0.008; 0.042)	*0.003*
Triglycerides (mg/dL)	−0.002	(−0.003; 0.000)	*0.013*
Glucose (mg/dL)	0.006	(0.000; 0.011)	*0.040*
C3 complement (g/l)	0.215	(−0.019; 0.449)	0.072
CRP (mg/L)	0.118	(0.065; 0.170)	*<0.001*
Cigarette (*n*/day)	0.002	(−0.006; 0.011)	0.610
Physical activity (metabolic equivalents h/week)	−0.001	(−0.002; 0.000)	0.157
			R^2=0.242 (P<0.001)
Plasma IL-18 as dependent			
BMI (kg/m^2)	−0.032	(−0.059; −0.005)	*0.021*
Total cholesterol/HDL	0.008	(−0.101; 0.117)	0.879
Triglycerides (mg/dL)	0.002	(−0.001; 0.005)	0.113
C3 complement (g/l)	0.563	(0.188; 0.938)	*0.003*
HOMA-IR	0.119	(0.030; 0.208)	*0.009*
Smoking time (years)	0.038	(0.010; 0.066)	*0.008*
			R^2=0.193 (P<0.001)

Domains are adiposity indicator, lipid markers, glucose marker, inflammatory marker and lifestyle features

Adjusted R^2 and all independent variables included in each model are presented in the table. Non-normally distributed variables were log-transformed prior to inclusion in linear regression

In italics are p values <0.05

smoking and cardiovascular risk [26]. On the other hand, IL-6 elicited in exercise has been proposed to have an anti-inflammatory effect and to regulate the food intake by the sensitization of insulin and leptin central action [35]. In general, the increase in IL-6 production in skeletal muscle occurs concomitantly to a decrease in TNF-α secretion, resulting in an anti-inflammatory effect [33]. However, in this case, IL-6 levels were neither related to physical activity nor to TNF-α concentration, suggesting a classical proinflammatory role of IL-6 in relation to obesity.

In this study, although higher plasma concentrations of IL-18 were not associated with increased central adiposity, this cytokine was related with a higher TC:HDL ratio, considered a surrogate of cardiovascular risk. It was also observed that insulin and triglycerides levels, and insulin resistance assessed as HOMA-IR, were influenced by IL-18 levels, even after adjusting for age and lifestyle. These predictions, although statistically significant, seem to have little biologic importance, once IL-18 has a very small influence in the values of metabolic and inflammatory traits.

IL-18 has been previously related to obesity and type 2 diabetes [45], atherosclerosis [12], and MetS [22]. Zorrilla et al. [46] reported that IL-18 modulates food intake, metabolism, and adiposity, suggesting a protective effect of this interleukin in obesity. These data were confirmed by Netea et al. [29] who, using genetically modified mice, observed that the absence of IL-18 induced hyperphagia, hyperglycemia, obesity, and insulin resistance, whereas the administration of recombinant IL-18 improved such metabolic defects. Taken together, these outcomes suggest that elevated levels of IL-18 associated with adiposity may occur due to resistance to the action of this interleukin, such occurs with insulin or leptin [45]. Studies correlating the plasma concentration of IL-18 to individual components of MetS have been previously reported [6], as well as the progressive increase in the levels of IL-18 in relation to the number of MetS components, regardless adjusting for age, gender, BMI, and insulin levels [22]. However, in the present study, IL-18 did not appear to be a good biomarker of MetS components in young healthy subjects as it was not able to detect early changes in metabolic features.

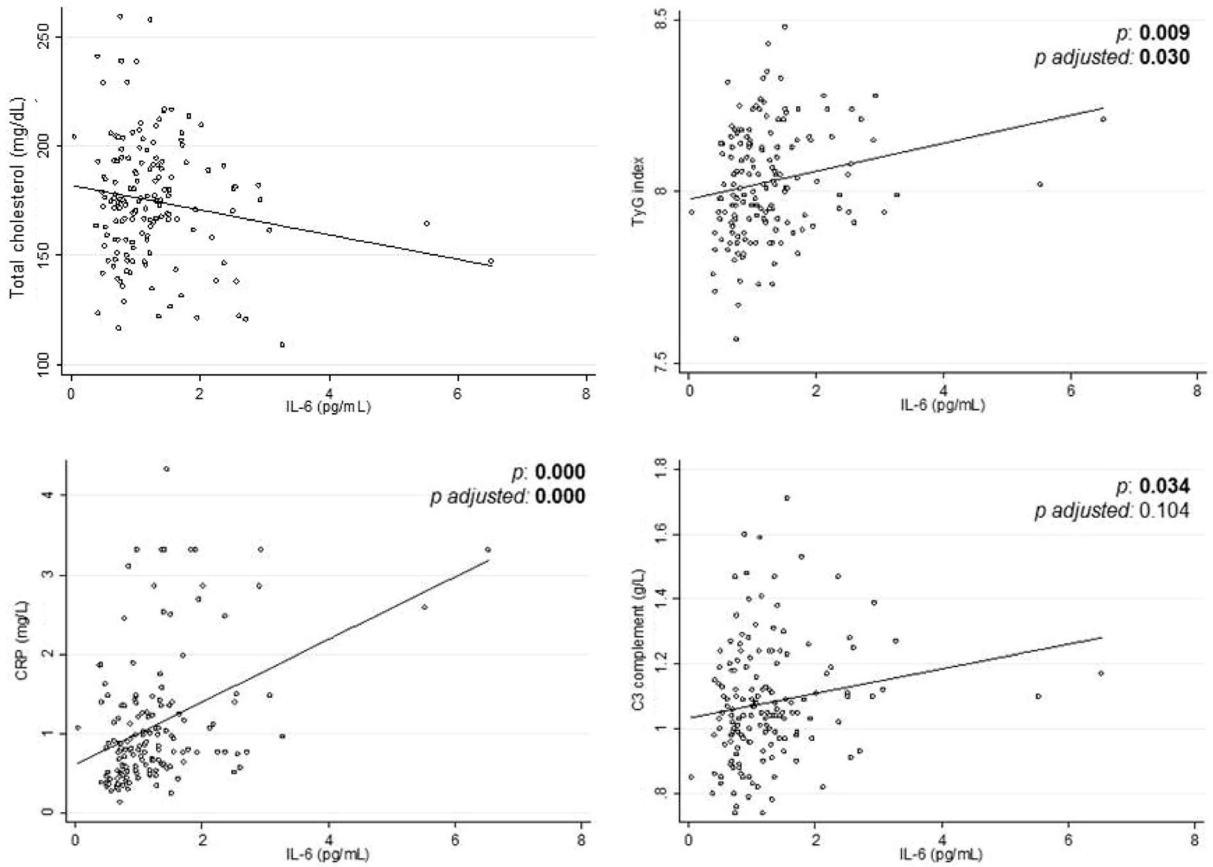

Fig. 2 Multiple linear regression analyses with IL-6 concentrations (pg/mL) as a predictor of total cholesterol, TyG index, CRP, and C3 complement adjusted by number of cigarettes smoked per day (n=153)

Regarding lipid metabolism, Blankenberg et al. [3] reported a positive correlation between IL-18 and serum triglycerides and a negative correlation with HDL. Although we have not observed a negative correlation between IL-18 and HDL, the higher TC:HDL ratio among individuals with higher circulating levels of IL-18 suggests a comparable cardiometabolic risk. As observed in our results, Blankenberg et al. [3] also found that smoking interfered in the concentrations of IL-6, but not in those of IL-18 [3].

In this study, differences in cytokine concentrations between genders were not observed. Men had a trend to higher levels of IL-6 but not significant. This result was similar to other results obtained in previous reports [5]. However, concerning IL-18, we have not observed differences between both genders. Although most of the studies have observed higher levels of IL-18 in men [30], Chen et al. [7] found similar levels of IL-18 between healthy men and women, but higher levels in men with MetS.

It is known that some components of the diet [19] and physical activity [24] can influence the inflammatory status. However, these relationships were not observed in the current study. The exception was the lowest phosphorus intake among individuals with higher levels of IL-6.

This study has some limitations, since relationships of cause and effect between the associations cannot be assumed due to the cross-sectional nature of the study. The sample composition (only young and apparently healthy volunteers, not including individuals with MetS diagnoses) does not allow the evaluation of potential associations of IL-6 and IL-18 with the disease. In fact, this experimental design was conducted in order to analyze these inflammatory mediators as early biomarkers of metabolic features/disorders even in young healthy subjects. A future research with this same population might help to clarify if these subjects with trend to insulin resistance really developed this disturbance.

In conclusion, the results of this study suggest that IL-6 concentrations may be linked to adiposity traits and

increased risk of insulin resistance, measured by TyG index, in young healthy subjects. Thus, IL-6 can be an early risk factor for the development of chronic diseases. In any case, such effects may be influenced by smoking habit, once the number of cigarette smoked per day was associated to higher concentrations of IL-6. Moreover, IL-6 seems to be a better early biomarker of metabolic traits in young healthy subjects than IL-18.

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Conflict of interest The authors declare that they have no competing interests.

Author contributions JCCC analyzed and wrote the manuscript. HHMH contributed in the design, field work, data collection, and analysis. BP contributed in the design, field work, and data collection. MAZ, FIM, and JB contributed in the design and analysis. JAM contributed in the general coordination, design, and financial management. All authors assisted in editing the manuscript as well as reading and approving the final manuscript.

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