Accuracy of plasma interleukin-18 and adiponectin concentrations in predicting metabolic syndrome and cardiometabolic disease risk in middle-age Brazilian men

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Resumo:
The aims of this cross-sectional study were to explore the ability of serum interleukin 18 (IL-18) and adiponectin to identify metabolic syndrome (MetS), and to verify their association with an index of central lipid overaccumulation (lipid accumulation product (LAP)) and cardiometabolic risk factors in a population of middle-aged Brazilian men. A group of 218 apparently healthy middle-aged Brazilian men (age, 50.3 [+ or -] 4.97 years) underwent anthropometric, clinical, sociodemographic, and standard serum biochemical assessments. LAP was calculated and the study participants were categorized into 3 groups according to serum IL-18 and adiponectin cut- points tertiles to verify the association of these biomarkers with cardiometabolic risk factors. The MetS group had more less active ($p = 0.03$) and obese ($p < 0.01$) individuals who exhibited higher IL-18 ($p < 0.01$) and lower adiponectin ($p < 0.01$) than did those in the group with no MetS. After adjustments (age, smoking, alcohol consumption, physical activity level, and total body fat), serum IL-18 [greater than or equal to] 336.4 [micro]g/mL was an independent factor for MetS occurrence and it was directly associated with LAP ([greater than or equal to]51.28), central obesity, hypertriglyceridemia, and hypertension ($p < 0.05$), but not with high-density lipoprotein cholesterol (HDL-C). Serum adiponectin [greater than or equal to] 7.02 [micro]g/mL was negatively associated with MetS occurrence, LAP, hypertriglyceridemia, and low HDL-C ($p < 0.05$), but not with central obesity and hypertension. In conclusion, both IL-18 and adiponectin demonstrated the ability to identify MetS in this population, with IL-18 being more accurate. The association of these biomamarkers with LAP and cardiometabolic risk factors highlights its relevance as a diagnostic tool.

Key words: cardiometabolic risk, adipokines, interleukins, metabolic syndrome.

Cette etude transversale se propose d'explorer l'utilisation de l'interleukine 18 (<<IL-18>>) et de l'adiponectine dans le serum pour identifier le syndrome metabolique (<<MetS>>) et de verifier leur association avec un indice de suraccumulation centrale de lipides (produit de l'accumulation des lipides (<<LAP>>)) et les facteurs de risque cardiometabolique dans une population de Bresiliens masculins d'age moyen. Un groupe de 218 Bresiliens masculins d'age moyen (age : 50,3 [+ or -] 4,97 ans) et apparemment en bonne sante participent a des seances de mesures anthropologiques, cliniques, sociodemographiques et serobiochimiques standards. On evalue LAP et on divise les participants en trois groupes selon les tertiles des valeurs seriques d'IL-18 et d'adiponectine pour verifier l'association de ces biomarqueurs avec les facteurs de risque cardiometabolique. Le groupe MetS comprend plus de personnes moins actives ($p = 0,03$) et obeses ($p < 0,01$) avec des valeurs plus elevees d'IL-18 ($p < 0,01$) et plus faibles d'adiponectine ($p < 0,01$) que le groupe exempt de MetS. Apres ajustements (age, tabagisme, consommation d'alcool, niveau d'activite physique et gras corporel total), une valeur serique d'IL-18 [greater than or equal to] 336,4 pg/mL constitue un facteur independant de l'occurrence de MetS et est associee directement a LAP ([greater than or equal to] 51,28), a l'obesite centrale, a l'hypertriglyceridemie et a l'hypertension ($p < 0,05$), mais pas au cholesterol de haute densite (<<HDL-C>>). Une valeur serique d'adiponectine > 7,02 [micro]g/mL est negativement associee a l'occurrence de MetS, a LAP, a l'hypertriglyceridemie et a un faible HDL-C ($p < 0.05$) et n'est pas associee a l'obesite centrale et a l'hypertension ($p < 0,05$). En conclusion, l'IL-18 et l'adiponectine peuvent etre utilisees pour verifier la presence de MetS dans cette population, l'IL-18 etant plus precise. L'association de ces biomarqueurs avec LAP et les facteurs de risque cardiometabolique souligne sa pertinence comme outil de diagnostic. [Traduit par la Redaction]

Mots-cles: risque cardiometabolique, adiponectine, interleukine, syndrome metabolique.

Texto completo:
Introduction

Metabolic syndrome (MetS) is a combination of cardiovascular and metabolic risk factors, including high blood pressure, hyperglycemia, dyslipidemia, and, mainly, central obesity, which predispose individuals to cardiovascular diseases and type 2 diabetes (Alberti et al. 2009; International Diabetes Federation (IDF) 2006; Gallagher et al. 2008). The prevalence of MetS and its components may be influenced by differences in genetic background, diet, levels of physical activity, population age, sex, and levels of over- and undernutrition (Cameron et al. 2004).

Improvement in the accuracy of identification of individuals at risk of MetS could improve detection and prevention of related diseases. Given the complexity and multifactorial nature of MetS, other diagnosis criteria such as those based on the levels of inflammatory biomarkers are proposed to increase the accuracy of its diagnosis in clinical practice (Licht et al. 2013; Osgood et al. 2013). The importance of the inflammatory mechanisms in cardiometabolic disorders, as well as the relevance of the pro-inflammatory and anti-inflammatory balance in the prevention of

cardiometabolic diseases have been demonstrated (de Gonzalo-Calvo et al. 2010). Chronic high concentrations of biomarkers, such as tumor necrosis factor-alpha (TNF-[alpha]) and pro-inflammatory interleukins (ILs) have been found to be positively associated with obesity, a low-grade systemic inflammatory state, and hence peripheral insulin resistance (IR) (Hermsdorff et al. 2012).

In this sense, serum IL-18, a pleiotropic pro-inflammatory cytokine upregulated by TNF-[alpha] (Dinarello et al. 2013), has been positively associated with MetS and other cardiometabolic risk factors in populations of middle-aged men with geographical and ethnic differences. For example, such an association was found in American (Zirlik et al. 2007), Australian (Hung et al. 2005), Asian (Yamaoka-Tojo et al. 2011), and European (Espinola-Klein et al. 2008; Jefferis et al. 2011, 2013; Stenholm et al. 2010) men. In a population of middle-aged Brazilian men, those who experienced major adverse cardiovascular events (i.e., cardiovascular death, new episode of acute coronary syndrome, and need for unplanned revascularization) exhibited high serum IL-18 levels (Furtado et al. 2009). However, until now there is no report on the association of IL-18 with MetS in this population.

Adiponectin, an anti-inflammatory adipokine, is in turn consistently present at high concentrations in healthy individuals, preventing the development of vascular dysfunctions as well as improving peripheral insulin sensitivity (Adamska et al. 2012; Kowalska et al. 2008; Turer and Scherer 2012). Indeed, adiponectin was negatively associated with insulin sensitivity and risk for MetS in different populations worldwide. For instance, such association was found in middle-aged men from Africa (Abdelgadir et al. 2013; Meilleur et al. 2010), America (Ai et al. 2011), Europe (Andreasson et al. 2012; Cote et al. 2011), and Asia (Ding et al. 2015; Hata et al. 2015; Kim et al. 2013). Nevertheless, either weak or no relationship of adiponectin with coronary heart disease risk factors was demonstrated in healthy middle-aged European men (Lindsay et al. 2005; Luc et al. 2010). In Brazilians, low levels of adiponectin were associated with high cardiovascular risk (Oliveira et al. 2012), whereas in Japanese-Brazilian men it was associated with glucose intolerance (Crispim et al. 2013; Vendramini et al. 2006). Thus, considering the increased morbidity and mortality by cardiometabolic diseases in Brazil (Ministerio da Saude 2012), investigating the relationship of such biomarker with MetS is of interest.

In concert, the lipid accumulation product (LAP), an index of central lipid overaccumulation based on waist circumference (WC) and blood triglycerides (TAG), exhibits positive relationship with MetS and cardiometabolic risk factors in different populations. For example, such association was observed in middle-aged European (Taverna et al. 2011), American (Ioachimescu et al. 2010; Kahn 2006), and Asian (Chiang and Koo 2012; Du et al. 2015; Gao et al. 2013; Xia et al. 2012) men. Despite that, Kahn et al. (2012) demonstrated a weak association between LAP and all-cause mortality in Americans. In the South American population, a unique study (i.e., Tellechea et al. 2009) demonstrated a positive association of LAP with MetS in Argentinean men. In Brazilians, however, such association is not known and if confirmed it could improve clinical predictors for cardiometabolic diseases.

Therefore, given the influence of ethnicity and acculturation on the prevalence of MetS and its components (Cameron et al. 2004; Gardener et al. 2013; Goel et al. 2004; Kandula et al. 2008; Moran et al. 2007; Shah et al. 2012; Tashiro et al. 2014), studies on pro- and anti-inflammatory biomarkers in middle-aged Brazilian men would add new insights into the relationship of such biomarkers with cardiometabolic features. The aims of this cross-sectional study were thus to explore the ability of serum IL-18 and adiponec tin to identify MetS and to test their relationships with LAP and other cardiometabolic risk factors in a population of middle-aged Brazilian men.

Materials and methods

Study population

This cross-sectional study was carried out between March and December 2011, in the city of Vicosa, MG, Brazil. The sample size was calculated using Epi Info version 6 (Dean et al. 1996). Looking at the total number of male staff at the Universidade Federal de Vicosa (UFV) in February 2011, aged between 40 and 59 years (1744 individuals), with a confidence level of 95%, an expected MetS prevalence of 19% in middle-aged Brazilian men (Gronner et al. 2011) and a 5% sampling error, resulted in 208 participants as the minimum required. Participants were selected by systematic sampling and replaced if they did not meet the inclusion criteria.

Among 884 interviewees, 666 individuals were not eligible according to the following exclusion criteria: body weight alterations [greater than or equal to]3 kg (n = 58); increase or decrease in daily physical activities (i.e., engagement in or dropout from regular programs), and/or food intake (i.e., special diet in the 3 months preceding the study (n = 51); occurrence of heart or cerebrovascular diseases, infectious, and/or inflammatory diseases, diseases of the gastrointestinal tract or liver, chronic kidney and/or history of kidney stones, cancer in the previous 10 years (n = 75); treatment using diuretics or drugs that could alter food intake and/or metabolism of nutrients (n = 434); use of pacemakers and/or prosthetic limbs (n = 2); and elite athletes (n = 1). Throughout the data collection, 45 individuals did not complete all phases and were excluded. Thus, 218 individuals (50 [+ or -] 5 years) concluded all steps of the present study.

The study is in accordance with the resolution 466/2012 from the Brazilian Ministry of Health regarding research involving human individuals and was approved by the Ethics Committee on Human Research of the UFV (protocol 069/2010/CEPH). All participants included in the study signed the consent form in accordance with the Declaration of Helsinki.

Anthropometric, blood pressure, and biochemical assessments

Anthropometric measures (weight, height, and WC) were performed using standard procedures, as previously described (Cocate et al. 2014). Total body scan was performed by dual-beam X-ray absorptiometry (LUNAR, GE, Encore software version 13:31, Madison, Wis., USA) to determine the percentages of total body fat (TBF) and obesity cut-off value was set at 25% (Bray et al. 1998). Body mass index (BMI) was calculated and a cut-off to diagnose obesity (BMI [greater than or equal to] 30 kg/[m.sup.2]) was used (World Health Organization (WHO) 2000).

Systolic (SBP) and diastolic blood (DBP) pressures were measured using an automatic inflation blood pressure monitor (BP3AA1-1, G-Tech, OnboElectronicCo, Schenzen, China), registered at ANVISA (No. 80275310004), following the VI Brazilian Guidelines on Hypertension (Brazilian Cardiology Society, Brazilian Hypertension Society, and Brazilian Nefrology Society 2010).

Blood samples were collected from the antecubital vein and the serum was separated by centrifugation at 2225g for 15 min at room temperature. Serum was aliquoted and frozen at -80[degrees]C until laboratorial analyses.

Blood glucose was measured by the glucose oxidase method using the Cobas Mira Plus equipment (Roche Diagnostics, GmbH, Montclair, N.J., USA). Insulin was measured by electrochemiluminescence using the Modular Analytics (E170, Roche Diagnostics, GmbH, Mannheim, Germany).

Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TAG levels were determined by an enzymatic colorimetric method using Cobas Mira Plus (Roche Diagnostics GmbH).

C-reactive protein (CRP) level was determined by an enzymatic immunoturbidimetric method with a commercially available kit (sensitivity from 0.03 mg/L; Quibasa Qufmica Basica LTDA, Belo Horizonte, MG, Brazil).

Serum IL-18 (sensitivity: < 1 pg/mL; Boster, Wuhan, China) and adiponectin (sensitivity: 0.5 ng/mL; SPIbio, Montigny-le-Bretonneux, France) levels were determined by a commercially used enzyme-linked immunosorbent assay with intra-assay and inter-assay coefficients of variability less than 6.9% and 7.5%.

Determination of MetS, LAP, and cardiometabolic risk factors

Metabolic syndrome was diagnosed in individuals who exhibited 3 or more factors according to the criteria and cut-off points suggested by Alberti et al. (2009) and central obesity was defined as WC [greater than or equal to] 90 cm (Alberti et al. 2009).

LAP was used to estimate the state of lipid overaccumulation using a combination of abdominal enlargement and elevated concentration of circulating TAG (Kahn and Valdez 2003; Taverna et al. 2011). The formula [WC (cm) - 65] x [TG (mmol/L)] for men includes the minimum WC value used to define sex-specific origin points (65 cm for men) used in the III National Health and Nutrition Examination Survey sample (Kahn 2005). In our study participants, the minimum WC value for men was 70.3 cm and its adjustment in the formula did not change the findings (data not shown). Thus, we used the original formula and the cut-off value of [greater than or equal to]51.82 (Taverna et al. 2011) for MetS diagnosis.

The following values were also set as cardiometabolic risk factors using VI Brazilian Guideline of Hypertension (Brazilian Cardiology Society, Brazilian Hypertension Society, and Brazilian Nefrology Society 2010) and Sposito et al. (2007): dyslipidemia (TC [greater than or equal to] 200 mg/ dL) and hypertension (SBP [greater than or equal to] 140 mm Hg and/or DBP [greater than or equal to] 90 mm Hg). The homeostasis model assessment (HOMA-IR) was used to detect IR using an equation proposed by Matthews et al. (1985) and a cut-off value (HOMA-IR [greater than or equal to] 2.71) suggested by Geloneze et al. (2006).

Lifestyle

Participants responded to questions about the frequency of smoking (yes/no) and about the frequency and quantity of alcoholic beverage consumption and were classified as consumers if consumption was higher than 21 units per week (Duncan 2013).

Habitual physical activity was estimated by the mean number of daily steps (7 consecutive days) measured by the digital pedometer (Digiwalker SW-200, Yamax Corp., Tokyo, Japan) (Tudor-Locke et al. 2005). In this study, 10 000 steps/day was considered an adequate cut-off point, since it was associated with health-related parameters, and was used to classify individuals as "active" (Cocate et al. 2014; Tudor-Locke et al. 2005).

Statistics

Descriptive data are presented as mean values and standard deviation or median and interquartile range for continuous variables, according to normality of the variable, while frequency was used for categorical variables. Normal distribution of data and homogeneity of variance were determined by the Shapiro-Wilk and Levene's test, respectively.

Statistical comparisons between 2 groups were performed using the Student's t test, Mann-Whitney U test, or [chi square] test as appropriate, and the Spearman test was used for correlation between pro-inflammatory and anti-inflammatory biomarkers, and LAP. To verify the effect of IL-18 and adiponectin on the cardiovascular risk factors, we categorized the individuals into 3 groups using the threshold of each tertile of these biomarkers (IL-18: < 206.5, 206.5 to 336.4, and [greater than or equal to] 336.4 pg/mL; adiponectin: < 4.83, 4.83 to 7.02, and [greater than or equal to] 7.02 [micro]g/mL). Thus, for comparison among 3 groups, 1-way ANOVA or Kruskal-Wallis followed by Tukey or Mann-Whitney post hoc test were deemed to be appropriate.

The odds ratio was determined by ordinal logistic multivariate regression with a confidence interval of 95% to assess the associations of IL-18 and adiponectin tertiles (independent variables) with the occurrence of LAP, MetS, and cardiometabolic risk factors (dependent variables) adjusted by age, smoking, alcohol consumption, physical activity level, and total body fat percentage. Non-normally distributed independent variables were log or square-root transformed before regression analyses.

All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, Ill., USA) for Windows 7 (Microsoft, Redmond, Wash., USA). The results were considered statistically significant at the 0.05 level.

Results

The prevalence ofhypertension, hyperglycemia, hypertriglyceridemia, and low HDL-C concentration was over 20%, while that of MetS was about 30% in the studied population. In addition, more than 40% were classified as sedentary and over 50% exhibited central obesity (Fig. 1A). Moreover, about 25% of them showed no components of MetS (Fig. 1B).

When individuals with MetS were compared with those without MetS (Table 1), no differences in the mean number of steps/day was observed. However, using a cut-off point for the physical activity level (10 000 steps/day), the MetS group had a higher number of less active individuals. Furthermore, the MetS group individuals had a higher prevalence of obesity (BMI > 30 kg/[m.sup.2] and TBF > 25%), higher IL-18 and CRP, and lower adiponectin concentrations compared with the non-MetS group individuals.

As expected, a positive correlation was observed between the inflammatory biomarkers CRP and IL-18 ($r = 0.87$ $p < 0.01$). However, although significant, adiponectin was poorly correlated with IL-18 and CRP ($r = -0.22$, $p < 0.01$ and $r = -0.25$, $p < 0.01$, respectively).

Serum IL-18 ($r = 0.48$, $p < 0.01$) and adiponectin ($r = -0.22$, $p < 0.01$) were associated with LAP (Fig. 2A and 2B). Although significant, poor correlations of IL-18 and adiponectin ([r.sup.2] = 0.16), as the independent variables, with LAP (dependent variable) were found.

Interestingly, as shown in Table 2, when we subdivided the studied

individuals according to IL-18 and adiponectin tertiles, those included in the highest tertile of IL-18 (> 336.4 pg/mL) had higher values of LAP, WC, TBF, glucose, insulin, HOMA-IR, TC, TAG, CRP, and blood pressure, and lower values of adiponectin, compared with those in the lowest tertile (< 206.5 pg/mL). In turn, individuals in the highest tertile of adiponectin (> 7.02 [micro]g/mL) exhibited lower values of LAP, WC, TBF, insulin, HOMA-IR, HDL-C, TG, and SBP, and higher values of IL-18, compared with those in the lowest tertile (< 4.83 [micro]g/mL).

The IL-18 concentration was an independent predictor of the prevalence of MetS and was positively associated with high LAP values (> 51.28), central obesity, and hypertriglyceridemia, after adjustment for age, smoking, excessive alcohol consumption, habitual physical activity level, and TBF (Table 3). In contrast, high adiponectin values ([greater than or equal to] 7.02 [micro]g/mL) were inversely associated with MetS occurrence (model 1), high values of LAP and hypertriglyceridemia, as well as with low values of serum HDL-C (models 1 and 2). However, we did not observe a relationship between the high adiponectin concentration and central obesity and hypertension.

Discussion

We demonstrated here that both serum IL-18 and adiponectin are good biomarkers for the identification of MetS in a population of middle-aged Brazilian men. Serum IL-18 was shown to be more accurate, independent of adjustments. In addition, serum IL-18 exhibited a positive association with LAP and other cardiometabolic risk factors, but not with HDL-C. Serum adiponectin showed a negative association with LAP and other cardiometabolic risk factors, except with WC and hypertension.

Two main aspects highlight these findings. First, serum IL-18 and adiponectin are important pro- and anti-inflammatory biomarkers, respectively, and their association with components of MetS confirms the effectiveness of such biomarkers to identify MetS in apparently healthy middle-aged Brazilian men. Second, the association of IL-18 and adiponectin with LAP observed here reinforces the reliability of LAP to identify MetS in the studied population. It is noteworthy that LAP is a simple, low-cost, and easy calculation index for identifying MetS (Kahn and Valdez 2003), which has demonstrated an association with MetS and cardiometabolic risk factors in middle-aged men of different ethnicity (Du et al. 2015; Gao et al. 2013; Ioachimescu et al. 2010; Kahn 2006; Taverna et al. 2011; Xia et al. 2012).

In the present study, when the participants were subdivided according to IL-18 tertiles, the values of the cardiometabolic features (TC, glucose, insulin, LAP, high blood pressure, and WC) were increased in the highest tertile (IL-18 [greater than or equal to] 336.4 pg/mL). In fact, the relationship of IL-18 with cardiometabolic risk factors has been reported in men of different geographical locations and ethnic backgrounds (Zirlik et al. 2007; Jefferis et al. 2011; Yamaoka-Tojo et al. 2011; Espinola-Klein et al. 2008). Given the ethnic miscegenation of the Brazilian population, our results suggest that the association of IL-18 with cardiometabolic risk factors may occur independently of ethnicity and geographical location. Importantly, unlike previous studies where the participant ages ranged from 18 to 75 years, our cross-sectional study focused on middle-aged men and confirmed that the above relationship in this population age group could allow for new cardiovascular events (de Padua Mansur and Favarato 2012). Indeed, the morbidity and mortality by cardiometabolic diseases has increased significantly in Brazil (Ministerio da Saude 2012).

Adiponectin is an adipose-specific secretory protein and its transcription is abundant in the adipocyte (Turer and Scherer 2012). This adipokine is an important hormone with anti-inflammatory properties and studies have clearly demonstrated its protective effects against metabolic disorders (Fantuzzi 2013). We also analyzed the association of adiponectin with MetS, LAP, and cardiometabolic risk factors and observed that individuals with adiponectin [greater than or equal to] 7.03 [micro]g/mL had a lower occurrence of MetS, hypertriglyceridemia, low HDL-C, and high LAP. These findings are in agreement with those previously reported in populations of middle-aged men from different ethnicity (Abdelgadir et al. 2013; Ai et al. 2011; Andreasson et al. 2012; Ding et al. 2015) and reinforce the relevance of the association of low concentrations of adiponectin with cardiometabolic diseases (Turer and Scherer 2012).

Our data showed that serum adiponectin was not associated with central obesity (WC [greater than or equal to] 90 cm). In addition, the use of TBF as an adjustment variable weakened the association of adiponectin with MetS occurrence, hypertriglyceridemia, and low HDL-C concentration. Despite being established as a robust biomarker for insulin sensitivity and cardiometabolic diseases (Turer and Scherer 2012), it has been demonstrated that many factors, i.e., physical activity level (de Lemos et al. 2012), diet (Flachs et al. 2006), smoking (Takefuji et al. 2007), and alcohol consumption (Sierksma et al. 2004), may increase or decrease serum adiponectin concentration. In fact, either weak or no relationship of adiponectin with coronary heart disease risk factors in healthy middle-aged European men was demonstrated (Lindsay et al. 2005; Luc et al. 2010). The reasons for differences between various studies are not clear. However, it may reflect underlying differences in the study populations. For example, the incidence of diabetes or obesity may affect the serum adiponectin levels (Lindsay et al. 2005; Pischon et al. 2004). In the present study, individuals were apparently healthy middle-aged men and our results are in keeping with those reported by Luc et al. (2010).

Despite the weak correlation of LAP with pro- and antiinflammatory biomarkers, the use of the cut-off point (LAP [greater than or equal to] 51.28) suggested by Taverna et al. (2011) exhibited positive and negative associations of LAP with IL-18 and adiponectin, respectively. This cut-off point is lower than that proposed by Tellechea et al. (2009) (LAP [greater than or equal to] 53.63) for an Argentinean population aged 18 to 65 years.

These different results reinforce the need for indicating the best cut-off for LAP in specific populations and motivate the use of this index as a predictor of MetS (Taverna et al. 2011; Chiang and Koo 2012).

As expected, a positive correlation was found between the pro-inflammatory biomarkers CRP and IL-18. However, although significant, adiponectin exhibited a poor correlation with proinflammatory biomarkers. The higher accuracy of serum IL-18 in diagnosing MetS as well as the stronger relationships with LAP and cardiometabolic risk factors compared with adiponectin observed in the present study could be explained by taking 3 aspects into account. First, nearly 90% of our subjects exhibited high alcohol consumption, and almost 60% were physically active, both of which may elevate adiponectin (de Lemos et al. 2012; Sierksma et al. 2004). Second, in this case, the pro-inflammatory state (i.e., IL-18) constitutes the primary response at the beginning of the inflammatory process, resulting in a relevant increase of this biomarker. Third, unlike adiponectin, IL-18 is secreted by nearly all cells in healthy humans and may act in homeostasis regulation (Dinarello et al. 2013). Thus, in individuals without the presence of other diseases (i.e., autoimmunity), a small variation ofIL-18 could help in the early diagnosis of MetS and other cardiometabolic diseases.

Nevertheless, there is no consensus on the dividing line values for inflammatory biomarkers in distinguishing healthy from unhealthy people, as well as eutrophic and obese individuals (Volp et al. 2008), as these values exhibit great variability within populations (de Lemos et al. 2012; Ferrucci et al. 2005). For example, Dinarello et al. (2013) reported, in a recent review, studies associating IL-18 with various diseases, and the cut-off points for IL-18 used varied widely (i.e., from 200-2000 pg/mL). In studies on MetS, the mean values of serum IL-18 concentrations were 62.9 (46.4-81.2) (Espinola-Klein et al. 2008), 302 (117.1-779.1) pg/mL (Jefferis et al. 2011), 280.2 [+ or -] 90.9 pg/mL (Richard et al. 2013), and 301 [+ or -] 220 pg/mL (Yamaoka-Tojo et al. 2011). Such variability in IL-18 circulating levels may be associated with factors such as health status, ethnicity, and IL-18 gene polymorphism (He et al. 2010; Presta et al. 2009; Thompson et al. 2007). Thus, the proposition of a cut-off point for potential clinical use is still premature and more studies on different populations according to age, sex, lifestyle, and ethnicity are necessary.

The present study has limitations. First, because of the limited value of cross-sectional designs, it is not possible to affirm that the reported associations are causal. Although we have controlled several potential covariates, additional evidence from prospective studies is necessary before a firm conclusion can be reached in this issue. Second, the use of a simple cut-off point for classifying physical activity level (10 000 steps/day) is limited because this does not provide for a clear distinction between those who we consider to be active (i.e., [greater than or equal to] 10 000 steps/day) and those we consider to be less active (i.e., < 10 000 steps/day). Thus, the impact of physical activity level on our study findings must be interpreted with caution.

In conclusion, the increase of serum IL-18 concentration showed a greater ability to identify MetS than adiponectin in a population of middle-aged Brazilian men, and serum IL-18 and adiponectin are associated with LAP and cardiometabolic risk factors in this population. These findings suggest LAP may be useful to identify MetS and cardiometabolic diseases in middle-aged Brazilian men. Nevertheless, although the relationship between inflammatory biomarkers, cardiometabolic risk factors and LAP were evidenced, further studies are necessary to clarify the best cut-off point for LAP in this specific population.

Conflict of interest statement

Authors declare that they do not have any conflict of interest.

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Table 1. General characteristics and inflammatory biomarkers in the study participants according to MetS occurrence. Without MetS, n = 154 With MetS, n = 64 Age, y > 51 (46-54) 51(47-54) Excessive alcohol 21(13.6) 10 (15.6) consumption (a) Smokers (b) 14 (9.1) 7 (10.9) Steps/d 11 279 [+ or -] 3940 10 573 [+ or -] 4026 Active lifestyle, 88 (63.6) 30 (47.6) [greater than or equal to] 10 000 steps/d (c) BMI, kg/[m.sup.2] 25.23 [+ or -] 3.00 28.19 [+ or -] 2.80 BMI < 30 kg/[m.sup.2] 146 (94.8) 45 (70.3) Nonobese, < 25% TBF 120 (77.9) 32 (50.0) CRP, mg/L 0.78 (0.38-1.63) 1.53 (0.75-3.36) Interleukin-18, pg/mL 244.5 (120.0-345.8) 327.9 (228.0-470.0) Adiponectin, 6.1 (4.7-7.9) 4.9 (3.9-7.2) [micro]g/mL P Age, y 0.685 Excessive alcohol 0.702 consumption (a) Smokers (b) 0.674 Steps/d 0.235 Active lifestyle, 0.029 * [greater than or equal to] 10 000 steps/d (c) BMI, kg/[m.sup.2] < 0.001 * BMI < 30 kg/[m.sup.2] < 0.001 * Nonobese, < 25% TBF < 0.001 * CRP, mg/L < 0.001 * Interleukin-18, pg/mL < 0.001 * Adiponectin, 0.011 * [micro]g/mL Note: Data are means [+ or -] SD or median (interquartile interval) or frequency (n (%)), as appropriated; P values from Student's t test or Mann-Whitney U test or [chi square], as appropriated; n, number of participants. BMI, body mass index; CRP, C-reactive protein; MetS, metabolic syndrome; TBF, total body fat. * Statistical difference between groups. (a) Higher than 21 units per week. (b) Frequent use. (c) Cut-off suggested by Cocate et al. (2014) and Tudor-Locke et al. (2005). Table 2. Anthropometric and cardiometabolic risk features according to tertiles of serum interleukin-18 (IL-18) and adiponectin in the study participants. Tertiles of IL-18, pg/mL < 206.5, n = 73 206.5-336.4, n = 72 LAP 23.7 (15.7-35.0) 37.3 (18.6-53.5) * WC, cm 85.7 (81.0-90.7) 90.9 (85.4-97.8) * TBF, % 18.1 (14.1-21.9) 21.5 (16.8-26.5) * Glucose, mg/dL 87.5 (80-93) 90 (84-97.8) HOMA-IR 0.9 (0.7-1.5) 1.2 (0.9-1.9) * Insulin, 4.2 (3.0-6.6) 5.1 (3.7-8.3) * [micro]U/mL TC, mg/dL 203 (176-232) 208 (189-243) HDL-C, mg/dL 45 (40-54) 44 (37-51) LDL-C, mg/dL 133.7 [+ or -] 30.5 137.6 [+ or -] 36.1 TAG, mg/dL 101 (81-133) 122 (81-174) IL-18, pg/mL 110.3 (68.7-164) 276.2 (229.3-310.2) * CRP, mg/L 0.3 (0.2-0.5) 0.9 (0.6-1.4) * Adiponectin, 6.6 (5.4-8.4) 5.4 (4.3-7.2) * [micro]g/mL SBP, mm Hg 122 (113-129) 127 (118-133) * DBP, mm Hg 80 (71-84) 82 (75-89) * Tertiles of IL-18, pg/mL [greater than or equal to] 336.4, n = 73 LAP 50.2 (27.5-83.2) *, ([dagger]) WC, cm 95.6 (90.1-102.5) * TBF, % 24.2 (19.1-29.5) *, ([dagger]) Glucose, mg/dL 90 (84-100.3) * HOMA-IR 1.5 (0.9-2.2) * Insulin, 6.8 (4.4-8.8) * [micro]U/mL TC, mg/dL 225 (196-251) * HDL-C, mg/dL 44 (37-53) LDL-C, mg/dL 147.1 [+ or -] 35.9 TAG, mg/dL 139 (103-225) * IL-18, pg/mL 407.7 (378.6-479.2) *, ([dagger]) CRP, mg/L 2.3 (1.5-4.6) *, ([dagger]) Adiponectin, 5.1 (4.1-7.4) * [micro]g/mL SBP, mm Hg 127 (118-137) * DBP, mm Hg 84 (77-89) * Tertiles of adiponectin, [micro]g/mL < 4.83, n = 73 4.83-7.02, n = 72 LAP 43.4 (25.5-79.5) 30.8 (18.7-50.2) * WC, cm 93.2 (91.0-95.4) 91.1(88.9-93.3) TBF, % 23.3 (20.4-22.2) 21.5 (19.8-23.1) Glucose, mg/dL 89.5 (82.0-99.8) 88.0 (83.0-92.5) HOMA-IR 1.5 (0.9-2.4) 1.1 (0.7-1.7) * Insulin, 6.9 (4.6-10.1) 5.1 (3.4-7.3) * [micro]U/mL TC, mg/dL 222 (194-251) 199 (183-229) HDL-C, mg/dL 41 (34-48) 44 (38-51) LDL-C, mg/dL 144.5 [+ or -] 34.9 136.7 [+ or -] 33.3 TAG, mg/dL 140 (104-224) 110 (74-159) * IL-18, pg/mL 237.1 (107.9-347.5) 255.6 (131.2-372.9) * CRP, mg/L 1.3 (0.6-2.2) 0.9 (0.4-2.3) Adiponectin, 4.0 (3.4-4.4) 5.9 (5.2-6.3) *

[micro]g/mL SBP, mm Hg 152 (110-197) 128 (66-187) * DBP, mm Hg 126 (120-136) 125 (115-130) Tertiles of adiponectin, [micro]g/mL [greater than or equal to] 7.02, n = 73 LAP 29.9 (19.0-43.3) * WC, cm 89.5 (87.5-91.6) * TBF, % 19.2 (17.6-20.8) * Glucose, mg/dL 91.0 (84.0-100.0) HOMA-IR 1.1 (0.8-1.6) * Insulin, 4.6 (3.5-6.8) * [micro]U/mL TC, mg/dL 211 (185-238) HDL-C, mg/dL 46 (40-58) * LDL-C, mg/dL 138.5 [+ or -] 35.3 TAG, mg/dL 110 (84-143) * IL-18, pg/mL 305.1(220.7-393.7) * CRP, mg/L 0.7 (0.3-1.6) * Adiponectin, 8.4 (7.5-9.7) *, ([dagger]) [micro]g/mL SBP, mm Hg 118.5 (54-174) * DBP, mm Hg 127 (116-136) Note: Data are means [+ or -] SD or median (interquartile deviation) according normality; n, number of participants; P values from ANOVA 1-way or Kruskall-Wallis followed by Tukey or Mann-Whitney post hoc as appropriated. CRP, C-reactive protein; BP, blood pressure; HOMA-IR, homeostasis model assessment-insulin resistance; HDL-C, high-density lipoprotein cholesterol; LAP, lipid accumulation product; LDL-C, low-density lipoprotein cholesterol; TAG, triacylglycerol; TBF, total body fat; TC, total cholesterol; WC, waist circumference. * Statistically different from the first tertile (p < 0.05). ([dagger]) Statistically different from the second tertile (p < 0.05). Table 3. Prevalence ratio (confidence interval 95%) to MetS, LAP, and cardiometabolic risk factors (dependent variables), according to tertiles of IL-18) and adiponectin (independent variables) in the study participants. Tertiles of IL-18, pg/mL < 206.5 206.5-336.4 MetS, no vs. yes Model 1 1 4.36 (1.80-10.59) * Model 2 1 3.72 (1.50-9.19) * LAP, < 51.28 vs. [greater than or equal to] 51.28 Model 1 1 2.37 (1.13-4.95) * Model 2 1 1.946 (0.85-4.43) * Central obesity, 1 no vs. yes, < 90 vs. [greater than or equal to] 90 cm Model 1 1 4.39 (2.08-9.24) * Model 2 1 4.09 (1.76-9.51) * Hypertriglyceredima, no vs. yes Model 1 1 2.46 (1.57-3.84) * Model 2 1 2.28 (1.40-3.69) * Low HDL-C, no vs. yes Model 1 1 1.31 (0.85-2.00) Model 2 1 1.29 (0.84-1.98) Hypertension, 1 no vs. yes Model 1 1 1.57 (0.95-2.59) Model 2 1 1.43 (0.85-2.39) Tertiles of IL-18, pg/mL [greater than or equal to] 336.4 MetS, no vs. yes Model 1 5.66 (2.37-13.54) * Model 2 4.10 (1.50-9.19) * LAP, < 51.28 vs. [greater than or equal to] 51.28 Model 1 7.12 (2.82-18.01) * Model 2 4.33 (1.60-11.77) * Central obesity, no vs. yes, < 90 vs. [greater than or equal to] 90 cm Model 1 9.44 (4.34-20.55) * Model 2 6.69 (2.80-15.99) * Hypertriglyceredima, no vs. yes Model 1 3.88 (2.47-6.11) * Model 2 3.12 (1.88-5.15) * Low HDL-C, no vs. yes Model 1 1.17 (0.76-1.79) Model 2 1.13 (0.72-1.77) Hypertension, no vs. yes Model 1 1.68 (1.03-2.73) * Model 2 1.40 (0.84-2.33) Tertiles of adiponectin, [micro]g/mL < 4.83 4.83-7.02 MetS, no vs. yes Model 1 1 1.21(0.54-2.74) Model 2 1 1.33 (0.57-3.09) LAP, < 51.28 vs. [greater than or equal to] 51.28 Model 1 1 0.38 (0.18-0.82) * Model 2 1 0.39 (0.16-0.93) * Central obesity, no vs. yes, < 90 vs. [greater than or equal to] 90 cm Model 1 1 0.84 (0.42-1.67) Model 2 1 1.03 (0.46-2.32) Hypertriglyceredima, no vs. yes Model 1 1 0.60 (0.26-1.36) Model 2 1 0.63 (0.27-1.47) Low HDL-C, no vs. yes Model 1 1 0.65 (0.31-1.38) Model 2 1 0.67 (0.31-1.39) Hypertension, no vs. yes Model 1 1 0.48 (0.20-1.16) Model 2 1 0.42 (0.17-1.07) Tertiles of adiponectin, [micro]g/mL [greater than or equal to] 7.02 MetS, no vs. yes Model 1 0.42 (0.20-0.88) * Model 2 0.50 (0.23-1.07) LAP, < 51.28 vs. [greater than or equal to] 51.28 Model 1 0.26 (0.11-0.60) * Model 2 0.30 (0.12-0.76) * Central obesity, no vs. yes, < 90 vs. [greater than or equal to] 90 cm Model 1 0.57 (0.29-1.13) Model 2 0.78 (0.35-1.74) Hypertriglyceredima, no vs. yes Model 1 0.30 (0.14-0.66) * Model 2 0.35 (0.16-0.77) * Low HDL-C, no vs. yes Model 1 0.31(0.15-0.68) * Model 2 0.31(0.15-0.65) * Hypertension, no vs. yes Model 1 0.84 (0.38-1.86) Model 2 0.67 (0.29-1.54) Note: IL-18, interleukin-18; HDL-C, high-density lipoprotein cholesterol; LAP, lipid accumulation product; MetS, metabolic syndrome; Model 1, adjusted by age, smoking, alcohol consumption and physical activity level; Model 2, further adjusted by the percentage of body fat; TAG, triacylglycerol; WC, waist circumference. * Denotes statistically significant relationship (p < 0.05).