Cytokine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Myostatin and adipokines: The role of the metabolically unhealthy obese phenotype in muscle function and aerobic capacity in young adults

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ARTICLE INFO

Keywords:
Adipokines
Myokines
Obesity
Metabolic Syndrome
Metabolism

ABSTRACT

Obesity is often associated with metabolic disorders. However, some obese people can present a metabolically healthy phenotype, despite having excessive body fat. Obesity-related cytokines, such as myostatin (MSTN), leptin (LP) and adiponectin (ADP) appear to be key factors for the regulation of muscle and energy metabolism. Our aim was to compare lipid, glucose-insulin and inflammatory (tumor necrosis factor alpha; TNF-α) profiles, muscle function, energy expenditure and aerobic capacity between healthy normal-weight (NW) adults, metabolically healthy obese (MHO) and metabolically unhealthy obese (MUHO) adults; to study the associations between these outcomes and the cytokines MSTN, ADP, LP; and to establish cutoffs for MSTN and LP/ADP to identify the MUHO phenotype. Sixty-one young adults (NW, n = 24; MHO, n = 16; MUHO, n = 21) underwent body composition (body fat -BF and muscle mass - MM), energy expenditure at rest (RER) and aerobic capacity (VO_{2peak}) evaluation, muscle strength and endurance tests and blood profile characterization (glucose-insulin homeostasis and serum MSTN, ADP, LP and TNF-α). MHO and MUHO had a BMI ≥ 30 kg m^{-2}. MUHO was defined as presenting ≥3 criteria for metabolic syndrome (NCEP/ATPIII) in association with insulin resistance (HOMA-IR ≥3.46). MSTN and LP/ADP were associated with MM, MetS and glucose-insulin profile; MSTN was associated with TNF-α and only LP/ADP was associated with parameters of obesity and $VO_{2peak.}$ Neither MSTN nor LP/ADP was associated with muscle functions ($p < .05$ for adjusted correlations). Both of them were able to discriminate the MUHO phenotype: MSTN [AUC(95%CI) = 0.71(0.55–0.86), MSTN > 517.3 pg/mL] and LP/ADP [AUC(95%CI) = 0.89(0.81–0.97), LP/ADP > 2.14 pg/ng]. In conclusion, high MSTN and LP/ADP are associated with MetS, glucose-insulin homeostasis impairment and low muscle mass. Myostatin is associated with TNF-α and leptin-to-adiponectin ratio is associated with body fatness and aerobic capacity. Neither MSTN nor LP/ADP is associated with energy expenditure, muscle strength and endurance. Myostatin and adipokines cutoffs can identify the metabolically unhealthy obese phenotype in young adults with acceptable accuracy.

1. Introduction

It has long been known that obesity is one of the major causes of preventable morbidity and mortality due to the development of metabolic and cardiovascular disorders [1]. However, in the past years much evidence has shown that some obese people, the so-called metabolically healthy obese, have a much lower likelihood of developing such conditions than those who, besides being obese, present additional metabolic impairment, such as metabolic syndrome and insulin resistance [2].

Obesity causes metabolic disorders essentially by inducing a subclinical inflammatory state, characterized by an unbalanced release of specific pro-inflammatory cells and fat-cell proteins called adipokines [3–6], among which leptin (LP) and adiponectin (ADP) stand out as

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https://doi.org/10.1016/j.cyto.2017.12.008
Received 20 April 2017; Received in revised form 16 August 2017; Accepted 6 December 2017
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having an important role in this condition. [7-9]. Leptin contributes to whole-body leptin production, food intake and adipose tissue metabolism regulation as well as to protein metabolism regulation. Adiponectin, in turn, plays a critical role in energy homeostasis and insulin signaling pathway, in mitochondrial biogenesis, lipid metabolism regulation and oxidative stress [10].

On the other hand, secretory myokines exert a variety of systemic effects and they are modulated to some extent by the action of the adipokines, which confirms the dynamic crosstalk between muscular and adipose tissues [10–12]. Myostatin (MSTN) [13], a member of the transforming growth factor β (TGF-β) superfamily, is an important negative regulator of skeletal muscle size and regeneration [12,14,15]. However, recent evidence, mainly from studies performed on animal models, has suggested that it may also be a key factor for energy metabolism regulation. In humans, its role is not fully elucidated, but it seems that a positive association exists between this myokine, obesity and metabolic disorders, such as metabolic syndrome, insulin resistance and diabetes [16,17].

The MSTN gene is also expressed to a lesser extent in adipose cells, where it could have an influence on adipogenesis and on increased energy expenditure [11,18] due to an increased expression of brown adipocyte markers in white adipose tissue [10,19]. Moreover, previous studies demonstrated that MSTN is related to weight loss [20], weigh regain [21] and to muscle and metabolism changes throughout exercise interventions [11,15,22]. In recent years, there has been growing interest on MSTN inhibition therapy to counteract the negative effects of obesity, osteoporosis and pathological or environmental conditions leading to varying degrees of muscle atrophy [23]. The benefits of such therapy would be to reduce fat accumulation, to improve muscle hypertrophy [15,24] as well as to increase bone mineral density [25].

Some authors have suggested that MSTN and obesity-specific cytokines [15,26-28] may also affect muscle strength and fatigability as well as aerobic capacity, all of which are considered main determinants of future physical disability and mortality [29,30]. These associations between biological markers and clinical measures, however, are yet to be explored, especially in at-risk populations, such as obese individuals with or without metabolic impairment.

Therefore, the present study aimed to: (1) compare lipid, glucose-insulin and inflammatory profiles, muscle function, aerobic capacity and energy expenditure between healthy normal-weight adults, metabolically healthy obese adults and obese adults with metabolic impairments; (2) to study the associations between these outcomes and the cytokines MSTN, ADP, LP and; 3) to establish cutoffs of MSTN and LP/ADP to identify individuals with an unhealthy metabolic phenotype.

2. Materials and methods

2.1. Study design, population and protocol overview

Sixty-one sedentary normal-weight and obese young adults (30 women; 31 men), aged 20–45 years were recruited from the community to participate in this cross-sectional study. After potential subjects responded to the first screening, they were submitted to the following evaluations over three non-consecutive days (at least 48 h-interval): (1) clinical anamnesis, physical activity questionnaire and spirometry; (2) maximal symptom-limited cardiopulmonary exercise testing (CPX); (3) blood sample collection, body composition assessment and muscle strength and endurance evaluation. Participants were subsequently allocated into the Normal-weight group (NW, n = 24), the metabolically healthy but obese group (MHO, n = 16) and the metabolically unhealthy obese group (MUHO, n = 21) according to their Body Mass Index (BMI): (1) NW ≤ 25 kg m^{-2}; and (2) MHO/MUHO ≥ 30 kg m^{-2}. Then, individuals were classified as MUHO if they had at least three out of five criteria for Metabolic Syndrome (MetS) according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) [31] and insulin resistance (HOMA-IR > 3.46) [32].

The exclusion criteria were: non-stable body mass for at least 6 months; individuals performing more than 50 mins per week of moderate-to-vigorous-intensity physical activity; pregnancy or premature menopause; history of gynecological and/ or orthopedic surgeries; smokers; alcohol drinkers; use of drugs influencing metabolism during the past 6 months, except oral contraceptives; neurological, pulmonary and cardiovascular diseases, diabetes and/or cognitive impairment. After study initiation, subjects presenting difficulty in understanding experimental procedures or inability to accomplish the whole protocol were excluded from the study.

The study was approved by the Ethics Committee of Federal University of São Carlos (CEP-UFSCar: opinion N. 326.607) and all volunteers signed a written informed consent.

2.2. Clinical evaluation – 1st day

During the clinical anamnesis, subjects answered the Baecke physical activity questionnaire, validated for Brazilian people [33], including questions about perceptual physical effort at work and during leisure time and sport activities.

Height and body mass (BM) were measured (Welmy 104-A, Santa Bárbara do Oeste, SP, Brazil) in standing barefoot position. Muscle mass (MM, in%) and body fat (BF, in%) were obtained from a tetrapolar bioelectrical impedance analyzer (Model BC-558, Ironmann, Tanita Corporation, Tokyo, Japan) after having completed at least 4 h of absolute fasting. Abdominal fat was assessed by waist circumference (WC). At least two measurements were taken from each marked location and the mean value was used for statistical analysis.

Baseline systolic (SBP) and diastolic (DBP) blood pressure were measured to the nearest 2 mmHg, after being seated for approximately 5 min.

Pulmonary function was investigated (Oxycon Mobile®, Mijnhardt/Jäger, Würzburg, German) to ensure inclusion of volunteers with normal lung function according to the reference values for spirometry in white Brazilian adults [34].

2.3. Cardiopulmonary exercise testing (CPX) – 2nd day

As previously described [35], a maximal symptom-limited cardiopulmonary exercise testing was conducted on a treadmill (Master Super ATL, Inbramed/Inbrasport, Porto Alegre, RS, Brazil) according to the Bruce protocol and breath-by-breath measures were collected using a portable metabolic system (Oxycon Mobile®, Mijnhardt/Jäger, Würzburg, German), from which the peak value of oxygen uptake (VO_{2peak}) was obtained. Heart rate and perceived exertion were also monitored and registered (data not shown). Energy expenditure at rest (RER), represented by the ratio between VCO_2/VO_2, was also evaluated in the resting condition before the exercise testing. All ergospirometric variables were determined as the highest 15-second averaged values.

2.4. Blood analysis, body composition and muscle function – 3rd day

For metabolic and inflammatory profile, a blood collection was performed in the morning, with volunteers fasted between 12 and 14 h. The volunteers were oriented not to exercise within 48 h of the exam, to maintain their usual diet and not to attend the exam if any inflammatory process was present.

Fasting glucose, insulin levels and subsequent insulin resistance index by the Homeostasis Model Assessment method (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI) and lipid profile (High density lipoprotein- [HDL-c] and triglycerides [TGL]) were quantified.

Sample tubes for subsequent cytokines analysis were centrifuged (Serocito, Model 2400, FANEM, Brazil) and aliquots obtained from - plasma were frozen at −80 °C. Samples were further analyzed in duplicate by the enzyme-linked immunosorbent assay (ELISA) method

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