

Clinical and Anthropometric Characteristics of the Metabolically Unhealthy Phenotype in Adolescents with Adequate and High BMI

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Abstract

Background The metabolically healthy (MH) and metabolically unhealthy (MUH) phenotypes have been discussed in the literature but the factors related to the development of these phenotypes, in adolescents with adequate and high body mass index (BMI), are not yet fully understood. **Objective** To evaluate the relationship between age during the menarche, serum leptin concentrations, body composition and MH and MUH phenotypes, in adolescents with adequate and high BMI.

Methods Observational and cross-sectional study made up of female adolescents attended at Centro de Referência do Adolescente, in Macaé, Rio de Janeiro. The stage of sexual maturation and the age at menarche were analyzed based on the self-declaration of the participants. The menarche was considered early (EM) when the first menstruation occurred up to 11 years of age; normal (NM) between 12 and 14 years old; and late after 15 years of age. Body mass and height were measured to calculate BMI, and the following body variables were analyzed: waist circumference (WC), waist/height ratio (WHR), body fat (BF%), fat body mass index (FBMI) and fat-free mass index (FFMI), visceral adiposity index (VAI). In addition, cardiometabolic components and serum leptin concentrations were measured.

Results 82% (n=114) of the adolescents were classified as MH and 18% (n=25) as MU. The mean age at menarche was 11.79 ± 1.39 years. 60% (n=15) of EM and 84% (n=21) of inadequacy of serum leptin were identified in the MUH group. Among eutrophic women, there was 85.7% (n=6) of inadequate WC among MUH adolescents and 2.5% (n=2) among MH ones ($p < 0.01$), while among adolescents with high BMI, 88.9% (n=16) and 28.6 (n=10) of the MUH and MH groups, respectively, showed inadequacy of this variable ($p < 0.01$). Among MUH adolescents, there was a strong correlation between the age at menarche and BF% ($r = -0.63$ $p < 0.01$); VAI and TG ($r = 0.87$ $p < 0.01$), BF% ($r = 0.63$ $p < 0.01$) and FFM ($r = 0.61$ $p < 0.01$).

Conclusion Age at menarche, serum leptin and WC are related to the MUH phenotype in adolescents and should be investigated, during clinical practice, to help prevent cardiometabolic diseases in adulthood.

Background

The expressive growth of the prevalence of overweight and obesity in children and adolescents is considered a big problem of the world public health, because changes in blood pressure, blood glucose and lipid profile, that follow the excess of body mass, may contribute for the development of cardiometabolic diseases during adulthood [1, 2].

Recently, however, individuals have been identified who present obesity, according with the body mass index (BMI), and a less compromised metabolic profile, denominated metabolically healthy (MH), whose prevalence varies between 6% and 36% among the population of children and adolescents [3]. In contrast, it is estimated that nearly 20% of the subjects considered eutrophic by the BMI are classified as metabolically unhealthy (MUH), due to presenting alterations in various cardiometabolic components [4, 5].

Although the factors related to the development of these phenotypes are not yet fully understood, it is believed that individuals with MH obesity present differentiated body composition, especially regarding the distribution of body fat, better lipidic profile and greater adequacy of hormones secreted by the adipose tissue, as the leptin, when compared to the MUH eutrophics.

Body composition and serum leptin, besides relating to the MH and MUH phenotypes, seem to be determinants to the pubertal development, especially among female adolescents, because hormonal and bodily changes, which occur during the sexual maturation phase, are fundamental for the appearance of the first menstruation [7, 8].

In the last decades, concomitantly with the increase of prevalence of overweight and obesity, and, consequently, with the elevated inadequacy of serum leptin concentrations in young populations, a significant reduction in the age at menarche has been observed, which has worried scientific communities, since evidence shows that early menarche is also a risk factor for the development of cardiometabolic diseases in adulthood [9, 10]. Despite that, to the best of our knowledge, there are no evidences linking the age at menarche with metabolic phenotypes. Thus, the aim of the present study is to assess the relationship between age at menarche, serum leptin concentrations, body composition and MH and MUH phenotypes in adolescents with adequate and elevated BMI.

Materials And Methods

Study Population

This cross-sectional study investigated female adolescents who were patients at a reference health center for adolescents (Centro de Referência do Adolescente) in Macaé, Rio de Janeiro state, Brazil. Posters about the study were displayed in the waiting room, and the overall adolescents who were patients at the center from February 2013 to July 2013 were invited to take part in the study.

Girls aged 10 to 19 who had medical records at the health clinic and had gone through menarche were included. Exclusion criteria were to be pregnant or lactating, to have physical conditions that prevented their anthropometric variables from being measured adequately and use of antipsychotic drugs.

The study was approved by the Research Ethics Committee of Hospital Universitário Clementino Fraga Filho, the teaching hospital attached to the Federal University of Rio de Janeiro. Informed consent forms were signed by the overall participants – by the adolescents who were aged 18 or over and by the parents/guardians of those who were under 18.

Sexual Maturity and Age at Menarche

Sexual maturity was self-assessed using a form showing the stages of breast development, based on the Tanner stages. Stage 1 was classified as prepubescent, while stages II, III, and IV were classified as pubescent, and stage V was classified as postpubescent [11, 12].

Information on menarche was obtained by asking the subjects their age (in years and months) and the time of their first period. Early menarche was ≤ 11 years old, normal menarche was 12–15 years old, and late menarche was ≥ 15 years old [13].

Anthropometric Variables

Weight and height were measured using the techniques recommended by Jelliffe [14], with the subjects barefoot and wearing shorts and a top. They were weighed on digital scales (Welmy, Santa Bárbara d'Oeste, Brazil) and their height was measured using a stadiometer (model 120; Tonelli, Criciúma, Brazil). Body mass index (BMI) was calculated by dividing body weight (kg) by height (m^2). Nutritional status was classified using the cutoff points established by the WHO [15] and the Brazilian nutrition surveillance system, Sistema de Vigilância Alimentar [16], in which normal weight is ≥ 3 rd percentile and < 85 th percentile, overweight is ≥ 85 th percentile, obesity is ≥ 97 th percentile, and severe obesity is ≥ 99 th percentile.

In order to assess body weight distribution and cardiovascular risk, the girls' waist circumference (WC) was measured using a flexible tape placed midway between the lowest rib and the iliac crest, as recommended by McCarthy [17]. The cutoff point used for calculating the inadequacy of WC was the 90th percentile, according to Fernández et al. [18].

The waist-to-height ratio (WHR) was calculated dividing WC (cm) by height (cm) and the cutoff point value adopted for this variable was 0.50 [19]

To estimate the amount of visceral adipose tissue, the visceral adiposity index (VAI) was calculated using the variables WC (cm), BMI (kg/m^2), TG (mmol/L) and HDL-c (mmol/L), according to a formula proposed by Amato et al. [20]:

$$VAI_{\text{women}} = \left(\frac{WC}{36.58 + (1.89 \times BMI)} \right) \times \left(\frac{TG}{0.81} \right) \times \left(\frac{1.52}{HDL-c} \right)$$

Body fat percentage (BF%) was calculated using the equations of Slaughter et al. [21]. The cutoff point value adopted for elevating BF% was $\geq 30\%$, as recommended by Williams et al. [22]. From this variable, fat body mass (FBM) was estimated in pounds, and lean body mass (LBM) was calculated by subtraction between total body mass (kg) and FBM (kg) [23]. Then, the fat body mass index (FBMI) and the fat-free mass index (FFMI) were calculated, according to the equations proposed by Vanitallie et al. [24]:

$$FBMI = \frac{FBM (kg)}{Height (m^2)}$$

$$FFMI = \frac{LBM (kg)}{Height (m^2)}$$

Blood Pressure and Blood Tests

Blood pressure was measured by the oscillometric method using a calibrated semi-automatic digital device. Two measurements were taken one minute apart, and mean was calculated.

Blood was drawn at least after a 12-hour fast for laboratory tests. Blood was taken from the antecubital vein by a trained nurse and stored in plastic tubes with separator gel and clot activator. Tubes were centrifuged at 2,000 RCF (relative centrifugal force) to separate out the plasma and serum and then frozen at -80°C until the analyses. The methods used to analyze triglycerides, HDL-C, and glucose were a lactate dehydrogenase UV assay, a direct method, and an enzymatic colorimetric method (using hexokinase), respectively. Serum concentrations of leptin were analyzed using an ELISA kit (CAN-L4260, DBC Inc., Canada) with the Basic Robotic Immunoassay Operator (BRIO, Italy). The cutoff point for adequate serum leptin was set at > 11.1 ng/mL, as recommended in the kit [25].

Metabolic Classification

The adolescent girls were classified as metabolically healthy (MH) and metabolically unhealthy (MUH) using the criteria established by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [26]. They were classified as MUH if at least three of the following criteria applied to them: WC \geq 90th percentile [18]; triglycerides \geq 150 mg/dL; HDL-C \leq 50 mg/dL; fasting blood glucose \geq 100 mg/dL [27]; blood pressure \geq 90th percentile [28].

Statistical analysis

For statistical analysis, the adolescents were stratified according to age groups, metabolic classification and BMI. The normality of the sample distribution was evaluated by the Kolmogorov-Smirnov test.

Descriptive analyses and the independent samples t-test were used to general characterization of the sample and the equality of means was analyzed by the Levene test.

The association between the categorical variables was analyzed by the Chi-square test (χ^2) and the association between the continuous variables by the Pearson correlation. In this study, strong correlation occurred when values were above 0.6, moderate correlation when values were between 0.4 and 0.59 and low correlation when values were below 0.39 [29].

The level of statistical significance adopted was $p < 0.05$. Analyses were carried out in the SPSS program, version 21.0.

Results

A total of 139 adolescents participated in the study, with a mean age at menarche of 11.79 ± 1.39 years and BMI of 23.52 ± 5.41 kg/m². The MH and MUH phenotypes were prevalent in 82% (n = 114) and 18% (n = 25) of the sample, respectively. This last one presented slightly higher averages of BMI, WC, WHR, FBMI and smaller averages of HDL-c, when compared with the MH group (Table 1).

There was a higher prevalence of EM (63.0%, n = 29) and inadequacy of leptin (80.0%, n = 36) among adolescents who were aged between 10 and 14 years when compared to those older than 15 ($p < 0.01$). Regarding the metabolic phenotypes, 52.0% (n = 13) of the MUH adolescents were in the pubertal phase of sexual maturation; 60.0% (n = 15) presented EM ($p = 0.04$), 84.0% (n = 21) demonstrated high serum leptin ($p = 0.01$). Regarding the BMI, 28.0% (n = 7) of the MUH group was classified as eutrophic, while 30.7% (n = 35), of the MH adolescents had a BMI $\geq p 85$ ($p < 0.01$) (Table 2).

Among the eutrophic ones, a higher prevalence of WC inadequacy was identified in the MUH group (85.7%, n = 6), when compared to the MH one (2.5%, n = 2) ($p < 0.01$). With regard to adolescents with a BMI $\geq p 85$, there was 61.1% (n = 11) and 28.1% (n = 9) of HDL-c inadequacy in MUH and MH groups, respectively ($p = 0.02$); 88.9% (n = 16) and 28.6% (n = 10) of PC inadequacy in MUH and MH adolescents, respectively ($p < 0.01$); and 77.8% (n = 14) in MUH ones and 48.6% (n = 17) in MH ones with elevated WHR ($p = 0.04$) (Table 3).

The correlation analysis between the variables, according to the MH and MUH phenotypes, is shown in Table 4. There was a strong correlation between BMI and other anthropometric variables, with emphasis on WC, WHR, FBMI and FFMI in both groups. Among the MUH adolescents, a moderate and negative correlation was identified between BMI and age at menarche ($r = -0.41$; $p < 0.05$) and a positive correlation between BMI and serum leptin ($r = 0.53$; $p < 0.01$).

Discussion

The MH and MUH phenotypes have recently been discussed in the literature [30, 31]. However, to our knowledge, this is the first study that evaluates the association of these metabolic profiles with the age at menarche, serum leptin concentrations and body variables, in eutrophic adolescents and those with excess of body mass.

Our data demonstrate a higher frequency of MUH adolescents in the pubertal phase of sexual maturation. Similarly, Reinehr et al. [32], in a longitudinal study with obese children and adolescents, observed that pubescent children were twice as likely to have an inadequate metabolic profile than those who were in the pre- or post-pubertal phase of sexual maturation.

Considering that the menarche is the main marker of sexual maturation in females, some authors have identified an association between age at first menstruation and the development of cardiometabolic risk factors during adulthood [33, 34]. However, with regard to metabolic phenotypes, studies that address this relationship have not yet been found.

In this present study, a high frequency of EM was identified among MUH adolescents with adequate and high BMI, and among those who were between 10 and 14 years old. These findings are relevant, since several authors have pointed to a trend of reduction in the age at menarche in recent decades, which can be justified by important changes in body composition that occur during puberty [35, 36, 8]. In our data,

among MUH adolescents, the significant correlation found between the age at menarche and body variables, such as BMI and BF%, corroborate this hypothesis.

The amount and distribution of body fat, in addition to being important influencers of menarche age, interfere with serum leptin concentrations, since adipose tissue is the main organ responsible for the production of this hormone [37, 7, 8]. In this sense, we highlight the high inadequacy of serum leptin levels, found in our sample, especially among adolescents with high BMI and MUH phenotype, as observed by Ding et al [38]. Despite this, it is noteworthy that, in the present study, high serum concentrations of this adipokine were also found between eutrophic and MH adolescents. This fact can be justified by the higher prevalence of adolescents in the pubic phase of sexual maturation, since pubertal staging is an important factor related to leptinemia in eutrophic individuals [39].

WC and WHR are anthropometric variables frequently used to estimate the distribution of body fat and the risk of developing cardiometabolic complications, as they have a strong association with insulin resistance markers and inflammatory biomarkers, such as C-reactive protein and adiponectin. However, there are still doubts about which of these variables is considered a better indicator of the MUH phenotype [31, 40, 41, 42, 43].

The findings of the present study demonstrate that WC was a more adequate predictor for the MUH phenotype than WHR, since a high inadequacy of this variable was observed, with a statistically significant difference, when compared to the MH and MUH groups, in eutrophic adolescents and the ones with high BMI. In addition, WC presented a higher correlation with VAI, in the MUH group, than WHR.

VAI is an anthropometric evaluation method created to estimate the amount of visceral adipose tissue (VAT), since this compartment is strongly related to the development of insulin resistance, metabolic syndrome, diabetes mellitus and cardiovascular diseases [39, 40, 41]. Regarding the MH and MUH phenotypes, Hwang et al [44] demonstrated that the accumulation of VAT contributed to individuals, initially classified as MH by the NCEP-ATP III [26], becoming MUH over a ten-year period.

Although the accumulation of VAT is an important risk factor for several cardiometabolic diseases in adults, it is believed, however, that, in the pediatric phase, metabolic components such as insulin resistance and high serum concentrations of TG may be better predictors of unfavorable metabolic outcomes [45]. In this sense, it is emphasized that, in the present study, there was a strong correlation between VAI and TG in the MUH group. In addition, MUH adolescents had higher mean VAI when compared to the MH ones, although without statistical significance. These findings become relevant due to the strong association found between this index and the MH and MUH phenotypes, as demonstrated by Kang et al [46].

It is also noteworthy the strong correlation found between VAI, BF% and FFBI, in the MUH group, and the highest means of these variables, observed in adolescents with inadequate phenotype. These data corroborate with results demonstrated by Oliveira et al. [47] who, when analyzing factors related to cardiometabolic risk in adolescents, identified that the overweight group had a higher FFBI when

compared to subjects with adequate BMI and WC. This characteristic can be justified by behavioral changes, such as decreased level of physical activity and poor eating habits, in addition to changes in glucose and lipid metabolism, which are common during adolescence [48, 42].

Data found in our study demonstrate that EM and serum leptin inadequacy are factors related to the MUH phenotype and that WC is an important risk indicator for this metabolic profile in eutrophic adolescents and the ones with high BMI. These findings illustrate the importance of this work since, to date, there are no studies that investigate the connection between these variables and the MH and MUH phenotypes, especially in adolescents in different classes of BMI. However, this study has limitations such as the reduced sample, the cross-sectional model, which prevents the analysis of causality between the variables analyzed, and the non-evaluation of the use of contraceptive drugs that could interfere with the investigated laboratory parameters.

Conclusion

During clinical practice, with individuals in the pediatric phase, it is recommended to investigate age at menarche, serum concentrations of leptin and WC in eutrophic and overweight individuals, for possible identification of the MUH phenotype, so that strategies to prevent the development of cardiometabolic diseases in adulthood can be developed.

Abbreviations

MH

Metabolically healthy; MUH–Metabolically unhealthy; EM–Early menarche; NM - Normal menarche; LM–Late menarche; BMI–Body mass index; WHO–World Healthy Organization; WC–Waist circumference; WHR–Waist-to-height ratio; TG–Triglycerides; HDL-c–High density lipoprotein cholesterol; VAI–Visceral adiposity index; BF% - Body fat percentage; FBM–Fat mass body; LBM–lean body mass; FBMI - Fat body mass index; FFMI - Fat-free mass index; BP–Blood pressure; SBP–Systolic blood pressure; DBP–Diastolic blood pressure; NCEP-ATP III - National Cholesterol Education Program Adult Treatment Panel III; VAT–Visceral adiposity tissue.

Declarations

Ethics approval and consent to participate

The study and method of consense were approved by the Research Ethics Committee at Hospital Universitário Clementino Fraga Filho, the teaching hospital attached to the Federal University of Rio de Janeiro. Informed consent forms were signed by all the participants – by the adolescents who were aged 18 or over and by the parents/guardians of those under 18.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publically available because of privacy concerns of the participants and because they are property of the Micronutrient Research Center/Institute of Nutrition Josué de Castro/Federal University of Rio de Janeiro, but are available from the corresponding author on reasonable request.

Competing of Interest

The authors declare that they have no conflicts of interest.

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Authors' contributions

ACLM research data, analyzed data and wrote the first version of the manuscript. APTP reviewed the analyses and the manuscript. NGO and ABFC collected the data. PCJ analyzed data and reviewed the manuscript. AR supervised collection of the data, reviewed the analyses and reviewed critically the manuscript. All authors read and approved the final manuscript.

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