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Trabajo Original

Pediatría

Relationship of age at menarche and serum leptin with the metabolically unhealthy phenotype in adolescents

Relación de la edad de la menarquia y la leptina sérica con el fenotipo metabólicamente no saludable en adolescentes

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Abstract

Objective: to analyze the relationship of age at menarche and leptin with the metabolically healthy (MH) and metabolically unhealthy (MUH) phenotypes in adolescent girls in different body mass index (BMI) categories.

Method: an observational and cross-sectional study consisting of 139 female adolescents attended to at the Adolescent Reference Center in Macaé, Rio de Janeiro**.** Menarche was classified as early (EM) when the first menstruation occurred at or before 11 years of age; normal menarche (NM) was categorized at ages 12 to 14; menarche was considered late (LM) when it occurred at age 15 or older. The factors required to ascertain the subjects' phenotype, as well as their leptin levels, weight, and height, were measured and their BMIs were calculated. The girls were classified as MH or MUH based on the NCEP-ATP III criteria as adapted for children and adolescents.

Results: 82 % (n = 114) of the girls were classified as MH and 18 % (n = 25) as MUH. Mean age at menarche was 11.79 ± 1.39 years. There was a higher prevalence of MUH amongst the girls who had EM ($p = 0.04$). A higher inadequacy of serum leptin concentrations was found in girls who had EM ($p = 0.05$) and in those classified as MUH ($p = 0.01$). The adolescents who were severely obese exhibited inadequate leptin levels ($p < 0.01$) and had gone through EM ($p = 0.02$). A total of 8.1 % (n = 7) of the normal-weight girls were classified as MUH, and 29.4 % (n = 5) of those who were severely obese were classified as MH ($p < 0.01$).

Conclusion: early menarche and high serum leptin concentrations are related with the MUH phenotype in adolescent girls in different BMI categories.

Keywords:

Menarche. Leptin. Metabolically healthy obesity. Body mass index. Adolescents.

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Resumen

Objetivo: analizar la relación de la edad de la menarquia y los niveles de leptina con los fenotipos metabólicamente saludables (MS) y metabólicamente no saludables (MNS) en adolescentes de diferentes categorías de índice de masa corporal (IMC).

Método: estudio observacional y transversal compuesto por 139 adolescentes de sexo feminino, atendidas en el Centro de Referencia para Adolescentes de Macaé, Río de Janeiro. La menarquia se clasificó como precoz (MP) cuando se produjo la primera menstruación a o antes de los 11 años de edad; la menarquia normal (MN) se clasificó como aquella sucedida a la edad de 12 a 14 años; la menarquia se consideró tardía (MT) cuando ocurrió a los 15 años o más. Se midieron los factores necesarios para determinar el fenotipo de los sujetos, y se midieron sus niveles de leptina, peso y altura, y se calculó su IMC. Las adolescentes se clasificaron como MS y MNS según los criterios de NCEP-ATP III, adaptados para niños y adolescentes.

Resultados: el 82 % (n = 114) de las adolescentes se clasificaron como MH y el 18 % (n = 25) como MUH. La edad media de la menarquia fue de 11,79 ± 1,39 años. Hubo una mayor prevalencia de MUH entre las adolescentes que tenían MP (p = 0,04). Se encontró una mayor insuficiencia de las concentraciones séricas de leptina en las adolescentes que tenían MP (p = 0,05) y en aquellas clasificadas como MNS (p = 0,01). Las adolescentes que eran severamente obesas exhibieron niveles inadecuados de leptina (p < 0,01) y habían pasado por una MP (p = 0,02). El 8,1 % (n = 7) de las adolescentes de peso normal se clasificaron como MNS y el 29,4 % (n = 5) de las que eran severamente obesas se clasificaron como MS (p < 0,01).

Conclusión: la menarquia temprana y las altas concentraciones séricas de leptina están relacionadas con el fenotipo MNS en las adolescentes de diferentes categorías de IMC.

Palabras clave:

Menarquia. Leptina. Obesidad metabólicamente saludable. Índice de masa corporal. Adolescentes.

INTRODUCTION

The increased prevalence of obesity in childhood and adolescence has been identified as a major global public health concern. According to the World Health Organization (WHO), the prevalence of overweight and obesity worldwide tripled over the last decades, and rose amongst children and adolescents by 18 % in 2016 (1).

Carrying excess weight at this stage of life is believed to be a major risk factor for the development of cardiometabolic diseases in adulthood (2). However, a subgroup of individuals, known as the metabolically healthy obese, seem to be better protected from such complications, as their metabolic profile is less susceptible to harmful effects. Individuals with this phenotype account for 6 % to 36 % of the population of children and adolescents (3). Conversely, an estimated 20 % of individuals classified as normal-weight by their body mass index (BMI) are at a higher metabolic risk, which is known as the metabolically unhealthy phenotype (4).

Although there are still aspects of the metabolically healthy (MH) and metabolically unhealthy (MUH) phenotypes that are yet to be fully understood, it is believed that the composition and distribution of body fat and hormones secreted by fat tissue, like leptin, play a significant role (5). It is also assumed that high serum leptin concentrations are strictly related to pubertal development, and therefore have an impact on the age at which menarche occurs (6).

Some researchers have found that early menarche is related to the development of cardiometabolic risk factors. Akter et al. (7) observed that women who had early onset of menarche exhibited higher serum triglyceride concentrations, and lower high-density lipoprotein cholesterol (HDL-c) levels, and were 1.55 times more at risk of developing metabolic syndrome.

Although there are some studies in the literature that address this topic, we could find none that investigates the relationship between age at menarche and the MH and MUH phenotypes. The purpose of this study was therefore to analyze the relationship between age at menarche and healthy/unhealthy metabolic profiles, relating them to different BMI categories, WC, and serum leptin concentrations in female adolescents.

METHODS

STUDY POPULATION

This cross-sectional study investigated female adolescents who were patients at a reference health center for adolescents (Adolescent Referral Center) in Macaé, Rio de Janeiro state, Brazil. Posters announcing the study were displayed in the waiting room, and all the adolescents who were patients there between February and July 2013 were invited to take part.

Inclusion criteria included girls aged 10 to 19 years who had medical records at the Adolescent Referral Center and had gone through menarche. Exclusion criteria included subjects who were pregnant or lactating, and those who had physical conditions that prevented their anthropometric variables from being measured adequately.

The study was 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/legal guardians of those under 18.

SEXUAL MATURITY AND AGE AT MENARCHE

Sexual maturity was self-assessed per a form showing the stages of breast and pubic hair development, based on Tanner's (9) stages. Stage I was classified as prepubescent, while stages II, III, and IV were classified as pubescent, and stage V was classified as post-pubescent (10).

Information on menarche was obtained by asking the subjects how old they were (in years and months) when they had their first period. Early menarche (EM) was at < 12 years of age, normal menarche (NM) was at 12-15 years, and late menarche (LM) was at > 15 years (11).

ANTHROPOMETRIC VARIABLES

Weight and height were measured using the techniques recommended by Jellife (12), with the subjects barefoot and wearing shorts and a top. They were weighed on digital scales (Welmy, Santa Bárbara d'Oeste, Brazil) and their heights were 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 (13) and the Brazilian nutrition surveillance system, Sistema de Vigilância Alimentar (14), in which normal weight is ≥ 3rd percentile and < 85th percentile, overweight is ≥ 85th percentile, obesity is ≥ 97th percentile, and severe obesity is ≥ 99th 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 (15).

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 the mean was calculated.

For the laboratory tests, blood was drawn after at least 12 hours' fasting. Blood was taken from the antecubital vein by a trained nurse and stored in plastic tubes with separator gel and clot activator. The tubes were centrifuged at 2,000 RCF to separate the plasma and serum, and then frozen at -80 °C until the analyses were carried out. 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 leptin concentrations 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 (16).

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) (15), as adapted for children and adolescents. They were classified as MUH if at least three of the following criteria applied to them: WC ≥ 90th percentile (17); triglycerides ≥ 150 mg/dL (18); HDL-c ≤ 50 mg/dL (17); fasting blood glucose ≥ 100 mg/dL (19); blood pressure ≥ 90th percentile (20).

STATISTICAL ANALYSIS

The adolescents were stratified according to their metabolic classification. The normality of the sample distribution was assessed by the Kolmogorov-Smirnov test. Descriptive analyses and the t-test of independent samples were used for the overall characterization of the sample, and the equality of the variances was analyzed by Levene's test. Associations between categorical variables were analyzed by the chi-squared test and Fisher's exact test. The variances' analysis was calculated by the ANOVA test. Statistical significance was set at $p < 0.05$. The analyses were performed using the SPPS, version 21.0, software program.

RESULTS

One hundred and thirty-nine female adolescents were included in the study: 33.1 % (n = 46) aged 10 to 14 and 66.9 % (n = 93) aged 15 to 19. Eighty-two percent (n = 114) of them were classified in the MH phenotype and 18 % (n = 25) were classified as MUH. Their mean age at menarche was 11.79 ± 1.39 years and their mean BMI was 23.52 ± 5.41 kg/m^2 (Table I).

It was found that 52 % (n = 13) of the girls who were MUH were pubescent according to their breast development ($p = 0.03$) and 64 % (n = 16) were pubescent according to their pubic hair growth ($p = 0.32$). A higher proportion of the girls from the younger age group ($p < 0.01$) and from the MUH group ($p = 0.04$) had early onset of menarche (Table II).

Serum HDL-c concentrations and WC were the variables with the highest percentages of inadequacy amongst normal-weight girls (17.9 %, n = 14, $p = 0.01$; 9.3 %, n = 8, $p < 0.01$, respectively) and were also found to gradually increase as BMI rose. These variables were also the ones with the highest levels of inadequacy amongst the girls classified as MH, 21.4 % (n = 22) of whom had low serum HDL-c ($p < 0.01$) and 10.5 % (n = 12) of whom had their WC classified in the 90th percentile ($p < 0.01$) (Table III).

Serum leptin concentrations were found to be high amongst 60.4 % (n = 84) of the sample group. When metabolic phenotypes were considered, it was found that inadequate leptin levels were more frequent amongst the MUH group, although 58.9 % (n = 63) of the girls from the MH group also had high concentrations of this hormone ($p = 0.01$). The analysis of age at menarche revealed that 73.2 % (n = 41) of the girls who had early menarche also exhibited high leptin levels, with no statistically significant difference between the groups. When cardiometabolic risk factors were assessed, over half the girls with an adequate WC were also found to have high levels of this hormone ($p < 0.01$).

The relationship between BMI and metabolic phenotypes, age at menarche, and serum leptin concentrations can be seen in table IV. The percentage of girls classified as MH gradually declined as BMI increased, and there was a statistically significant

Table I. Characterization of the adolescents as a whole and in their metabolic classification groups (NCEP-ATPIII)

	Total n = 139 (Mean ± SD)	MH 82 % (n = 114) (Mean ± SD)	MUH 18 % (n = 25) (Mean ± SD)	p-value*
Age (years)	15.20 ± 1.98	15.32 ± 1.94	14.64 ± 2.13	0.49
Age at menarche (years)	11.79 ± 1.39	11.92 ± 1.38	11.24 ± 1.30	0.95
Sexual maturity - Breasts	2.28 ± 0.47	3.82 ± 0.86	4.28 ± 0.93	0.76
Sexual maturity - Pubic Hair	2.26 ± 0.45	3.92 ± 0.80	3.92 ± 1.07	0.07
BMI (kg/m^2)	23.52 ± 5.41	22.30 ± 4.35	29.07 ± 6.35	< 0.01
WC (cm)	73.9 ± 10.97	71.49 ± 8.88	84.86 ± 12.96	0.04
TG (mg/dL)	78.82 ± 39.41	79.69 ± 41.49	74.84 ± 28.33	0.47
HDL-c (mg/dL)	51.39 ± 11.19	53.36 ± 11.32	43.28 ± 5.70	< 0.01
Blood glucose (mg/dL)	78.83 ± 6.40	78.82 ± 6.30	78.88 ± 6.97	0.94
SBP (mmHg)	100.33 ± 14.22	97.82 ± 12.44	111.80 ± 16.34	0.07
DBP (mmHg)	63.22 ± 10.75	61.51 ± 10.05	71.00 ± 10.56	0.89

**Statistically significant values (p < 0.05) as compared to the means of the MH and MUH groups; t-test of independent samples; Levene test; SD: standard deviation; MH: metabolically healthy; MUH: metabolically unhealthy; BMI: body mass index; WC: waist circumference; TG: triglycerides; HDL-c: high density lipoproteins-cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

Table II. Characteristics of the adolescents by age group and metabolic classification (NCEP-ATP III)

	10-14 years old % (n) 33.1 (46)	15-19 years old % (n) 66.9 (93)	p-value*	MH % (n) 82 (114)	MUH % (n) 18 (25)	p-value*
Sexual maturity - Breasts						
Pubescent	82.6 (38)	64.5 (60)	0.03	74.6 (85)	52.0 (13)	0.03
Post-pubescent	17.4 (8)	35.5 (33)		25.4 (29)	48.0 (12)	
Sexual maturity - Pubic hair						
Pubescent	84.8 (39)	66.7 (62)	0.02	74.6 (85)	64.0 (16)	0.32
Post-pubescent	15.2 (7)	33.3 (31)		25.4 (29)	36.0 (9)	
Menarche						
EM	63.0 (29)	31.2 (29)	< 0.01	37.7 (43)	60.0 (15)	0.04
NM	37.0 (17)	68.8 (64)		62.3 (71)	40.0 (10)	

**Statistically significant values (p < 0.05); chi-squared test; MH: metabolically healthy; MUH: metabolically unhealthy; EM: early menarche; NM: normal menarche.*

difference between severe obesity and the other BMI classifications ($p < 0.01$).

It was found that 69.8 % (n = 60) of the normal-weight girls were in the normal-age group at menarche, while 76.5 % (n = 13) of the girls who were severely obese had early onset of menarche. The difference between these two groups was statistically significant ($p < 0.01$).

As for serum leptin concentrations, 51.9 % (n = 42) of the normal-weight girls had inadequate levels of this hormone, but the level of inadequacy was much higher for those over the 99th percentile. Again, a statistically significant difference was found between the normal-weight and severely obese girls ($p < 0.01$).

DISCUSSION

Recently, some studies have been published in the literature regarding the metabolically healthy and unhealthy phenotypes. To our knowledge, however, this is the first study designed to analyze the relationship between the MH and MUH profiles and

Table III. Association between the components of the metabolic classification and BMI

	Normal weight % (n) 61.9 (86)	Overweight % (n) 18.7 (26)	Obese % (n) 7.2 (10)	Severely obese % (n) 12.2 (17)	p-value*
HDL-c†					
Adequate	82.1 (64)[a]	70.8 (17)	60.0 (6)	43.8 (7)[a]	0.01
Inadequate	17.9 (14)	20.2 (7)	40.0 (4)	56.3 (9)	
WC					
Adequate	90.7 (78)[a]	69.2 (18)[b]	60.0 (6)[c]	17.6 (3)[a,b,c]	< 0.01
Inadequate	9.3 (8)	30.8 (8)	40.0 (4)	82.4(14)	
TG					
Adequate	95.3 (82)	96.2 (25)	80.0 (8)	82.4 (14)	0.08
Inadequate	4.7 (4)	3.8 (1)	20.0 (2)	17.6 (3)	
Blood pressure					
Adequate	96.5 (83)[a]	96.2 (25)[b]	90.0 (9)[c]	52.9 (9)[a,b,c]	< 0.01
Inadequate	3.5 (3)	3.8 (1)	10.0 (1)	47.1 (8)	
Blood glucose					
Adequate	98.8 (85)	100.0 (26)	100.0 (10)	100.0 (17)	0.89
Inadequate	1.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	

*†Serum HDL-c concentrations for 128 adolescents; [a,b,c]Statistically significant values ($p < 0.05$) between the BMI classes; *Statistically significant values ($p < 0.05$); chi-squared test; ANOVA test; BMI: body mass index; HDL-c: high density lipoproteins-cholesterol; WC: waist circumference; TG: triglycerides.*

Table IV. Association between the adolescents' characteristics according to their BMI

	Normal weight % (n) 61.9 (86)	Overweight % (n) 18.7 (26)	Obese % (n) 7.2 (10)	Severely obese % (n) 12.2 (17)	p-value*
Metabolic classification					
MH	91.9 (79)[a]	88.5 (23)[b]	70.0 (7)[c]	29.4 (5)[a,b,c]	< 0.01
MUH	8.1 (7)	11.5 (3)	30.0 (3)	70.6 (12)	
Menarche					
Early	30.2 (26)[a]	53.8 (14)	50.0 (5)	76.5 (13)[a]	0.02
Normal Age	69.8 (60)	46.2 (12)	50.0 (5)	23.5 (4)	
Leptin†					
Adequate	48.1 (39)[a]	28.0 (7)	10.0 (1)	6.3 (1)[a]	< 0.01
Inadequate	51.9 (42)	72.0 (18)	90.0 (9)	93.8 (15)	

*†Serum leptin concentrations for 132 adolescents; [a,b,c]Statistically significant values ($p < 0.05$) between BMI classes; *Statistically significant values ($p < 0.05$); chi-squared test; ANOVA test; BMI: body mass index; MH: metabolically healthy; MUH: metabolically unhealthy.*

age at menarche, serum leptin levels in adolescents with different BMI categories.

Although some researchers have investigated the factors related to the development of these metabolic phenotypes, determining their prevalence amongst children and adolescents is hampered by the absence of a standard methodology in the literature. For instance, in a study of obese adolescent boys and girls, Bervoets and Massa (21) used two criteria to differentiate individuals with metabolically healthy obesity. The criteria of the International Diabetes Federation (18) yielded a

total of 18.6 % while, by applying the criterion of insulin resistance, 19.2 % of the subjects were identified as metabolically healthy obese (5).

The criteria adopted in this study for classifying the adolescents as metabolically healthy (MH) or unhealthy (MUH) were based on the NCEP-ATP III criteria (17), as adapted for children and adolescents, as this procedure is widely used in epidemiological studies and has variants adapted for this specific group.

Karellis et al. (5) regard insulin resistance as the best indicator of the MH and MUH phenotypes because of the importance of its role in increasing cardiometabolic risk. However, during puberty, insulin sensitivity may suffer a physiological reduction by about 30 %, affecting the other cardiovascular risk factors, and prepubertal conditions may be resumed after puberty (22). This means it is indispensable to consider the stages of sexual maturity when classifying children and adolescents, whatever the methodology utilized.

In this study, pubescence was an indicator of risk for the development of cardiometabolic diseases, since 64 % of the MUH girls were classified as pubescent by the development of their pubic hair. When assessed by their breast development, 52 % of the MUH group were also found to be at the same stage of sexual maturity. In this direction, in a study of children and adolescents with obesity, Reinehr et al. (23) found that the pubescent individuals were twice as likely to have an unhealthy metabolic profile than those who were prepubescent or post-pubescent, and Marra et al. (24) demonstrated a high prevalence of the MUH phenotype in adolescents in early pubertal stages.

Insofar as menarche is the main marker of sexual maturity for females, some authors have investigated the association between age at first menstruation and the development of cardiometabolic risk factors in adult life (7,8,11). However, regarding metabolic phenotypes, studies addressing this relationship are yet to be found. In this study, it was discovered that a higher proportion of the girls who had EM were classified as MUH. Also, more of the younger adolescents started menstruating earlier than the girls aged 15 to 19. This is an important observation, since some authors have shown a tendency for a reduction in age at menarche in recent decades, which could be associated with the major hormonal and body composition modifications that occur during puberty (11,25).

The literature demonstrated that leptin plays an important role in the regulation of the menstrual cycle and in reproductive health due to its action on the hypothalamic-pituitary-gonadal axis (6,25). In this sense, the inverse relationship between the concentrations of this hormone and age at menarche found in the present study is corroborated by other studies in the literature (26,27).

Leptin is primarily produced by fat tissue. This justifies the high, inadequate serum leptin levels in severely obese adolescents; however, data from our study demonstrate a high prevalence of inadequate serum leptin levels also in the normal-weight group. This could be down to the higher prevalence of pubescent girls (as assessed by their breast and pubic hair development), since the stage of puberty is an important factor related to increased leptin levels in normal-weight individuals (28).

Aside from influencing the time at which sexual maturity occurs, leptin may also play an important role in the development of the MUH phenotype, since a high percentage of inadequate levels of this hormone was found in this group. Few studies have so far investigated the association between serum leptin and the MH/MUH phenotypes (29,30). In those that have been done, no significant association was found between these groups, contrary to the findings of our study. This could be justified by the homogeneity of the BMI ranges observed in these publications since they were performed exclusively with normal-weight or excess body weight individuals, respectively, contrary to our study, in which different BMI categories were analyzed.

Other factors that deserve attention, apart from early menarche and high leptin levels, are the inadequate serum HDL-c concentrations and WC measurements identified in our sample. Low HDL-c and high WC were found in adolescents considered to be of normal weight, and a gradual increase in the inadequacy of these variables was found with increased BMI. These variables were also the ones that showed the highest percentage of inadequacy amongst the adolescent girls classified as MUH.

WC is an important indicator for the development of metabolic complications since it has a strong association with markers of insulin resistance and inflammatory biomarkers such as C-reactive protein and adiponectin. Some studies have used this anthropometric variable to estimate body fat distribution since the accumulation of visceral adipose tissue is related to unfavorable outcomes such as metabolic syndrome, diabetes mellitus, and cardiovascular diseases (23,11).

The association between visceral adipose tissue and the development of metabolic phenotypes has recently been discussed by some authors, as demonstrated by Hwang et al. (31), in a ten-year longitudinal study of Japanese American adults, in which the authors observed that the quantity of visceral fat and serum HDL-c concentrations were two factors that contributed significantly to the development of the MUH profile.

Data from the literature show that age at first menstruation is a risk factor for the development of cardiometabolic diseases in adulthood (22), and that serum leptin concentrations are related to the higher risk metabolic profile (27,28). However, this study is the first to investigate the relationship between age at menarche and leptin levels with the MH and MUH phenotypes in adolescents in different BMI categories. It is, however, limited by the size of the sample and the fact that it did not evaluate the influence of visceral/subcutaneous fat, nor did it consider the use of contraceptive methods, which may interfere in laboratory evaluations. Likewise, it should be noted that this study presents a cross-sectional analysis that does not allow to verify causality relationships between variables.

CONCLUSION

Data from this study demonstrate a relationship between early menarche and high serum leptin concentrations with presence of the metabolically unhealthy phenotype in adolescent girls in

different BMI categories. Therefore, it is important that these factors are analyzed during clinical practice in individuals of this age group, in order to formulate strategies to prevent the development of cardiometabolic diseases in adulthood.

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