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Relationship between serum concentrations of uric acid, insulin resistance and metabolic alterations in adolescents

Relação entre concentrações séricas de ácido úrico, resistência insulínica e alterações metabólicas em adolescentes

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ABSTRACT

Objective: To verify the possible relationship between serum uric acid concentrations and insulin resistance in adolescents. **Methods:** This is a cross-sectional study with 74 participants from a public school in São Luís, Maranhão, aged between 10 and 19 years. The study was approved by the Ethics and Research Committee of the University Hospital of the Universidade Federal do Maranhão (UFMA) under report 2,673,791. Anthropometric measurements, blood pressure and blood collection were performed. The participants were divided into two groups: group 1 (with hyperuricemia) and group 2 (without hyperuricemia). Data analysis was performed by means of the Stata program. **Results:** Anthropometric measurements, such as body mass index and waist circumference, had statistical significance ($p < 0.05$) among groups with hyperuricemia and without hyperuricemia, as well as the percentage of body fat ($p = 0.0423$) and systolic and diastolic blood pressure ($p = 0.0235$). Biochemical parameters for total cholesterol ($p = 0.0172$), triglycerides ($p = 0.0268$), glucose ($p = 0.0284$) and TyG index ($p = 0.0416$) had statistical significance in the hyperuricemia group when compared to the group without hyperuricemia. **Conclusion:** According to the obtained results, the participants with insulin resistance calculated by the TyG index presented high serum acid levels, demonstrating a statistically significant correlation.

Key words: insulin resistance; adolescent; uric acid; obesity; ICA.

RESUMO

Objetivo: *Verificar a possível relação entre concentrações séricas de ácido úrico e resistência insulínica em adolescentes.* ***Métodos:*** *Estudo transversal com 74 participantes de uma escola pública de São Luís, Maranhão, com idade entre 10 e 19 anos. O estudo foi aprovado pelo Comitê de Ética em Pesquisa do Hospital Universitário da Universidade Federal do Maranhão (UFMA) sob o parecer 2.673.791. Medidas antropométricas, pressão arterial e coleta de sangue foram feitas. A divisão dos participantes foi realizada em dois grupos: grupo 1 (com hiperuricemia) e grupo 2 (sem hiperuricemia). A análise de dados foi realizada por meio do programa Stata.* ***Resultados:*** *As medidas antropométricas, como índice de massa corporal (IMC) e circunferência da cintura, tiveram significância estatística (*$p < 0,05$*) entre os dois grupos, assim como a porcentagem de gordura corporal (*$p = 0,0423$*) e a pressão arterial sistólica e diastólica (*$p = 0,0235$*). Os parâmetros bioquímicos referentes a colesterol total (*$p = 0,0172$*), triglicerídeos (*$p = 0,0268$*), glicose (*$p = 0,0284$*) e índice TyG (*$p = 0,0416$*) tiveram significância estatística no grupo com hiperuricemia, quando comparados com o grupo sem hiperuricemia.* ***Conclusão:*** *De acordo com os resultados obtidos, os participantes com resistência insulínica, a partir do cálculo pelo índice TyG, apresentaram níveis séricos elevados de ácido úrico, demonstrando correlação estatística significativa.*

Unitermos: *resistência insulínica; adolescente; ácido úrico; obesidade; ICA.*

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RESUMEN

Objetivo: *Verificar la posible relación entre concentraciones séricas de ácido úrico y resistencia a la insulina en adolescentes.* ***Métodos:*** *Estudio transversal con 74 participantes de una escuela pública en São Luís, Maranhão, con edades entre 10 y 19 años. El estudio es aprobado por el Comité de Ética e Investigación del Hospital Universitario de la Universidad Federal de Maranhão (UFMA) bajo dictamen 2.673.791. Se realizaron mediciones antropométricas, de presión arterial y extracción de sangre. Los participantes se dividieron en dos grupos: grupo 1 (con hiperuricemia) y grupo 2 (sin hiperuricemia). El análisis de datos se realizó utilizando el programa Stata.* ***Resultados:*** *Las medidas antropométricas, como el índice de masa corporal (IMC) y la circunferencia de la cintura, tuvieron significancia estadística (*$p < 0,05$*) entre los dos grupos, así como el porcentaje de grasa corporal (*$p = 0,0423$*) y la presión arterial sistólica y diastólica (*$p = 0,0235$*). Los parámetros bioquímicos referentes a colesterol total (*$p = 0,0172$*), triglicéridos (*$p = 0,0268$*), glucosa (*$p = 0,0284$*) e índice TyG (*$p = 0,0416$*) fueron estadísticamente significativos en el grupo con hiperuricemia, en comparación con el grupo sin hiperuricemia.* ***Conclusión:*** *De acuerdo a los resultados obtenidos, los participantes con resistencia a la insulina, en base al cálculo mediante el índice TyG, presentaron niveles séricos elevados de ácido úrico, mostrando una correlación estadísticamente significativa.*

Palabras clave: *resistencia a la insulina; adolescente; ácido úrico; obesidad; ICA.*

INTRODUCTION

Adolescence is an important phase of biological, cognitive, emotional and social changes. Habits and learning from this period have effects on behavior in many aspects throughout life, such as diet, individual health, preferences and psychosocial development[1].

According to the World Health Organization (WHO) (2013), adolescence covers the period between 10 and 19 years, and to the United Nations (UN), between 15 and 24 years, a criterion used mainly for statistical and political purposes. The term "young adults" is also used to encompass the age group of 20 to 24 years old. Therefore, adolescence corresponds to a wide age group, with important differences between them, principally in body composition and biochemical profile. In the initial phase, there is the growth spurt and the development of secondary sex characteristics, with greater deposition of body fat and, consequently, greater change in lipid levels; in the other phases, the maximum growth peak is reached[2].

Insulin resistance (IR) can be defined as a decreased response to biological effects of insulin, an abnormality that occurs mainly due to an inadequate action of insulin in peripheral tissues, such as adipose, muscle and liver tissue. It is associated with the excess of body fat and metabolic changes, such as diabetes mellitus (DM), dyslipidemia and systemic arterial hypertension (SAH), which together constitute the metabolic syndrome (MS)[3].

Beta cells of the pancreas increase insulin production and secretion, as a compensatory mechanism when there is IR, while glucose tolerance remains normal. This has been regarded as a collective health issue, affecting several age groups[4].

Uric acid (UA) is the final product of purine metabolism, produced in the liver tissue and excreted via the kidney, with a recognized antioxidant action when its blood levels are within physiological limits. However, its increase in serum levels, called hyperuricemia, is considered an independent risk factor for cardiovascular diseases and also plays a role in the development of metabolic diseases[5].

Strong evidence indicates the relationship between UA level and advanced cardiovascular diseases. However, little is known if there is also a relationship with early stages of atherosclerosis, demonstrated by the carotid intima-media thickness, carotid plaque, carotid distensibility and brachial artery flow-mediated dilation[6]. According to a study carried out with 1,985 young adults, serum UA levels are associated with cardiovascular risk markers, especially with body mass index; however, it was not shown that the UA would play an independent role in the pathophysiology of early atherosclerosis[7].

Epidemiological studies have associated high levels of UA with both the occurrence of MS and its individual components and a higher incidence of cardiovascular disease[3].

In this context, although hyperuricemia has been considered another link between obesity and IR, studies with adolescents are still scarce. Therefore, the objective of this research was to investigate the possible relationship between serum UA levels and IR in adolescents.

METHODS

Cross-sectional study with 74 participants from a public school in São Luís, Maranhão, aged between 10 and 19 years. The study was approved by the Research Ethics Committee of the University Hospital of the Federal University of Maranhão (UFMA) under report 2.673.791.

The students were provided with explanations about the research and took the free informed consent form to their parents to authorize participation in the research. The adolescents also signed the informed consent form. After receiving the informed consent forms, a suitable place was organized to carry out the research steps (an air-conditioned interview room supplied with the necessary material and equipment) able to receive five students at a time. It should be emphasized that only the students who had authorization from their parents to participate in the research signed the informed consent form.

The anthropometric data were collected in a private environment. Obtaining anthropometric measurements was guided by the protocol of the Food and Nutrition Surveillance System[8]. Height was measured with a wall stadiometer with an accuracy of 0.1 cm. Body weight was measured with a 0.1 kg-precision digital scale. Obesity was defined as a body mass index (BMI) above the 95th percentile according to age and sex. Waist circumference (WC) was measured with a measuring tape with subdivisions of 0.1 cm at the midpoint between the iliac crest and the lowest rib. The hip circumference (HC) is the largest measure, over the trochanters; it was measured with the participant standing erect, using an inelastic tape. Body fat composition (BFP) was assessed through bioelectrical impedance analysis, following the guidelines of Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica (Brazilian Association for the Study of Obesity and Metabolic Syndrome)[9].

Blood pressure (BP) measurement followed the guidelines of the Brazilian Society of Cardiology performed with adolescents who were kept resting, in a seated position, for five minutes, before the first BP assessment[10]. The second assessment took place two minutes after the first. The average of the two assessments determined the values of systolic (SBP) and diastolic (DBP) blood pressure. In order to assess BP, an automatic arm digital blood pressure monitor, model Omron®, was used. After physical examination, blood was collected by venipuncture by a duly qualified professional. The biochemical evaluation was performed on venous blood samples (8 ml) with a fasting time of 10 to 12 hours, using sterile and disposable materials. The samples were properly conditioned and transported to the place of analysis, the clinical biochemistry laboratory of the UFMA Pharmacy Department. Fasting blood glucose, UA, total cholesterol (TC), triglycerides (TG)[11]. IR was analyzed with the triglyceride-glucose (TyG) index using the formula [log (fasting triglycerides (mg/dl) × fasting blood glucose (mg/dl)]/2[12]. The study participants were divided into two groups: group 1 (with hyperuricemia) and group 2 (without hyperuricemia). To define (divide) the groups according to the UA concentration, hyperuricemia was used: UA values > 6 mg/dl for women and > 7 mg/dl for men[13].

The results were expressed as mean ± standard deviation of the measurements and analyzed using the Shapiro-Wilk normality test followed by the Student's *t* test for independent samples. All statistical discussions were carried out at the 95% significance level in the SPSS® statistical program.

RESULTS

Seventy-four adolescents were evaluated, 42 of which were females (56.7%) and 32 were males (43.2%), with a mean age of 16 years. The average concentration of UA in the participants was 5.28 mg/dl, with 30.26% showing high levels.

Table 1 shows anthropometric measurements, such as BMI and WC, which were statistically significant ($p < 0.05$) between groups with hyperuricemia and without hyperuricemia (group 1) and without hyperuricemia (group 2), as well as the percentage of body fat ($p = 0.0423$), SBP and DBP ($p = 0.0235$). **Table 2** lists the biochemical parameters related to TC ($p = 0.0172$), TG ($p = 0.0268$), glucose ($p = 0.0284$) and the TyG index ($p = 0.0416$). These parameters were statistically significant when comparing the groups with hyperuricemia and without hyperuricemia.

TABLE 1 – Anthropometric and blood pressure data according to serum level of UA of adolescents from public schools in São Luís, Maranhão, Brazil, in 2018

Assessed characteristics	Total of patients ($n = 74$)	Group 1 ($n = 23$)	Group 2 ($n = 51$)	*p*-value
BMI (kg/m²)	21.54 ± 4.67	22.82 ± 5.86	20.46 ± 2.63	0.0343
WC (cm)	69.12 ± 7.77	70.56 ± 7.28	67.16 ± 5.83	0.0339
HC (cm)	90.21 ± 7.34	91 ± 8.05	89.42 ± 6.56	0.3462
BFP (%)	25.97 ± 10.47	29.48 ± 8.96	24.05 ± 9.14	0.0423
SBP (mmHg)	116.62 ± 11.63	120.41 ± 11.18	114.26 ± 11.48	0.0235
DBP (mmHg)	67.19 ± 7.25	69.03 ± 6.92	65.34 ± 7.18	0.0235

UA: uric acid; BMI: body mass index; WC: waist circumference; HC: hip circumference; BFP: body fat percentage; SBP: systolic blood pressure; DBP: diastolic blood pressure. Data were presented as mean ± standard deviation. Student's t *test was used for independent samples.*

TABLE 2 – Biochemical parameters according to serum levels of UA of adolescents from public schools of São Luís, Maranhão, Brazil, 2018

Biochemical parameters	Total of patients (n = 74)	Group 1 (n = 23)	Group 2 (n = 51)	p-value
BG	80.28 ± 17.78	85.38 ± 16.5	76.81 ± 16.38	0.0284
TG	193.17 ± 116.39	226.76 ± 119.89	169.31 ± 91.22	0.0268
TC	129.34 ± 50.93	142.97 ± 55.51	115.71 ± 42.35	0.0172
TyG	2.05 ± 0.13	2.08 ± 0.12	2.02 ± 0.12	0.0416

BG: blood glucose; TG: triglycerides; TC: total cholesterol; TyG: triglyceride-glucose index. Data presented as mean ± standard deviation. Student's t *test was used for independent samples.*

DISCUSSION

In the present study carried out with adolescents, anthropometric indices, BP and biochemical levels were correlated between the group that presented hyperuricemia and the group without this condition. The main finding was verifying the association between serum UA levels and IR in the participating adolescents. This finding corroborates those of other authors[5], who also observed an association between UA levels and IR in a study involving children in a more restricted age group. We also point out that the elevated serum UA can be an indicator of early metabolic alteration associated with other characteristics of IR[14].

UA is a compound endogenously produced in the human body, as a metabolite of purine, formed by adenosine, inosine, hypoxanthine, adenine and guanine, being the main hydrophilic antioxidant in the body. Thus, UA is able to inhibit the action of free radicals on organic molecules, such as those that make up the cell membrane and the genetic material. However, the sharp increase in UA concentration can induce intracellular and mitochondrial oxidative stress. Xanthine oxidase, which is one of the two interconvertible isoforms of xanthine oxidoreductase, uses molecular oxygen as an electron acceptor, generating superoxide anion and other reactive oxygen species (ROS) as by-products, thus generating oxidative stress that can contribute to cardiovascular diseases[15].

In this context, the first relevant result of the present study was the detection of higher UA concentrations in individuals with higher BMI, WC and body fat, what corroborates the findings of other authors who observed that individuals with high BMI, WC and body fat percentage and lower muscle mass index presented higher UA concentrations[16]. In fact, leptin, a hormone that has its secretion directly related to the degree of adiposity, seems to induce oxidative stress in endothelial cells and, thus, increase UA concentrations. Besides this fact, leptin and IR may reduce renal excretion of UA, contributing to its increase and metabolic changes[17].

In the present study, it was also possible to observe a statistically significant difference between the groups regarding BP values, both SBP and DBP, confirming another study entitled "Serum UA levels are associated with cardiometabolic risk factors in healthy young and middle-aged adults", in which they affirm the correlation of UA with laboratory variables and BP, revealing significant associations[15]. Serum UA was directly associated with BMI, WC, glucose, SBP and DBP. Still in the study, they concluded that higher levels of UA are associated with greater body adiposity, unfavorable lipid phenotype, greater oxidative stress and impaired endothelial function. Reduced UA excretion is reported in patients with MS and seems to reflect changes in renal UA excretion, secondary to increased sodium reabsorption in the proximal tubule, mediated by hyperinsulinemia. Another plausible mechanism refers to UA action inhibiting the bioavailability of nitric oxide, a potent vasodilator[17].

In this context, another study has correlated BP levels with hyperuricemia, which describes that the relationship between arterial hypertension and UA concentrations was identified as significant[17]. Such a result has been described in other publications, with a sample number of 756 individuals, in which a direct association of BP with UA was found[18].

In the biochemical parameters, blood glucose, TG and TC presented values of statistical significance between groups. In another research, the authors concluded that in relation to the variables of lipid metabolism, an association has been demonstrated between UA levels and the means of TG and HDL-c, being inverse with the latter, thus, we ratify the findings of the study carried out by them[19]. The mechanisms underlying the relationship between UA and TG are still unknown, but there are some possible explanations[15]. According to one of them, UA can induce lipogenesis in the liver and can block the oxidation of fatty acids. Other researchers suggest that hepatic fatty acid synthesis is associated with "de novo" purine synthesis, with subsequent acceleration in UA production[15, 20].

The focus of this study was the adolescent, regardless of sex, skin color or socioeconomic condition, but it is worth highlighting that the Brazilian Society of Cardiology underlines that the lipid profile of adolescents is different between sexes, due to sexual maturation, suffering variations during the phase of growth and development, with differences according to age, by the action of sex hormones in this phase.

In girls, there is a progressive increase in HDL-c beginning at 10 years of age, which is higher than that of boys in late adolescence. LDL-c and TC also increase progressively from 14 to 15 years old in girls, being higher than in boys around 17 to 18 years old. Perhaps menarche is important in triggering this phenomenon. In boys, sexual maturation leads to a progressive

decrease in TC, LDL-c and HDL-c, depending on the evolution of Tanner's pubertal stages[2].

UA concentrations are positively correlated with blood arterial pressure, regional and total adiposity, fasting blood glucose levels, insulin, TG, in addition to being inversely correlated with HDL-c levels in adolescents. These facts, described in different studies, allow us to infer that UA levels could also be included in the definition of MS[21].

The finding of hyperglycemia in children and adolescents is unusual, since the most frequent manifestation of glucose metabolism is IR, which is a compensatory mechanism, while glucose tolerance remains normal[19].

IR changes glucose uptake by cells and may be accompanied by a group of disorders such as arterial hypertension, hypertriglyceridemia, reduced levels of HDL-c, glucose intolerance, central obesity, hyperuricemia, MS and polycystic ovary syndrome. This set of changes is considered one of the major risk factors for cardiovascular diseases (CVD) and its evaluation has received considerable attention in recent years[22].

The methods for determining IR have multiplied and one of them can be grouped in the model based on static, or instantaneous, measurements of one or more plasma constituents, most frequently insulin, glucose, proinsulin and C-peptide, represented by the homeostasis model indexes assessment (HOMA)[23].

Another method for determining IR is the TyG index. To calculate the TyG index, in our study, we adopted the formula: product of the serum concentration of triglycerides and fasting blood glucose, as it presents proven sensitivity. TyG is obtained by the formula: GJ (mg/dl) × TG (mg/dl)/2 for with IR-correlated analysis[24]. Thus, the routine analysis of the TyG index and HOMA-IR can positively affect reduction in the number of individuals who will develop diabetes mellitus, as it allows early detection of changes in lipid metabolism and possible health intervention; besides reducing economic health costs by means of education and prevention actions[25]. Recently, the TyG index has been used in studies to assess IR in adults and adolescents, as it presents a good discriminatory power for the diagnosis of IR[12].

In another study, the authors stated that the main finding was the association between UA levels and IR in children and adolescents, even after adjustments for age, obesity and sex. After adjusting for these variables, it was observed that for each 1 mg/dl increase in UA concentration, there would be a 91% increase in the chance of IR. Even when analyzing the obese group and the control in isolated manner, the UA and the BMI showed a correlation with the HOMA-IR[5].

Although the pathophysiological mechanisms of the link between hyperuricemia and IR are not fully established, hyperuricemia is often pointed out as the result of the reduction in renal UA excretion under the action of hyperinsulinemia[5]. However, the study cited by another author opposes this idea because it understands that hyperuricemia precedes IR[26].

Obesity is considered an important risk factor for IR and the development of type 2 diabetes mellitus, since, in obese individuals, adipose tissue releases substances involved in the development of IR, such as non-esterified fatty acids, hormones and pro-inflammatory cytokines[27, 28].

The adipose tissue is capable of secreting cytokines and growth factors that participate in various metabolic processes. Some of these cytokines, with pro-inflammatory characteristics increased in obesity, are directly associated with IR: leptin, tumor necrosis factor (TNF)-alpha and visfatin. On the other hand, adiponectin, a cytokine with anti-inflammatory characteristic, is reduced in the presence of obesity and is described as inversely associated with IR[28].

Thus, one of the possible links between hyperuricemia and IR appears to be endothelial dysfunction[29]. UA is responsible for attenuating the production of nitric oxide by reducing the interaction between the enzyme endothelial nitric oxide synthase (eNOS) and calmodulin[30].

High levels of UA are associated with impaired vascular function in children and adolescents. Thus, endothelial dysfunction mediated by hyperuricemia could result in less insulin uptake due to reduced blood flow in peripheral tissues (less supply of nitric oxide)[31, 32]. Besides interfering with the production of nitric oxide, UA can also be responsible for its degradation. Although, in physiological concentrations, UA has an antioxidant effect and is, therefore, an endothelial protection factor, increased serum levels make it assume a pro-oxidant role, since its formation pathway by xanthine oxidase produces ROS and hydrogen peroxide, which in excess, will react with the endothelial nitric oxide and form the peroxynitrite, an important oxidizing agent[33].

In this sense, it appears that the increase in the serum level of UA has a positive relationship with IR.

CONCLUSION

According to the obtained results, the patients who presented greater IR were the same ones who achieved higher UA levels. The biochemical parameters relating to TC, TG, glucose and the TyG index had statistical significance in the group with hyperuricemia, when compared with the group without hyperuricemia. We noticed statistical relevance when we related UA to BMI, WC, body fat percentage and BP levels (both SBP and DBP). Therefore, further studies are needed to corroborate our results and present more explanatory data regarding this phenomenon.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

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