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Hyperuricemia and impaired metabolic profile in community-dwelling older adults: A Bayesian approach

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Highlights

- Serum uric acid levels have stood out as a candidate biomarker of cardiometabolic dysfunction.
- The aging process is associated with a body adiposity increase.
- Visceral Adiposity Index and Lipid accumulation product are indicators of adipose tissue dysfunction.
- TyG index has been reported as a surrogate marker of insulin resistance.
- Visceral Adiposity Index, Lipid accumulation product, and TyG were higher in hyperuricemic older aldults

Abstract

Serum uric acid (UA) levels have stood out as a candidate for biomarker of several pathological processes, especially from cardiometabolic diseases.

Purpose

This study aimed to compare biomarkers of cardiometabolic dysfunction in community-dwelling older adults with normal and high levels of UA.

Methods

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Cross-sectional study including 228 community-dwelling older adults, clinically stratified as with or without hyperuricemia, according the cutoff point of serum uric acid ≥6 mg/dL for women and ≥7 mg/dL for men. Venous blood withdrawal was conducted and used to obtain UA, triglycerides, and glucose levels. Anthropometric measurements were conducted to record height, body mass, and waist circumference. From serum and anthropometric parameters, triglyceride/glucose index (TyG), lipid accumulation product (LAP), and visceral adiposity index (VAI) were calculated. Linear mixed model analysis was used to determine between-group differences in cardiometabolic parameters (VAI, LAP, and TyG), taking groups as fixed factor and sex, use of hypoglycemiant and hypolipemiant medications as random factors. The Bayesian analysis was conducted to check the magnitude of the evidence.

Results

The community-dwelling older adults with high serum UA exhibited statistically higher values ($p<0.05$) of TyG (mean difference=0.24 [95% CI=0.39 to 0.90]), VAI (mean difference=0.75 [95% CI=0.25 to 1.25]) and LAP (mean difference=15.56 [95% CI=3.98 to 27.15]). The Bayesian analysis indicated moderate to strong posterior probabilities favoring the alternative hypothesis.

Conclusion

Our results shed light on the relationship between hyperuricemic state in community-dwelling older adults and adipocyte dysfunction, ectopic lipid deposition, and insulin resistance.

Previous Next

Keywords

Uric acid; Obesity; Glycemic control; Dyslipidemia

1. Introduction

The prevalence of non-communicable diseases (NCD) is increasing worldwide, especially among older adults, since the aging process favors the development of several comorbidities. This high prevalence has important socioeconomic consequences, with elevated health burden [1]. Thus, recognizing associated factors and cost-effective biomarkers could facilitate NCD screening.

Serum uric acid (UA) levels have stood out as a candidate for biomarker of several pathological processes, especially from cardiometabolic diseases, which have been evidenced over the last 100 years [2,3]. Indeed, high serum UA levels characterize a systemic pro-oxidant and pro-inflammatory state, which cause endothelial disfunctions [4], and lipidic and glucose metabolism impairments [5]. This points justifythe increasing body of evidence regarding the relationship between high serum UA levels and various NCD, (e.g. hypertension [6], cardiovascular diseases [7], diabetes [8], and obesity [9]).

In this sense, the use of metabolic indices has also been widespread as an important assessment tool. Thus, lipid accumulation product (LAP) [10] and visceral adiposity index (VAI) [11] are proposed as adipose tissue dysfunction indexes and triglyceride/glucose index (TyG) is related to the glucose and lipid toxicity.

Owing to the aging process, older adults are naturally more susceptible to cardiometabolic disease, therefore, the maintenance of high serum UA levels may represent an additional risk factor for cardiometabolic dysfunctions in this population, especially because hyperuricemia is associated with advanced age [9]. This concern highlights the need to find biomarkers associated with cost-effectiveness or predictive value, allowing the development of s. Thus, the present study aimed to compare biomarkers of cardiometabolic dysfunction in normouricemic and hyperuricemic community-dwelling older adults.

2. Methods

2.1. Study description

Cross-sectional analysis of a cohort study involving all community-dwelling older adults (≥60 years old) from Aiquara, Bahia, Brazil. All community-dwelling older adults were home-visited and invited to participate in this study. Each subject underwent experimental procedures under the same instructions and conditions. Questionnaires were used to collect data on smoking habit, self-reported diagnoses of hypertension, and diabetes, and the use of hypoglycemiant and hypolipemiant medications. A total of 289 volunteers were screened; however, bedridden individuals or those with severe cognitive impairment (n=20) were excluded. In addition, 11 volunteers did not consent to blood withdrawal, and 30 had technical problems with their blood sample storage, then, 228 older adults comprised the study population. Data were collected between January and July 2015.

All procedures were conducted in conformity with the Helsinki Declaration and the study was submitted and approved by the human research ethics committee from the Universidade Estadual do Sudoeste da Bahia (protocol # 10786212.3.0000.0055). Written informed consent was obtained from all subjects, and all volunteers underwent the experimental procedures under the same instructions and conditions.

2.2. Studied variables

Volunteers were scheduled to attend Aiquara Municipal Hospital, where they underwent a venous blood withdrawal (10 mL from the antecubital vein) in a 12-h fast for measurement of the serum levels of uric acid, triglycerides, and glucose following laboratory methods recommended by the manufacturers of kits and equipment. The studied population was stratified into two groups according to the serum UA levels: normouricemic and hyperuricemic. The cutoff point was set as serum UA ≥ 6 mg/dL for women and ≥7 mg/dL for men, as used by Ekundayo et al. [12] and Passos et al. [13].

Anthropometric measurements were obtained using standardized procedures, and height, body mass (BM), and waist circumference (WC) were recorded. From these variables, the body mass index (BMI), an indicator of general obesity, was calculated. Based on blood glucose and triglycerides, the TyG was calculated as proposed by Simental-Mendia et al. [14] and Guerrero-Romero et al. [15]. The following visceral adiposity indicators were used: LAP [10] and VAI [11]. Table 1 presents the formula for the studied cardiometabolic indexes.

Table 1. Cardiometabolic indexes used in this study and their respective formulas.

Cardiometabolic Index	Equation
Triglyceride/glucose index (TyG)[a]	$$\mathbf{TyG} = \mathbf{ln}\,(\mathbf{fasting\ triglycerides} \times \mathbf{fasting\ glucose}\ /\mathbf{2})$$
Visceral Adiposity Index (VAI)**	For women: $$\mathbf{VAI} = \left(\frac{\mathbf{WC}}{\mathbf{36.58+(1.89\ x\ BMI)}}\right)\mathbf{x}\left(\frac{\mathbf{triglycerides}}{\mathbf{0.81}}\right)\mathbf{x}\left(\frac{\mathbf{1.52}}{\mathbf{HDL}}\right)$$ For men: $$\mathbf{VAI} = \left(\frac{\mathbf{WC}}{\mathbf{39.68+(1.88\ x\ BMI)}}\right)\mathbf{x}\left(\frac{\mathbf{triglycerides}}{\mathbf{1.03}}\right)\mathbf{x}\left(\frac{\mathbf{1.31}}{\mathbf{HDL}}\right)$$
Lipid accumulation product (LAP)**	For women: $$\mathbf{LAP} = (\mathbf{WC} - \mathbf{58}) \times \mathbf{triglycerides}$$

Cardiometabolic Index	Equation
	For men: $\mathbf{LAP} = \mathbf{((WC - 65) \times triglycerides)}$

a Fasting glucose and fasting triglycerides calculated as mg/dl; **serum triglycerides and HDL cholesterol calculated as mmol/l; WC=waist circumference; BMI=body mass index.

2.3. Statistical analysis

The chi-square or exact Fisher's test, when appropriate, were used to analyze possible associations between categorical variables (i.e., sex, diabetes, use of hypoglycemiant and hypolipemiant medications) and the studied outcome. Categorical data were presented as absolute and relative frequencies.

Linear mixed model analysis was used to determine between-group differences in cardiometabolic parameters (VAI, LAP, and TyG), taking groups as fixed factor and sex, use of metformin, glibenclamide, and statins as random factors. These random factors were chosen owing to statistical and theoretical basis, since sex, metformin, glibenclamide, and statins may influence directly the studied cardiometabolic parameters. The critical alpha was set at 0.05 and all procedures were conducted in SPSS (SPSS Inc., Chicago, IL).

Results are presented as mean±SD, mean difference between groups, and 95% confidence interval (95% CI). The mean differences and its 95% CI were reported and interpreted as a measure of the effect size, since this approach allows identifying the direction and magnitude of the effect, justifying the use as an adequate effect size measure [16].

Bayes Factor hypothesis testing analyses was used to check the qualitative outcomes and the probability to replicate the same results (i.e., the magnitude of the evidence). Individual comparisons are based on the default *t*-test with a Cauchy (0, r=1/sqrt) prior [17]. The "U" in the Bayes factor denotes that it is uncorrected. The outcomes were classified as anecdotal (BF_{10}=1 to 3), moderate (3–10), strong (10–30), very strong (30–100), and extreme (>100) favoring the alternative hypothesis; or anecdotal (BF_{10}=1 to 0.33), moderate (0.33–0.1), strong (0.1–0.03), very strong (0.03–0.01) and extreme (<0.01) favoring the null hypothesis (Lee and Wagenmakers' classification) [18]. To calculate the probability to find the same results again, we divided the actual BF_{10} value by BF_{10}+1. The BF analysis was conducted through the JAMOVI®.

3. Results

The mean age of the studied community-dwelling older adults was 71.8±7.8 years old (Normouricemic=72.4±7.5; Hyperuricemic=71.6±8.1 years old), and the prevalence of hyperuricemia was 66.2% (n=151). Table 1 presents the characteristics of the studied population according to serum uric acid status. No significant difference was found in the distribution of sex, smoking habit, DM, and hypertension diagnosis, as well as the use of hypoglycemiant and hypolipemiant medications between groups (p>0.05).

Community-dwelling older adults with high serum UA exhibited significantly higher values of TyG (mean difference=0.24 [95% CI=0.39 to 0.90]), VAI (mean difference=0.75 [95% CI=0.25 to 1.25]) and LAP (mean difference=15.56 [95% CI=3.98 to 27.15]) (p<0.05). According to Bayes Factor analyses, a posterior probability of 87.3% and 88.2% to observe a difference in TyG and LAP between groups was observed. These Bayes Factor indicated that the posterior probability favoring the alternative hypothesis were moderate. For VAI, the Bayes Factor analyzes indicated a posterior probability of 95.8%, indicating strong posterior probability favoring the alternative hypothesis. The results from inferential and Bayesian statistics are presented in Table 2.

Table 2. Inferential and Bayesian analysis comparing cardiometabolic indexes between community-dwelling older adults stratified according to serum uric acid concentration (cut-off point=7mg/dL for men and 6mg/dL for

women).

Variable	Normouricemic	Hyperuricemic	Mean difference (95% CI)§	p-value	$BF_{10, U}$	Probability (%)
TyG	8.86 (8.02–9.69)	9.09 (8.27–9.92)	0.24 (0.39–0.90)	0.002*	6.85M	87.3
VAI	1.94 (1.47–2.41)	2.69 (2.33–3.05)	0.75 (0.25–1.25)	0.003*	23.0S	95.8
LAP	41.88 (30.96–52.81)	58.79 (50.92–66.66)	15.56 (3.98–27.15)	0.009*	7.48M	88.2

Letters indicate the outcome classified as: A=anecdotal; M=moderate; S=strong evidence favoring the alternative hypothesis. (§) Adjusted by sex, use of metformin, glibenclamide and statins. Mean difference as hyperuricemic minus normouricemic; (*) Significantly different ($p<0.05$).

4. Discussion

The present study aimed to compare biomarkers of cardiometabolic dysfunction in community-dwelling older adults with normal and high levels of UA. Our results showed that community-dwelling older adults with high levels of UA have higher values of cardiometabolic indicators of adipose tissue dysfunction (VAI and LAP) and glucose and lipid toxicity (TyG), indicating that the hyperuricemic state seems to be associated with a worse cardiometabolic profile.

Reports of the potential impact of hyperuricemia on cardiometabolic parameters date back more than 100 years ago [2], with the current body of evidence corroborating this potential [2,3]. Our study contributes to this body of evidence since our data were focused on community-dwelling older adults, while numerous studies include only young adults or merge this population with older adults.

It is known the paradoxical effect of UA on the control of oxidative status, since it has chemical characteristics of an antioxidant, but could exert a pro-oxidant action in several circumstances, such as in blood plasma [19]. In fact, adipocytes exposure to high UA concentrations leads to an increase in reactive oxygen species production and activation of the local renin-angiotensin system [[19], [20], [21]]. Additionally, the exposure of endothelial cells to high concentrations of UA stimulates the activation of pro-inflammatory pathways, culminating in the expression of cytokines, such as C-reactive protein, which, in turn, justifies the installation of a systemic pro-inflammatory condition [19,22,23].

In our study, VAI and LAP were significantly higher in hyperuricemic older adults. These indicators are mathematic models proposed to investigate adipocyte dysfunction [10,11], especially owing to its the association with central visceral adiposity. The Bayesian analysis indicated that the posterior probability was 88.2 and 95.8% to observe between-group difference in LAP and VAI, respectively. These probabilities are interpreted as moderate and strong, respectively.

Recent studies have shown that VAI and LAP are also able to identify people prone to disorders of carbohydrates metabolism, such as insulin resistance, and lipids metabolism, such as dyslipidemia [24,25], for this reason, they have the status of promising predictors of cardiovascular risk [26,27].

The association between high UA concentrations and adiposity tissue dysfunction is especially relevant for community-dwelling older adults since the aging process is associated with a body adiposity increase [28] and metabolic disorders [29]. It is worthwhile to highlight that it is widely reported the association between VAI and LAP values with insulin resistance [24,30,31].

TyG index has been reported as a surrogate marker of insulin resistance in several populations and age groups [14,23,32]. It is a simple and low-cost method for screening insulin resistance, and demonstrates sensitivity compatible with the HOMA-IR index [15,33], the gold-standard in this matter. Our results showed that hyperuremic [illegible] higher values of the TyG index, suggesting they are prone to insulin resistance state. It is important to note that, in this study, the diagnosis of diabetes mellitus, and the use of hypoglycemiant drugs used as a random

factor in the linear mixed model. The Bayesian analysis indicated that the posterior probability was 87.3% to observing between-group difference in TyG. This probability is interpreted as moderate, but it is important to note that many other factors, besides hyperuricemia, could also influence the investigated relationship between serum UA concentrations and TyG index, as well as LAP and VAI.

Association between hyperuricemia and insulin resistance has been widely reported in young adults [34,35]. The present study bring results from community-dwelling older adults, a population prone to develop insulin resistance due to the aging process [36,37]. The relationship between a pro-oxidant and pro-inflammatory state on the development of insulin resistance is known, which may justify our findings, since high serum AU leads to a systemic pro-oxidant and pro-oxidative condition, as previously discussed.

Results of VAI, LAP, and TyG can be highly interrelated, not only because they are all predictors of insulin resistance, but because VAI and LAP are considered indicators of adipocyte dysfunction, and indicators of ectopic deposition of lipids (e.g., liver and muscles), which culminates in lipotoxicity [24,38], with consequent dysfunction in the liver's glucose metabolism and peripheral resistance to the action of insulin, especially in muscle tissue. It is worthwhile to highlight that the observed link between serum uric acid concentration and biomarkers of insulin resistance and adipocyte dysfunction in community-dwelling older adults could guide further studies aiming to investigate the causality of this relationship, as well as, new therapeutic target in the treatment and prevention of cardiometabolic diseases, focused on serum UA control.

5. Conclusions

Our results shed light on the relationship between hyperuricemic state in community-dwelling older adults and adipocyte dysfunction, ectopic lipid deposition and insulin resistance. These findings could guide possible further studies aiming to investigate new therapeutic target in the treatment and prevention of cardiometabolic diseases, focused on serum UA control.

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Author's credit statements

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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