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Association between serum uric acid levels and incidence of nonalcoholic fatty liver disease in users of preventive medicine service in southern Brazil: a retrospective study

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is a silent disease with increasing prevalence. High levels of serum uric acid (SUA) have been associated with cardiometabolic diseases, yet the possible association between SUA levels and NAFLD is not elucidated. This article aim is to evaluate the possible association between SUA and NAFLD in a Brazilian population.

Methods: This retrospective study evaluated patients submitted to two evaluations between 2015 and 2016 at a preventive medicine service. The diagnosis of NAFLD was performed through abdominal ultrasound, and its progression was defined as favorable or unfavorable according to the degrees of steatosis. Patients with hyperthyroidism, pregnancy, viral hepatitis, use of methotrexate or anabolic steroids, significant alcohol consumption were excluded. Possible confounding factors were evaluated through a multivariate model.

Results: A total of 279 patients were included in the final sample. In the first evaluation, 20.1% were women and the mean age was 46.9 ($\pm$ 7.9) years, with a mean body mass index of 27.3 ($\pm$ 4.0) kg/m^2. About 26.9% of the individuals were diagnosed with NAFLD, and the mean of SUA levels was 5.7 ($\pm$ 1.4) mg/dL; a favorable progression of NAFLD was observed in 79.2% of the patients, and the SUA levels at baseline were not significantly associated with the NAFLD progression ($p = 0.43$).

Conclusions: Despite NAFLD high prevalence, SUA levels were not significantly associated with NAFLD progression in one year in this sample.

Keyword: Nonalcoholic fatty liver disease, Urate, Hyperuricemia, Preventive medicine

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Background

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic hepatopathy in the world, affecting about 24% of the global population, and characterized by lipid accumulation in more than 5% of the hepatocytes (Younossi et al. 2018). NAFLD encompasses a spectrum of diseases, ranging from simple hepatic steatosis to chronic inflammation in the liver (steatohepatitis), in the absence of secondary causes such as medications and excessive alcohol consumption (Perumpail et al. 2017).

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The clinical diagnosis of the disease is hampered by the lack of obvious symptoms, and complementary image tests are usually necessary (Younossi et al. 2018). Due to this difficulty, noninvasive biomarkers have been studied to facilitate the early diagnosis and reduce the costs related to imaging and invasive procedures (Neuman et al. 2014). Previous studies had already shown the association between the components of the metabolic syndrome (MS), such as visceral obesity, diabetes and dyslipidemia, and the development of NAFLD (Asrih and Jornayvaz 2015; Hadi et al. 2019).

Uric acid (UA) is the final product of the metabolism of purines (Lombardi et al. 2016). It has been suggested in other species, such as termites and rats, that it may have an antioxidant role and contribute to longevity (Tasaki et al. 2017; Mikami and Sorimachi 2017). It has been shown in vitro that, in the absence of proteins, the UA could contribute to hepatic antioxidant capacity (Mikami and Sorimachi 2017).

Nevertheless, in humans this remains debatable, as it is known that the main antioxidant mechanisms in human liver are proteins (Mikami and Sorimachi 2017). Moreover, high serum uric acid (SUA) levels usually coexist with insulin resistance, obesity, and hypertension. Most studies suggest that hyperuricemia is associated with MS and a possible risk factor for the development of NAFLD, acting as a pro-inflammatory marker (Brennan et al. 2020). The mechanism behind it evokes insulin resistance and oxidative stress, similar as shown with other biomarkers such as ferritin (Lombardi et al. 2016; Brennan et al. 2020). In addition, TNF-alpha, high-sensitive C-reactive protein and IL-6, considerate inflammatory markers, are also increased in NAFLD, suggesting once again SUA relation with oxidative stress and inflammation in humans (Neuman et al. 2014; Brennan et al. 2020).

However, the studies evaluating the possible link between SUA levels and the development and progression of NAFLD are still controversial. Some suggest a positive epidemiological relation while others argue that there is no connection at all (Wijarnpreecha et al. 2017; Zhou et al. 2016; Jaruvongvanich et al. 2017). In this sense, this study aimed to evaluate the presence of NAFLD in ultrasound reports and the SUA levels in apparently healthy patients who underwent preventive medicine evaluation in southern Brazil.

Methods
Population and study design
This retrospective study evaluated medical records of individuals from Curitiba/PR and metropolitan regions who underwent an executive check-up examination in Marcelino Champagnat Hospital in Curitiba/PR. The patients did not seek medical care due to specific complaints or diseases and were evaluated in two moments: in 2015 and in 2016.

The preventive medicine service database contains anthropometric, lifestyle, biochemical, and image data and interviews with trained health professionals. This research was approved by the local ethics committee (process nº 1.564.582) in accordance with the Brazilian Resolution 466/2012.

All patients who underwent two or more evaluations in the check-up service between 2015 and 2016 were included in the study. Individuals with a history of hyperthyroidism, pregnancy, positive serology for viral hepatitis, use of methotrexate or anabolic steroids, significant alcohol consumption (over 21 alcohol units/week for men and over 14 alcohol units/week for women) were excluded from the study. Participants with missing data, such as the absence of ultrasound records, were also excluded.

Clinical, laboratory, and radiological evaluation
Baseline clinical variables were collected in both evaluation 1 and evaluation 2, including gender, age, weight, height, body mass index (BMI), abdominal circumference (AC), blood pressure, heart rate, current smoking status, physical activity, alcohol consumption, and history of acute myocardial infarction, stroke, diabetes mellitus, dyslipidemia, systemic arterial hypertension, and medication use.

Blood samples were performed in all patients, and the analysis was performed by the local laboratory. The presence of diabetes was defined through the presence of at least one of the following: fasting glycemia ≥ 126 mg/dL, glycated hemoglobin ≥ 6.5, serum random glucose ≥ 200 mg/dL (American Diabetes Association 2020), or use of hypoglycemic drugs. Dyslipidemia was defined by LDL cholesterol ≥ 130 mg/dL (Mco et al. 2017) or the use of cholesterol-lowering drugs. Coronary artery disease was defined as a history of infarction, angina, or myocardial revascularization procedures (Mco et al. 2017). Moreover, systemic arterial hypertension was defined by values greater than 140/90 mmHg in two evaluations or the use of antihypertensive drugs (Malachias et al. 2016). Hyperuricemia was defined by a value greater than 7 mg/dL in men and greater than 6 mg/dL in women (Mikami and Sorimachi 2017), or the use of uricosuric drugs.

BMI values were classified according to diagnostic criteria of the World Health Organization (WHO). In addition, AC values were considered elevated if over 80 cm for women and 94 cm for men (Xavier et al. 2013). Alcohol abuse was defined as alcohol consumption over 21 standard doses per week for men and 14 standard doses per week for women. The alcohol intake per week

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was reported by patients and, due to that, it may be underestimated.

The abdominal ultrasound was performed at the local Radiology Image Clinic by an experienced radiologist blind to the study. The ultrasound was the chosen method due to the accessibility and noninvasiveness of the method, not requiring ionizing radiation (Ferraioli and Monteiro 2019). Besides, biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelets count, albumin, bilirubin, haptoglobulin were not used due to their lack of specificity or sensibility in the diagnosis of NAFLD or in the assessment of its severity (Neuman et al. 2014). The dosage of other biomarkers associated with NAFLD progression, as ghrelin and hyaluronic acid (Neuman et al. 2014), was not available in our research center.

The degree of hepatic steatosis (HS) in the ultrasound was graded according to Hamaguchi score, as seen in Table 1 (Ferraioli and Monteiro 2019; Hamaguchi et al. 2007).

The progression of hepatic steatosis was defined as favorable when patients did not have steatosis in evaluation 1 and continued without steatosis in evaluation 2 or improved the degree of steatosis in evaluation 2 in relation to evaluation 1. Unfavorable progression occurred when patients did not have steatosis in evaluation 1 and presented the disease in evaluation 2 or did not change the degree or worsened the degree of steatosis in evaluation 2 in relation to evaluation 1. The favorable or unfavorable progression of HS was related to the analysis of other variables evaluated in two visits, with emphasis on SUA levels.

Statistical analysis

The variables were described as mean ± standard deviation or by frequency (percentage). The Student's t test was used for independent samples while the Fisher's exact test was used for categorical variables. The Wald's test and logistic regression model was used for multivariate models. Odds ratio (OR) values were used with 95% confidence intervals, and $p < 0.05$ denoted statistical significance.

To analyze the effect of SUA in the progression of NAFLD, gender, abdominal circumference, dyslipidemia, physical activity practice, and glycated hemoglobin were included, and logistic regression models were adjusted for the progression of steatosis. For these logistic regression models, those with statistical significance in the univariate analysis of variables of the first evaluation of the patient were included as covariates. The analyses were conducted with statistical software STATA version 16.0 (StataCorpLp, Texas, USA).

Results

A total of 855 medical records of patients with two evaluations at the executive check-up were initially evaluated (mean interval of 12 ± 3 months). The absence of a second abdominal ultrasound excluded 285 records and 291 were excluded by any of the following: excessive alcohol consumption, diagnosis of viral hepatitis, pregnancy, use of tapazol, methotrexate, or anabolic agents. Thus, the final sample resulted in 279 patients.

The majority of the patients evaluated were male (79.9%), and in the first evaluation, the mean overall age was 46.9 ± 7.9 years (47.3 ± 8.1 years among men and 45.9 ± 7.2 in women), the mean BMI was 27.3 ± 4.0 kg/m^2 (27.8 ± 3.8 kg/m^2 in men, 25.4 ± 3.9 kg/m^2 in women) and the mean abdominal circumference was 97.4 ± 10.9 cm in men and 86.9 ± 11.8 cm in women (Table 2).

Most of the individuals were healthy and had a low prevalence of cardiovascular diseases and cardiometabolic risk factors. About 6.5% were smokers, 4.0% diabetics, and 16.6% hypertensive. NAFLD was diagnosed in 26.9% of the analyzed sample, being more prevalent in men (32.3%) in comparison with women (5.4%). The mean SUA levels dosage in a fasting sample was 5.7 ± 1.4 mg/dL in the general sample, and men presented higher levels when compared to women (mean

Table 1 Degree of hepatic steatosis according with alterations found in the abdominal ultrasound (Ferraioli and Monteiro 2019; Hamaguchi et al. 2007)

Grade of HS	Meaning	Alterations in the abdominal ultrasound
Grade 0	Normal or absence of HS	No sonographic alteration
Grade 1	Mild HS	Characterized by increased echogenicity of the hepatic parenchyma in relation to the renal cortex and spleen, with adequate visualization of the vascular walls and diaphragm
Grade 2	Moderate HS	Characterized by increased echogenicity, inadequate visualization of vascular walls, and partial visualization of the diaphragm
Grade 3	Severe HS	Characterized by increased echogenicity, non-visualization of vascular walls parallel to the sounding beam, non-visualization of the diaphragm, and posterior surface of the right hepatic lobe by subcostal window

HS, hepatic steatosis

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Table 2 Progression of steatosis and demographic and clinical variables in the first evaluation

Variable	Classification	Progression of steatosis		p*
		Favorable ($n = 221$)	Unfavorable ($n = 58$)	
Age (years)**		46.5 ± 8.0	48.1 ± 7.8	0.180
Sex	Male	167 (74.9)	56 (25.1)	
	Female	54 (96.4)	2 (3.6)	< 0.001
Weight (kg)		78.8 ± 13.5	92.9 ± 15.1	< 0.001
BMI (kg/m²)***		26.5 ± 3.5	30.3 ± 4.3	< 0.001
AC (cm)β		92.6 ± 10.6	105.4 ± 10.9	< 0.001
E1#-Physical activity (%)		155 (83.8)	30 (16.2)	0.011
E1#-SAHα (%)		26 (56.5)	20 (43.5)	< 0.001
E1#-Diabetes mellitus (%)		5 (45.5)	6 (54.6)	0.013
E1#-Alcohol consumption (%)		184 (78.6)	50 (21.4)	0.820
E1#-Current smoking (%)		12 (66.7)	6 (33.3)	0.228
E1#-Acute myocardial infarction (%)		1 (100)	0 (0)	1
E1#-Stroke (%)		2 (100)	0 (0)	1
E1#-Dyslipidemia (%)		75 (67)	37 (33)	< 0.001
Total cholesterol (mg/ dL)		187.8 ± 34.3	189.8 ± 53.2	0.795
Triglycerides (mg/ dL)		117.1 ± 53.6	181.8 ± 96.4	< 0.001
HDL cholesterol (mg/ dL)		51.7 ± 12.5	41.6 ± 11.2	< 0.001
LDL cholesterol (mg/ dL)		113.3 ± 33.4	113 ± 46.8	0.967
NON-HDL cholesterol (mg/ dL)		134.8 ± 33.9	150 ± 55.7	0.074
Gamma-GT (U/ L)		31.3 ± 28.1	41.7 ± 48.8	0.143
Glucose (mg/dL)		91.3 ± 10.9	97.5 ± 14.9	0.004
Glycated hemoglobin (HbA1c%)		5.5 ± 0.6	5.8 ± 0.6	0.029
GOT (U/ L)		21.5 ± 8.0	24.4 ± 14.8	0.153
GPT (U/ L)		23.2 ± 10.5	34.1 ± 24.8	0.002

*Student t-test for independent samples (quantitative variables); Fisher's exact test (categorical variables); $p < 0.05$. **Described by mean $\pm$ standard deviation (minimum–maximum) or by frequency (percentage). ***BMI (body mass index). βCA (abdominal circumference). αSAH (systemic arterial hypertension). #E1 (evaluation 1)

6.0 ± 1.2 mg/dL and 4.2 ± 0.9 mg/dL, respectively) (Table 2).

In the first ultrasound evaluation, NAFLD was observed in 75 (26.9%) cases (15.4%, 8.2%, and 3.2% with grades 1, 2, and 3, respectively). Among women, this percentage was 5.4%, and among men, it was 32.3% ($p < 0.001$). After an average of one year, ultrasound results indicated 24.4% ($n = 68$) of cases with NAFLD (15.4%, 5.7%, and 3.2% with grades 1, 2, and 3, respectively), 3.6% among women, and 29.6% among men ($p < 0.001$). Favorable progression in NAFLD was observed in 79.2% ($n = 221$) of the patients, while unfavorable progression was noted in 20.8% ($n = 58$) of the patients (Fig. 1).

Patients with unfavorable progression of steatosis presented higher BMI ($p < 0.001$), waist circumference ($p < 0.001$), weight values ($p < 0.001$), and higher levels of triglycerides ($p < 0.001$), glycemia ($p = 0.004$), glycated hemoglobin ($p = 0.029$), glutamic-pyruvic transaminase (GPT) ($p = 0.002$), and lower levels of HDL cholesterol ($p < 0.001$) (Table 2).

In comparison with the group with unfavorable progression of steatosis, the group of patients with favorable progression presented a lower mean SUA level in both evaluations (5.5 ± 1.3 mg/dL versus 6.3 ± 1.2 mg/dL, $p < 0.001$, and 5.6 ± 1.3 mg/dL versus 6.6 ± 1.4 mg/dL, $p < 0.001$, respectively). The difference between SUA levels in each year was also significant in the intragroup analysis ($p = 0.010$). However, no significant difference in the variation by year of SUA levels between the groups with favorable and unfavorable progressions was observed (mean 0.12 ± 0.86 versus 0.25 ± 1.14 mg/dL, $p = 0.431$).

In order to analyze the effect of SUA levels on the progression of NAFLD, logistic regression models were adjusted and included as covariates of those which presented statistical significance in the univariate analysis of the first evaluation of the patients (Table 1). The estimated odds ratio (OR) values with respective 95% confidence intervals are presented in Table 3.

HS in the 2nd evaluation*	HS in the 1st evaluation				Total
	Absence	**Grade 1**	**Grade 2**	**Grade 3**	
Absence	187	16	5	3	211
Grade 1	**16**	**18**	7	2	43
Grade 2	**1**	**7**	**7**	1	16
Grade 3	**0**	**2**	**4**	**3**	9
Total	204	43	23	9	279

Fig. 1 Progression of hepatic steatosis (HS) in both evaluations. *Favorable progression (in light gray, $n = 221$): they had not and continued without steatosis or improved the degree of steatosis. Unfavorable progression (in dark gray, $n = 58$): They had not and started to have or did not change/worsened the degree of steatosis

Discussion

The results of the present study showed a 26.9% prevalence of NAFLD in the analyzed sample, predominant in men, and similar to the worldwide prevalence (Younossi et al. 2018; Hamaguchi et al. 2012). This fact may be related to the possible protective effect of estrogens against NAFLD in premenopausal women (Hamaguchi et al. 2012; Gutierrez-Grobe et al. 2010).

In however with women, men also presented higher means of BMI, dyslipidemia, SUA levels, and alcohol consumption. Despite this, the majority of the studied population reported regular physical activity and were slightly overweight without obesity, with a low prevalence of cardiovascular risk factors and cardiovascular outcomes. The elevated prevalence of NAFLD in apparently healthy individuals observed in our analysis is a fact commonly present in other studies, especially in Asiatic populations, enhancing the hypothesis that obesity may not be necessary for the development of the disease (Hsu et al. 2019; Wei et al. 2015).

The pathogenesis of NAFLD is not yet completely understood; however, it is a consensus that cardiometabolic risk factors such as systemic arterial hypertension, obesity, sedentary lifestyle, and increased abdominal circumference contribute to the development of the disease (Hadi et al. 2019; Friedman et al. 2018; Rinella 2015). These factors may produce a continuous inflammatory state and oxidative stress in the liver, with consequent mitochondrial dysfunction and lipid accumulation in the hepatocytes (Seki et al. 2002; Day 2002).

Uric acid also plays a pro-inflammatory role in the cells, releasing proinflammatory mediators (TNF-alpha and interleukin-6) and contributing to the oxidation of lipoproteins, causing metabolic disorders and oxidative stress in the liver (Choi et al. 2014; Lanaspa et al. 2012). Also, hyperuricemia may increase blood pressure through endothelial dysfunction and contribute to the development of insulin resistance, the central mechanism of the MS. However, the pathophysiological relationship between SUA levels and NAFLD is still not completely elucidated.

Hyperuricemia is thought to induce radical oxygen species (ROS) and to activate the NLRP3 inflammasome, which inhibits the protein kinase B AKT response to insulin. As an effect, AKT decreases its phosphorylation while the insulin receptor substrate-1 increases. These foster the onset of insulin resistance (Zhu et al. 2014). The ROS growth and the NLRP3 inflammasome activation may also cause lipid metabolism impairment. Moreover, ROS production induces endoplasmic reticulum stress, a well-known cause of lipid accumulation in the liver (Lombardi et al. 2016; Brennan et al. 2020). All these pathways may lead to NAFLD onset.

Several reports had already demonstrated the positive relationship between SUA levels and NAFLD, suggesting that uric acid may be a possible biomarker for predicting the presence of NAFLD (Lombardi et al. 2016; Liang et al. 2015; Zheng et al. 2017). However, there is still a lack of studies proposing to evaluate the effects of SUA-lowering therapies on the severity of NAFLD (Paschos et al. 2018). In the present study, we observed that patients that presented an unfavorable progression of NAFLD had higher SUA levels in both first and second evaluations (6.3 mg/dL and 6.6 mg/dL, respectively), but

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Table 3 Results of the adjustment of multivariate models for steatosis progression considering variables of the first evaluation of patients

	Variables included in the model	*p**	OR**	IC 95%***
Model 1	E1# Uric acid	< 0.001	1.68	1.30–2.16
Model 2	E1# Uric acid	0.008	1.46	1.10–1.93
	Sex	0.055	4.48	0.96–20.91
Model 3	E1# Uric acid	0.410	1.16	0.81–1.65
	Sex	0.190	2.94	0.58–14.9
	E1# AC$	< 0.001	1.10	1.05–1.15
Model 4	E1# Uric acid	0.479	1.14	0.79–1.65
	Sex	0.185	3.06	0.58–16.2
	E1# AC$	< 0.001	1.01	1.05–1.14
	E1# Physical activity	0.137	0.55	0.25–1.21
Model 5	E1# Uric acid	0.534	1.12	0.78–1.62
	Sex	0.243	2.72	0.50–14.8
	E1# AC$	< 0.001	1.09	1.04–1.14
	E1# Physical activity	0.110	0.52	0.23–1.16
	E1# Dyslipidemia	0.012	2.7	1.24–5.89
Model 6	E1# Uric acid	0.181	1.38	0.85–2.23
	Sex	0.570	1.67	0.28–10.1
	E1# AC$	0.064	1.06	1.00–1.12
	E1# Physical activity	0.118	0.45	0.16–1.24
	E1# HbA1c%	0.583	1.23	0.59–2.57
Model 7	E1# Uric acid	0.269	1.32	0.80–2.16
	Sex	0.548	1.73	0.28–10.7
	E1# AC$	0.103	1.05	0.99–1.11
	E1# Physical activity	0.066	0.37	0.13–1.08
	E1# Dyslipidemia	0.050	2.84	0.98–8.17
	E1# HbA1c%	0.760	1.12	0.54–2.33

*Logistic regression model and Wald test, $p < 0.05$. **OR (odds ratio). ***IC95% (95% confidence intervals). #E1 (evaluation 1). $AC (abdominal circumference). %HbA1c (glycated hemoglobin)

the variation of SUA levels between the two evaluations was not significant to justify the unfavorable progression of NAFLD. According to the multivariate analysis, only dyslipidemia and abdominal circumference were associated with the unfavorable progression of NAFLD (models 3, 4, and 5, Table 3), but the results could not differentiate whether the progression was related to dyslipidemia, to the abdominal circumference, or both factors.

A recent meta-analysis of five observational studies has also found no significant relationship between SUA levels and fibrosis severity in NAFLD (Jaruvongvanich et al. 2017). A cross-sectional study in Japan showed that individuals with biopsy-proven NAFLD had significantly lower SUA levels in the advanced fibrosis group in comparison with the mild fibrosis group (Nakahara et al. 2014). Similarly, Huang et al. conducted a study evaluating the correlation between biopsy-proven nonalcoholic

steatohepatitis (NASH) and SUA levels, and the results showed that normal SUA levels were associated with advanced fibrosis stages (Huang et al. 2015). This could be partially explained by the possible antioxidant effect of UA in hepatic tissue, suggested by some articles (Mikami and Sorimachi 2017).

Contrary to these results, other studies had shown an association between hyperuricemia and the worsening of NAFLD progression (Liu et al. 2017; Sandra et al. 2019). Another analysis conducted by an elastography-based approach demonstrated that higher SUA levels were significantly associated with the severity of NAFLD in a fibrosis scale (Sandra et al. 2019). Another study showed that this association was present even in nonobese individuals on advanced histological inflammation of the liver which was associated with worse SUA levels (Liu et al. 2017). In our study, the proportion of patients with hyperuricemia is low, which could partially explain the contrasting results. The threshold for an independent pro-inflammatory and independent activity of SUA in NAFLD may be higher than our current observed levels in our patients.

The present study has some considerable limitations. The first one is related to the low number of individuals included in the final analysis; therefore, these results may not apply to the general population. In addition, the NAFLD diagnosis was made by an ultrasound-based approach, which is not considered the gold-standard method for the NAFLD evaluation since it is not sensitive enough to detect mild variation in hepatic steatosis. Nevertheless, the high sensibility and specificity of this method make it acceptable for use in epidemiological studies as this one. Furthermore, the alcohol intake parameters were obtained by interview, and thus the exact amount of alcohol consumption in grams was not possible to be obtained.

Conclusions

Despite the absence of longitudinal association, the results reinforce the elevated prevalence of NAFLD found in asymptomatic individuals. This fact holds up the need for rigorous investigation of the disease, including patients with normal or lower BMI. Also, despite a high prevalence of NAFLD in an otherwise healthy adult population, SUA levels were not independent predictors of NAFLD incidence in a 12-month follow-up period. Future studies should focus on longer follow-ups between evaluations and repeated measures of the SUA levels.

Abbreviations
NAFLD: Nonalcoholic fatty liver disease; SUA: Serum uric acid; MS: Metabolic syndrome; UA: Uric acid; BMI: Body mass index; AC: Abdominal circumference;

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WHO: World Health Organization; HS: Hepatic steatosis; OR: Odds ratio; GPT: Glutamic-pyruvic transaminase; NASH: Nonalcoholic steatohepatitis; ROS: Reactive oxygen species.

Author contributions
All authors contributed to the study conception and design. Data collection and writing of the manuscript were performed by ABH, MFL, and PABMJ. Design of the study, data interpretation, and revision of the manuscript were performed by GLM and CPB. Statistical analysis was performed by MO. All authors read and approved the final manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This research was approved by the *Pontifícia Universidade Católica do Paraná* ethics committee (process nº 1.564.582) in accordance with the Brazilian Resolution 466/2012. The consent to participate is not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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