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Fructose intake: is there an association with uric acid levels in nondialysis-dependent chronic kidney disease patients?

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Abstract

Introduction: **Fructose intake has increased dramatically in consequence of the consumption of fructose-based sweetened foods and beverages. Research suggests that high fructose intake has a strong association with uric acid (UA) levels and worse prognosis of chronic kidney disease (CKD).**

Objective: **The aim of this study was to investigate the influence of fructose intake on plasma UA levels in non-dialysis-dependent CKD patients.**

Methods: **Fifty-two patients on stages 3-5 (64.2 ± 9.6 years, 24 men, glomerular filtration rate of 30.5 ± 10.3ml/min) were divided into two groups: high fructose intake (>50g/d, n=29, 61.7 ± 9.3years) and low fructose intake (<50g/d, n=23, 65.8 ± 9.7years). Blood samples were collected to determine lipid profile and plasma levels of UA, inflammatory (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP)) and cardiovascular markers (monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)). The energy, protein and fructose intake was estimated using 3-day 24-hour food recall.**

Results: **High fructose intake was observed in 55.8% of patients and the mean UA levels were 7.7 ± 1.3 and 6.2 ± 1.6mg/dl in patients with high and low fructose intake, respectively (p<0.05). According to the regression analysis, fructose intake was the only variable able to affect the AU levels (β=0.42, p=0.016) after adjustment for gender, BMI, energy and protein intake, cardiovascular markers and lipid profile.**

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LA INGESTA DE FRUCTOSA: ¿EXISTE UNA ASOCIACIÓN CON LOS NIVELES DE ÁCIDO ÚRICO EN PACIENTES CON ENFERMEDAD RENAL CRÓNICA NO DEPENDIENTE DE DIÁLISIS?

Resumen

Introducción: **El consumo de fructosa ha aumentado dramáticamente en consecuencia del consumo de alimentos y bebidas azucaradas a base de fructosa. Pesquisas sugieren que el alto consumo de fructosa tiene una fuerte asociación con niveles de ácido úrico (AU) y empeora el pronóstico de la enfermedad renal crónica (ERC).**

Objetivo: **El objetivo de este estudio fue investigar la influencia del consumo de fructosa en los niveles plasmáticos de ácido úrico en pacientes con ERC que no son dependiente de diálisis.**

Métodos: **Cincuenta y dos pacientes en fases 3-5 (64,2±9,6 años, 24 hombres, tasa de filtración glomerular de 30,5±10,3ml/min) se dividieron en dos grupos: alto consumo de fructosa (>50g/día, n=29, 61,7±9,3 años) y bajo consumo de fructosa (<50g/día, n=23, 65,8±9,7 años). Muestras de sangre fueron recogidas para determinación del perfil lipídico y niveles plasmáticos de AU, citocinas inflamatorias (interleucina-6 (IL-6), factor de necrosis tumoral-α (TNF-α), proteína C-reactiva (CRP)), y marcadores cardiovasculares (proteína quimiotáctica de monocitos-1 (MCP-1), molécula de adhesión intercelular-1 (ICAM-1) y molécula de adhesión vascular-1 (VCAM-1)). El consumo de energía, proteína y fructosa fue estimulado utilizando 3 días de recordatorio alimentar de 24 horas.**

Resultados: **El alto consumo de fructosa fue observado en el 55,8% de los pacientes y los niveles medios de AU fueron 7,7±1,3 y 6,2±1,6mg/dl en pacientes con alto y bajo consumo de fructosa, respectivamente (p<0,05). De acuerdo con el análisis de regresión, el consumo de fructosa fue la única variable capaz de afectar los niveles de AU (β=0,42, p=0,016) después del ajuste para el género, composición corporal, energía y proteína, marcadores cardiovasculares y el perfil lipídico.**

Conclusions: **These findings support a potential role for fructose in hyperuricemia in these patients.**

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Keywords: *Chronic kidney disease. Uric acid. Fructose. Inflammation. Cardiovascular disease.*

Conclusiones: **Estos resultados apoyan un papel potencial de la fructosa ocasionando la hiperuricemia en estos pacientes.**

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Palabras clave: *Enfermedad renal crónica. Ácido úrico. Fructosa. La inflamación. Las enfermedades cardiovasculares.*

Abbreviations

UA: uric acid
CKD: chronic kidney disease
GRF: glomerular filtration rate
CRP: C-reactive protein
ICAM-1: intercellular adhesion molecule-1
MCP-1: monocyte chemoattractant protein-1
TNF-α: tumor necrosis factor-alpha
IL-6: interleukin-6
BMI: body mass index
WC: waist circumference

Introduction

Fructose is a monosaccharide found naturally in fruits, root vegetables and honey[1]. Over the last century, the introduction of fructose-based sweetener as well as the increased intake of foods and beverages containing sucrose (glucose plus fructose disaccharide) as sweetener have led to dramatical increases in fructose consumption[1-3].

Excessive fructose intake have been linked with the development of hypertension and renal injury probably via uric acid (UA) production[4-7]. As fructokinase has no negative feedback, all fructose entering the cell is rapidly phosphorylated which can result in ATP depletion. In turn, this depletion activates enzymes of purine metabolism which degrade adenine nucleotides to UA via xanthine oxidoreductase[1].

Hyperuricemia seems to be associated with inflammation, oxidative stress, endothelial disfunction and activation of the renin-angiotensin system[8,9]. Particularly in chronic kidney disease (CKD) patients, the decreased glomerular filtration rate (GFR) itself can result in UA retention which is related to hypertension, inflammation and oxidative stress[10-12]. However, little is known about the relationships among fructose intake, uric acid and systemic inflammation in nondialysis CKD patients.

Brymora et al. [2012][13] showed that a low-fructose diet in CKD patients (stages 2 and 3) could reduce inflammation and cardiovascular risk (evaluated by c-reactive protein [CRP] and intercellular adhesion molecule-1 [ICAM-1], respectively) with some potential benefits for blood pressure. Thus, given the importance of this subject for this population and the gap that still exists in the area, this study aimed to evaluate the fructose intake and its relationship with UA levels and inflammation in nondialysis-dependent CKD patients.

Methods

Patients and study design

This was a cross-sectional study of 52 nondialysis-dependent CKD patients (stages 3-5) recruited from the School Hospital Luiz Gioseffi Jannuzzi, Valença, Rio de Janeiro, Brazil. Inclusion criteria were age between 18 and 75 years and none dietary prescription prior to the study. Patients with cancer, AIDS, autoimmune and infectious diseases, uncontrolled blood pressure, chronic alcoholics and those using lipid-lowering medicines were excluded. Patients using allopurinol, hydrochlorothiazides and steroids, medicines that can affect serum acid uric levels, were also excluded.

The main causes of CKD were hypertensive nephrosclerosis (53%), followed by diabetic nephrosclerosis (21%), chronic glomerulonephritis (19%), and other diseases or unknown causes (7%). All of the patients presented with controlled hypertension and regarding anti-hypertensive medications, 12 patients (27.9%) were receiving ACE inhibitors, 10 patients were receiving β-blockers (23.2%), 8 (18.6%) patients were receiving calcium channel blockers, and 13 patients (30.3%) were receiving angiotensin receptor blockers.

After obtaining blood sample and demographic, anthropometric and dietetic data collection, patients received adequate dietary counseling. The study protocol was approved by the Ethics Committee of the School of Medicine at Federal Fluminense University (085/11), and fully informed consent was obtained in writing from all of the participants.

Sample processing and analytic procedures

Blood samples were drawn in the morning after overnight fasting. The blood was centrifuged, and the plasma was stored at -80°C until analysis. Biochemical parameters (urea, creatinine, triglycerides, HDL-cholesterol, and LDL-cholesterol and glucose)

were measured using standard laboratory methods in the clinical laboratory of the School Hospital Luiz Gioseffi Jannuzzi.

The UA levels were determined using enzymatic colorimetric method endpoints and the values considered as references were 2.5 to 7.0 mg/dl for adult men and 1.5 to 6.0 mg/dl for women[14]. A homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as following: [fasting glucose (g/dl) × fasting insulin (μU/ml)]/405[15]. The insulin was measured by ELISA (DRG diagnostics GmbH, Frauenbergstr, Marburg, Germany). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to GFR estimation[16].

Cardiovascular markers (vascular cell adhesion molecule-1 [VCAM-1], ICAM-1 and monocyte chemoattractant protein-1 [MCP-1]) were measured by an enzyme immunometric assay manufactured by Boster Immunoleader® (Fremont, CA, USA). Inflammatory markers (CRP, tumor necrosis factor-alpha [TNF-α] and interleukin-6 [IL-6]) were measured with an enzyme immunometric assay manufactured by R&D Systems® (Minneapolis, MN, USA).

Nutritional assessment

Body weight and height were measured to calculate the body mass index (BMI) following the formula: weight/(height)^2. Waist circumference (WC) was measured at a level midway between the lowest lateral border of the ribs and the uppermost lateral iliac crest and classified as proposed by NCEP[17].

Dietary intake

Dietary intake was assessed 3 days by 24-hour food recall. Patients were carefully instructed by a dietician to record all kinds and amounts of food (including beverages) ingested, using various models of food and measuring tools to estimate portion sizes and to improve the accuracy of record. Daily ingestion of energy and protein was estimated by software developed by the Federal University of São Paulo - Nutwin®. The nutrient contents of foods not contained in this software were searched on Brazilian Table of Food Composition[18]. Fructose intake was estimated using fructose content of different foods proposed by Brazilian Association for Study of Metabolic Syndrome and Obesity[19]. After evaluating the intake of fructose, the patients were divided into two groups: those with high fructose intake (> 50 g/day) and low fructose intake (<50 g/day)[20,21].

Statistical analysis

The Kolgomorov-Smirnov normality test was used to characterize data distribution. The results are expressed as the mean ± standard deviation (SD), medians (25th and 75th percentiles) or percentages, as applicable. The differences between groups were analyzed using the Mann-Whitney or t-test for equality of means, as appropriate. Pearson's or Spearman's coefficient correlation was calculated for univariate analyzes. Regression analyzes were performed to determine variables that had independent associations with UA levels. Statistical significance was accepted as $p < 0.05$. All statistical analyses were performed using the SPSS software (Chicago, IL, USA), version 19.0.

Results

The study included 52 nondialysis CKD patients: 28 women and 24 men (64.2 ± 10.0 years and 64.1 ± 9.2 years, respectively; $p > 0.05$). The average GFR was 30.5 ± 10.3 mL/min: 7.7% were in stage 3A, 42.3% in stage 3B, 42.3% in stage 4 and 7.7% in stage 5. Regarding BMI, 14 patients (26.9%) were normal weight, 35 (67.3%) were overweight or obese and only 3 patients (5.8%) were underweight. The values of WC were greater than normal in 48% of patients. Clinical, anthropometric and biochemical characteristics of the subjects are shown in table I.

Energy intake was consistent with the daily recommendation for weight maintenance (30 – 35 kcal/kg/day) for all patients (average of 33.6 ± 10.7 kcal/kg/day). The patients consumed more than the recommended daily dose of protein (0.6 – 0.8g/kg/day), with an average of 1.0 ± 0.4 g/kg/d. High fructose intake was observed in 55.8% of patients and those that had high fructose intake (>50 g/d) presented higher WC, BMI, plasma uric acid and urea levels than the patients who had low fructose intake (< 50g/d) (Table I).

In our study, 50% of female and 52% of male patients were hyperuricemic. Regarding lipid profiles, 20 patients (38.5%) had elevated levels of triglycerides, 20 patients (38.5%) presented hypercholesterolemia, 22 (42.3%) had elevated levels of LDL, and 41 patients (78%) presented HDL-cholesterol levels below the recommended value. There were no differences in plasma concentrations of inflammatory and cardiovascular markers according fructose intake (Table II), gender or the presence of diabetes.

Univariate and multivariate analyzes

Fructose intake was associated with plasma levels of uric acid ($r = 0.36$, $p = 0.01$), WC ($r = 0.43$, $p = 0.01$), BMI ($r = 0.33$, $p = 0.02$), urea ($r = 0.34$, $p = 0.014$) and caloric intake ($r = 0.36$, $p = 0.009$). According to the regression analysis the only independent variable able to affect the levels of uric acid was fructose intake ($\beta = 0.42$, $p = 0.016$) after adjustment for BMI, gender, energy and protein intake, cardiovascular markers and lipid profile.

Uric acid was significantly associated with triglyceride levels ($r = 0.34$, $p = 0.02$) and LDL cholesterol

Table I
Demographic, anthropometric and biochemical characteristics of the patients

Parameters	*Total of patients (n= 52)*	*Patients with fructose intake >50g/day (n=29)*	*Patients with fructose intake <50g/day (n=23)*	*p-value between groups*
Fructose intake (g/day)	55.5±17.9	72.1 ± 13.2	43.3 ± 9.6	0.0001
Age (years)	64.2 ± 9.6	61.7 ± 9.3	65.8 ± 9.7	NS
WC (cm)	93.4 ± 13.1	110.0 ± 13.8	88.4 ± 10.5	< 0.02
BMI (kg/m²)	27.3 ± 4.4	29.1 ± 3.5	25.7 ± 4.4	< 0.02
Uric acid (mg/dL)	6.8 ± 1.6	7.7 ± 1.3	6.2 ± 1.6	< 0.02
Urea (mg/dL)	81.6 ± 37.0	96.0 ± 36.2	70.8 ± 34.9	< 0.02
Creatinine (mg/dL)	2.2 ± 0.8	2.4 ± 0.9	2.1 ± 0.8	NS
GFR (ml/min)	30.5 ± 10.3	29.6 ± 9.5	31.0 ± 9.6	NS
Triglycerides (mg/dL)	161.2 ± 79.7	166.0 ± 81.5	154.9 ± 79.5	NS
Cholesterol (mg/dL)	199.0 ± 48.7	190.3 ± 58.3	203.5 ± 42.3	NS
HDL (mg/dL)	49.6 ± 12.7	47.0 ± 10.5	51.5 ± 14.0	NS
LDL (mg/dL)	112.1 ± 45.9	110.1 ± 47.1	112.6 ± 46.5	NS
HOMA-IR	9.5 (2.3 – 45.6)	5.5 (1.7 – 39.0)	12.8 (2.7 – 49.8)	NS
Glucose (mg/dL)	105.5 ± 46.3	110.5 ± 54.7	98.9 ± 32.2	NS

NS, nonsignificant
WC, waist circumference; BMI, body mass index; GFR, glomerular filtration rate; HDL, high density lipopprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance.

Table II
Inflammatory and cardiovascular markers of the patients

Parameters	*Total of patients (n= 52)*	*Patients with fructose intake >50g/day (n=29)*	*Patients with fructose intake <50g/day (n=23)*	*p-value between groups*
MCP-1 (pg/dL)	44.0 ± 8.1	44.4 ± 9.5	43.5 ± 6.6	NS
VCAM-1 (ng/dL)	893.2 ± 250.6	878.0 ± 276.0	909.0 ± 226.7	NS
ICAM-1 (ng/dL)	203.7 ± 91.2	197.0 ± 89.0	215.0 ± 94.4	NS
IL-6 (pg/dL)	27.2 (24.8-101.2)	25.9 (24.8-53.3)	28.7 (24.8-101.2)	NS
TNF-α (pg/dL)	130.7 ± 97.5	139.0 ± 87.3	122.1 ± 103.0	NS
PCR (mg/L)	2.9 ± 2.6	2.6 ± 2.6	3.3 ± 2.6	NS

NS, nonsignificant
MCP-1, monocyte chemoattractant protein-1; VCAM-1, vascular cell adhesion molecule-1; ICAM, intercellular adhesion molecule-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein.

(r = 0.37, p = 0.009), but not with age, GFR, inflammatory markers or protein intake.

Discussion

Excessive fructose intake appears to be related to the current obesity epidemic[22,23]. In the present study, more than half the patients presented fructose intake higher than 50g/day and, in fact, it was observed association between fructose intake and obesity (evaluated by BMI and WC), confirming that high fructose intake could be associated with weight gain.

In addition to causing obesity, high fructose diets have been shown to increase UA levels in animals and humans[1,2,4,24]. To date, few studies evaluated fructose intake in CKD patients. In a study conducted in 28 non-diabetic patients with stages 2-3 CKD, Brymora et al. [2012][13] observed that low-fructose diet (12g/day for 6 weeks) tended to improved blood pressure and UA levels and reduced CRP and ICAM levels were also observed with low fructose-diet. Zawiasa and Nowicki

[2013][25] reported that nondialysis CKD patients presented increase in serum UA concentration following oral administration of 70g of fructose. In this way, the present study is very important because it reported that the only independent variable able to affect UA levels in nondialysis CKD patients was usual fructose intake.

In the present study, no associations were found among fructose intake and markers of inflammation or cardiovascular disease but previous study from our group showed positive correlations between UA and inflammatory and cardiovascular markers (IL-6, CRP, TNF-α, VCAM-1) in hemodialysis patients[12]. The fructose-induced hyperuricemia could be considered a mechanism for cardiorenal disease since UA could alter vascular smooth muscle cell proliferation, release of chemotactic and inflammatory substances and monocyte chemotaxy[4].

Hyperuricemia is common in CKD[26] [Jalal et al., 2013] but data regarding the relationship between plasma UA and long-term outcomes in this specific population have been limited. In nondiabetic CKD patients, Kanbay et al. [2011][27] showed that serum UA is an independent predictor of endothelial dysfunction. In stage 3-4 CKD, hyperuricemia appears to be an independent risk factor for all-cause and cardiovascular mortality[28] [Madero, 2009] which could be associated to association among UA, TG and LDL observed in the present study. Fructose stimulates the activity of liver enzymes resulting in increased lipid synthesis and, consequently, higher levels of total fat and low density lipoproteins[29].

Experimental evidence have also suggested that UA itself may harm CKD patients by contributing to increased inflammation and CKD progression[26] [Jalal et al., 2013]. Besides that, elevated serum UA could be an independent risk factor for incident kidney disease in the general population[30,31]. Thus, the factors associated to elevated levels of uric acid must be known and controlled in the CKD population.

Although excessive fructose intake has been implicated to cardiometabolic events[3,32], it is important to pointed out that not all fructose sources may be the same. Thus, natural fruits also are rich in antioxidants, ascorbate, polyphenols, potassium and fiber that may counter the harmful fructose effects[10,33].

This study was cross-sectional and, because of that, it is not possible to infer causality from the observed associations. Another limitation is that nutrient intake was assessed with a 24-hour recall which despite being a low-cost method and relatively rapid in determining the dietary intake of patients, has limitations that can compromise the accuracy of the evaluation since it depends entirely upon the honesty and memory of the patient and might overestimate or underestimate the dietary data provided to the interviewer[34]. In addition, more reliable results for fructose intake could have been produced from more accurate methods for fructose intake assessment, such as specific semi-quantitative food frequency questionnaires, still lacking in the literature.

In conclusion, the present study reported that fructose intake was associated with uric acid levels in non-dialysis-dependent CKD patients. As uric acid has been associated with inflammation and cardiovascular risk factors, it is reasonable to suggest that reassessing fructose intake in these patients might ensure better control of uric acid levels and, consequently, fewer associated metabolic complications.

Declaration of interest

The authors declare there are no conflicts of interest.

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References

1. Hallfrisch J. Metabolic effects of dietary fructose. *Faseb J*. 1990;4:2652-60.
2. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, et al. Sugar, uric acid, and the etiology of diabetes and obesity. *Diabetes*. 2013;62:3307-15.
3. Karalius VP, Shoham DA. Dietary sugar and artificial sweetener intake and chronic kidney disease: a review. *Adv Chronic Kidney Dis*. 2013;20:157-64.
4. Johnson JR, Segal, SM, Sautin Y, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr.* 2007;86:899-906.
5. Nakayama T, Kosugi T, Gersch M, et al. Dietary fructose causes tubulointerstitial injury in the normal rat kidney. *Am J Physiol Renal Physiol*. 2010;298:712-20.
6. Lecoultre V, Egli L, Theytaz F, Despland C, Schneiter P, Tappy L. Fructose-induced hyperuricemia is associated with a decreased renal uric acid excretion in humans. *Diabetes Care*. 2013;36:e149-50.
7. Dissard R, Klein J, Caubet C, et al. Long term metabolic syndrome induced by a high fat high fructose diet leads to minimal renal injury in C57BL/6 mice. *PLoS One*. 2013;8:e76703.
8. Sánchez-Lozada LG, Soto V, Tapia E, et al. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. *Am J Physiol Renal Physiol*. 2008;295:F1134-1141.
9. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. *J Hypertens*. 2010;28:1234-1242.
10. Jalal DI, Smits G, Johnson RJ, et al. Increased fructose associates with elevated blood pressure. *J Am Soc Nephrol*. 2010;21:1543-1549.
11. Sung CC, Hsu YC, Chen CC, Lin YF, Wu CC. Oxidative stress and nucleic acid oxidation in patients with chronic kidney disease. *Oxid Med Cell Longev.* 2013;2013:301982.
12. Lobo JC, Stockler-Pinto MB, Nóbrega ACL, Carraro-Eduardo JC, Mafra D. Is there association between uric acid and inflammation in hemodialysis patients: *Ren Fail*. 2013;35:361-6.

13. Brymora A, Flisiński M, Johnson RJ, Goszka G, Stefańska A, Manitius J. Low-fructose diet lowers blood pressure and inflammation in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2012;27:608-12.
14. Oliveira PE, Burini CR. High plasma uric acid concentration: causes and consequences. *Diabetology & Metabolic Syndrom*. 2012;4:12.
15. Turner RC, Rudenski AS, Matthews DR, Levy JC, O'Rahilly SP, Hosker JP. Application of structural model of glucose-insulin relations to assess beta-cell function and insulin sensitivity. *Horm Metab Res Suppl*. 1990;24:66-71.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-12.
17. National Cholesterol Education Program. Executive summary of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *J Am Med Assoc*. 2001;285:2486-97.
18. Tabela Brasileira de Composição de Alimentos – TACO. 4ª ed. Campinas, Universidade Estadual de Campinas, 2011.
19. Associação Brasileira para Estudo da Obesidade e da Síndrome Metabólica – ABESO. Consumo de frutose. 2013. Avaiable in: www.abeso.org.br
20. Johnson RJ, Murray R. Fructose, exercise and health. *Curr Sports Med Rep*. 2010;9:253-8.
21. Stephan BCM, Wells JCK, Brayne C, Albanese E, Siervo M. Increased fructose intake as a risk factor for dementia. *J Gerontol A Biol Sci Med Sci*. 2010;65:809-14.
22. Marriott BP, Olsho L, Hadden L, Connor P. Intake of added sugars and selected nutrients in the United States, National Health and Nutrition Examination Survey (NHANES) 2003–2006. *Crit Rev Food Sci Nutr.* 2010;50:228-58.
23. Cox CL, Stanhope KL, Schwarz JM, et al. Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women. *Eur J Clin Nutr.* 2012;66:201-8.
24. Cirillo P, Sautin YY, Kanellis J, et al. Systemic inflammation, metabolic syndrome and progressive renal disease. *Nephrol Dial Transplant*. 2009;24:1384-7.
25. Zawiasa A, Nowicki M. Acute effects of fructose consumption on uric acid and plasma lipids in patients with impaired renal function. *Metabolism* 2013;62:1462-9.
26. Jalal DI, Chonchol M, Chen W, Targher G. Uric acid as a target of therapy in CKD. *Am J Kidney Dis*. 2013;61:134-46.
27. Kanbay M, Ylmaz IM, Sonmez A, et al. Serum uric acid level and endothelial ysfunction in patients with nondiabetic chronic kidney disease. *Am J Nephrol*. 2011;33:298-304.
28. Madero M, Sarnak MJ, Wang X, et al. Uric acid and long-term outcomes in CKD. *Am J Kidney Dis*. 2009;53:796-803.
29. Stanhope KL, Schwarz JM, Havel PJ. Adverse metabolic effects of dietary fructose: results from the recent epidemiological, clinical, and mechanistic studies. *Curr Opin Lipidol*. 2013;24:198-206.
30. Weiner DE, et al. Uric acid and incident kidney disease in the community. *J Am Soc Nephrol*. 2008;19:1204-11.
31. Zhu P, et al. Serum acid uric is associated with incident chronic kidney disease in middle-aged populations: a meta-analysis of 15 cohort studies. PloS One. 2014;9:e100801.
32. Ha V, Jayalath VH, Cozma AI, Mirrahimi A, de Souza RJ, Sievenpiper JL. Fructose-containing sugars, blood pressure, and cardiometabolic risk: a critical review. *Curr Hypertens Rep*. 2013;15:281-97.
33. Forman JP, Choi H, Curhan GC. Fructose and vitamin C intake do not influence risk for developing hypertension. *J Am Soc Nephrol*. 2009;20:863-71.
34. Anjos LA, Souza DR, Rossato SL. Desafios na medição quantitativa da ingestão alimentar em estudos populacionais. *Rev Nutr*. 2010;22:151-61.