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 nondialysis-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 ($b=0.42$, $p=0.016$) after adjustment for gender, BMI, energy and protein intake, cardiovascular markers and lipid profile.

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 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 ($p<0,05$). Según el regresión, el consumo de fructosa fue el único variable capaz de afectar los niveles de AU ($b=0,42$, $p=0,016$) 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.

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. 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 dramatic increases in fructose consumption.

Excessive fructose intake have been linked with the development of hypertension and renal injury probably via uric acid (UA) production. 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.

Hyperuricemia seems to be associated with inflammation, oxidative stress, endothelial disfunction and activation of the renin-angiotensin system. 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. However, little is known about the relationships among fructose intake, uric acid and systemic inflammation in nondialysis CKD patients.

Brymora et al. [2012] 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 Jamnuzzi, 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 alcoholic 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 nephropathy (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 Jamuzzi.

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. A homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as following: [(fasting glucose (g/dl) × fasting insulin (μU/ml)]/405. 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.

Cardiovascular markers (vascular cell adhesion molecule-1 [VCAM-1], ICAM-1 and monocyte chemotactrant 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).

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 - Nutwi®. The nutrient contents of foods not contained in this software were searched on Brazilian Table of Food Composition. Fructose intake was estimated using fructose content of different foods proposed by Brazi.

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.

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

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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 (<50 g/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 (β = 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.
Fructose intake: is there an association with uric acid levels in nondialysis-dependent chronic kidney disease patients?

**Discussion**

Excessive fructose intake appears to be related to the current obesity epidemic. 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. 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] 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

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

**Table II**

Inflammatory and cardiovascular markers of the patients

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

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

Acknowledgments

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