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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 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.

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772
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 chemotactant 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 dramatical 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 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 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 Jamuzi.
The UA levels were determined using enzymatic co-
lorimetric 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\(^\text{11}\). A homeostatic model
assessment of insulin resistance (HOMA-IR) was cal-
culated as following: [fasting glucose (g/dl) × fasting
insulin (\(\mu U/ml\))] / 405\(^\text{12}\). The insulin was measured by
ELISA (DRG diagnostics GmbH, Frauenbergstr, Mar-
burg, Germany). The Chronic Kidney Disease Epide-
miology Collaboration (CKD-EPI) equation was used to
GFR estimation\(^\text{16}\).
Cardiovascular markers (vascular cell adhesion
molecule-1 [VCAM-1], ICAM-1 and monocyte che-
moattractant protein-1 [MCP-1]) were measured by an
enzyme immunometric assay manufactured by Boster
Innolife leader\(^\text{8}\) (Fremont, CA, USA). Inflammatory
markers (CRP, tumor necrosis factor-alpha [TNF-\(\alpha\)]
and interleukin-6 [IL-6]) were measured with an enzy-
me immunometric assay manufactured by R&D Sys-
tems\(^\text{8}\) (Minneapolis, MN, USA).
Nutritional assessment
Body weight and height were measured to calcula-
te the body mass index (BMI) following the formula:
weight/(height)\(^2\). Waist circumference (WC) was mea-
sured at a level midway between the lowest lateral
border of the ribs and the uppermost lateral iliac crest
and classified as proposed by NCEP\(^\text{17}\).

**Dietary intake**

Dietary intake was assessed 3 days by 24-hour food
call. Patients were carefully instructed by a dietetic
ator to record all kinds and amounts of food (including be-
verages) ingested, using various models of foods and
measuring tools to estimate portion sizes and to im-
prove the accuracy of record. Daily ingestion of en-
ergy and protein was estimated by software developed
by the Federal University of São Paulo - Nutwin\(^\text{8}\).
The nutrient contents of foods not contained in this
software were searched on Brazilian Table of Food
Composition\(^\text{18}\). Fructose intake was estimated using
fructose content of different foods proposed by Bra-
zilian Association for Study of Metabolic Syndrome and
Obesity\(^\text{19}\). 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)\(^\text{20,21}\).

**Statistical analysis**

The Kolgomorov-Smirnov normality test was used to
caracterize data distribution. The results are expres-
sed as the mean ± standard deviation (SD), medians
(25\(^th\) and 75\(^th\) 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 co-
relation was calculated for univariate analyzes. Re-
gression analyzes were performed to determine vari-
ables 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. Re-
garding 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 recom-
dend 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 recommen-
ded daily dose of protein (0.6 – 0.8g/kg/day), with an
average of 1.0 ± 0.4 g/kg/day. 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 pa-
tients 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 pa-
tients (78%) presented HDL-cholesterol levels below
the recommended value. There were no differences in
plasma concentrations of inflammatory and cardio-
vascular 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 trigly-
ceride 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>
<thead>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Fructose intake (g/day)</td>
<td>55.5±17.9</td>
<td>72.1 ± 13.2</td>
<td>43.3 ± 9.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.2 ± 9.6</td>
<td>61.7 ± 9.3</td>
<td>65.8 ± 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>93.4 ± 13.1</td>
<td>110.0 ± 13.8</td>
<td>88.4 ± 10.5</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 4.4</td>
<td>29.1 ± 3.5</td>
<td>25.7 ± 4.4</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>81.6 ± 37.0</td>
<td>96.0 ± 36.2</td>
<td>70.8 ± 34.9</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.2 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>2.1 ± 0.8</td>
<td>NS</td>
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<tr>
<td>GFR (ml/min)</td>
<td>30.5 ± 10.3</td>
<td>29.6 ± 9.5</td>
<td>31.0 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>161.2 ± 79.7</td>
<td>166.0 ± 81.5</td>
<td>154.9 ± 79.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>199.0 ± 48.7</td>
<td>190.3 ± 58.3</td>
<td>203.5 ± 42.3</td>
<td>NS</td>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>MCP-1 (ng/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>
<td>NS</td>
</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.

NS, nonsignificant

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

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.
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. 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.

Hyperuricemia is common in CKD 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] 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 [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.

Experimental evidence have also suggested that UA itself may harm CKD patients by contributing to increased inflammation and CKD progression [Jalal et al., 2013]. Besides that, elevated serum UA could be an independent risk factor for incident kidney disease in the general population. 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, 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.

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. 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.

**Acknowledgments**

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