

The association of dietary inflammatory index with urinary risk factors of kidney stones formation in men with nephrolithiasis

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Research note

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Abstract

Objective: Inflammation plays a leading role in the pathogenesis of nephrolithiasis. The association of the dietary inflammatory index (DII) with urinary lithogenic factors is unclear. This study aimed to evaluate the relation of DII to urinary risk factors of kidney stones formation.

Results: Of 264 participants, 61.4% (n= 162), 72% (n=190), 74.6% (n=197), 68.6% (n=181), and 80.3% (n=212) had hyperoxaluria, hypercreatininuria, hypercalciuria, hyperuricosuria, hypocitraturia, respectively. There was a significant increasing trajectory in urinary calcium, uric acid, and creatinine as well as a decreasing trend in urinary citrate across tertiles of DII score (all $P \leq 0.001$). After multivariate adjustment for energy intake, age, physical activity and body mass index, high DII scores were associated with elevated odds of having hypercreatininuria ($OR=2.80$, 95%CI: 1.10-7.12, $P_{trend}=0.04$), hypercalciuria ($OR=7.44$, 95%CI: 2.62-21.14, $P_{trend} \leq 0.001$), hyperuricosuria ($OR=2.22$, 95%CI: 1.001-4.95, $P_{trend}=0.05$), and hypocitraturia ($OR=5.84$, 95%CI: 2.14-15.91, $P_{trend} \leq 0.001$). No association was identified between DII and hyperoxaluria.

Introduction

Nephrolithiasis is one of the most prevalent urologic disorders and impose a substantial burden on human health globally [1]. The high recurrence rate of kidney stones is yet unsolved [2 3], mostly due to the lack of suitable management of the associated risk factors. Thus, there is an urgent need to target modifiable risk factors to prevent the development and recurrence of renal stones.

Cumulative data have identified that higher urinary excretions of oxalate, calcium, creatinine, and uric acid as well as lower excretions of citrate are potential modifiable urinary lithogenic risk factors involved in the formation of kidney stones [4-6]. Inflammation is also another mechanism which plays a leading role in the pathogenesis of nephrolithiasis [7]. Dietary modifications toward decreasing inflammation may have a potential to prevent kidney stones or their recurrence. Previous studies have shown that several micronutrients or foods such as magnesium, vitamin E, vitamin C, carotenoids, polyphenols, polyunsaturated fatty acids (PUFAs), whole grains, vegetables, fruits, and fish had an anti-inflammatory impact [8-11]. In contrast, simple sugars, red meats, high-fat dairy products, and refined grains are associated with elevated inflammatory markers [12]. Nevertheless, nutrients or foods are not consumed separately but as part of the whole diet [13-15]. The Dietary Inflammatory Index (DII) is developed to measures the overall inflammatory potential of diets [16], which has been recognized to be related to the biomarkers of inflammation, including interleukin-6 [17], homocysteine [18], and C-reactive protein (CRP) [19]. A proinflammatory diet has been found to be related to the reduced kidney function [20]. However, there is no study investigating the relation of DII to urinary lithogenic factors. Therefore, this study aimed to assess the association of DII with hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and **hypercreatinuria** in patients with nephrolithiasis.

Methods

Subjects

This cross-sectional study was performed on a total of 264 stone former men (aged 18- 89 years) in Tehran, Iran in 2016. Participants were recruited from the Urology Research Center of Sina Hospital, Tehran, Iran, using a convenience sampling method. Inclusion criteria for this study were having a history of kidney stone formation and age \geq 18 years. People with a history of, thyroid disease, fatty liver disease, malignancy, stroke, diabetes, cardiovascular disease, and hypertension were excluded from the present study because of the possible change in their dietary pattern. Participants who had missing data regarding dietary intake in food frequency questionnaire (FFQ), those with unlikely total daily energy intake (< 500 kcal/day and > 4200 kcal/day), and those who were on medications such as corticosteroids, diuretics, anti-cancer drugs, multivitamins, potassium citrate, calcium, and vitamin D or C supplements were not eligible for this study. Furthermore, all alcohol drinkers and drugs abusers were excluded. Patients were included in the study after signing written informed consents.

Dietary assessment

Usual food intake of patients during the previous year was measured by a validated semi-quantitative 168-item food frequency questionnaire (FFQ) [21]. In this study, DII was calculated using the method reported by Shivappa et al. [22]. The DII is based on 1943 scientific papers published during 1950 to 2010 scoring 45 food parameters based on whether they elevated (+1), reduced (-1) or had no impact (0) on six inflammatory biomarkers (C-reactive protein, interleukin (IL)-1 beta, IL-10, IL-4, IL-6, and tumor necrosis factor-alpha). Papers were weighted by study features; using these weighted values, a particular inflammatory effect score was derived for each of the 45 food components. The DII score was calculated with the use of the corresponding 32 nutrients or food parameters available from the FFQ, including energy, protein, total fat, carbohydrate, dietary fiber, mono-unsaturated fatty acids, n-3 fatty acids, n-6 fatty acids, poly-unsaturated fatty acids, saturated fatty acids, cholesterol, trans fatty acids, vitamin A, thiamin, niacin, riboflavin, Vitamin B-6, folate, vitamin B-12, vitamin E, vitamin C, Vitamin D, b-carotene, iron, magnesium, zinc, selenium as well as caffeine, onion, green/black tea, paper, and garlic. The inflammatory effect scores for dietary components used for calculation of DII in this study are reported in Table S1. To calculate the DII score for each participant, the mean intake of each nutrient or food parameter was standardized by subtracting mean global intake of food items from the actual individual's intake and dividing it by the global SD to create a z-score. These z-scores then were converted to proportions and centered by multiplying values by 2 and subtracting 1 to normalize the scoring system and to avoid skewness. The centered percentile values for food items were then multiplied by the corresponding food item-specific inflammatory effect scores to obtain the food item-specific DII scores. The overall DII score for each individual was calculated by summing food item-specific DII scores [22]. Higher DII scores indicate a more pro-inflammatory diet, while lower DII scores indicate a more anti-inflammatory diet.

Measurements of study outcomes

The 24-h urine samples were collected from all participants and urine was analyzed to evaluate urinary levels of calcium, citrate, creatinine, oxalate, and uric acid by using an AutoAnalyzer as described previously [23]. Hyperoxaluria was defined as the urinary oxalate \geq 40 mg/day, hypocitraturia as urinary citrate of <450 mg/day, hyperuricosuria as urinary uric acid over 0.8 g/day, hypercreatininuria as urinary creatinine of \geq 24 mg/day, and hypercalciuria as a urinary calcium \geq 250 mg/day [23].

Measurement of other variables

Information on education level, age, marital status and occupation was obtained using interview by a trained interviewer. Physical activity was measured using of the International Physical Activity Questionnaires (IPAQ) [24]. Body weight was measured in minimal clothing after removal of shoes by a digital scale (Seca, Germany) with a precision about 0.1 kg. Height of individuals was assessed in standing position, without shoes, using a calibrated stadiometer (Seca, Germany) to the nearest 0.1 cm. BMI was calculated as weight divided by the square of height (kg/ m²).

Statistical analyses

DII was categorized into tertiles: T1 (- 3.72 to - 0.74); T2 (- 0.73 to 0.92); T3 (0.93 to 3.99). Analysis of variance (ANOVA) and chi-square tests were used to compare continuous and nominal/ordinal variables across tertiles of DII, respectively. Continuous variables are reported as mean \pm SE and nominal/ordinal variables as frequency. Odds ratio (OR) and 95% confidence interval (CI) for the relation of DII to study outcomes was calculated using the logistic regression analysis. Statistical significance was set at $p \leq 0.05$ for all tests. All analyses were undertaken using the statistical Package for Social Science (Version 22.0; SPSS Inc., Chicago IL, USA).

Results

Participants in the highest tertile of the DII had significantly higher total daily energy intake ($P = \leq 0.001$) and lower physical activity ($P = 0.01$) than those in the other tertiles. There was a significant increasing trajectory in urinary calcium ($P = \leq 0.001$), uric acid ($P = \leq 0.001$), and creatinine ($P = \leq 0.001$) and a decreasing trend in urinary citrate ($P = \leq 0.001$) across tertiles of DII score (Table 1).

DII score and urinary lithogenic factors

In the crude model, it was found that higher adherence to the DII was significantly related to the increased odds of hypercreatininuria (OR= 7.60, 95%CI: 3.28-17.61, $P_{trend} \leq 0.001$), hypercalciuria (OR= 10.45, 95%CI: 3.84-28.39, $P_{trend} \leq 0.001$), hyperuricosuria (OR= 4.40, 95%CI: 2.16-8.94, $P_{trend} \leq 0.001$), and hypocitraturia (OR= 6.04, 95%CI: 2.35-15.55, $P_{trend} \leq 0.001$). After multivariate adjustment for energy intake, age, physical activity and BMI, high DII scores were associated with elevated odds of having hypercreatininuria (OR= 2.80, 95%CI: 1.10-7.12, $P_{trend}=0.04$), hypercalciuria (OR= 7.44, 95%CI: 2.62-21.14, $P_{trend} \leq 0.001$), hyperuricosuria (OR= 2.22, 95%CI: 1.001-4.95, $P_{trend}= 0.05$), and hypocitraturia (OR= 5.84,

95%CI: 2.14-15.91, $P_{trend} \leq 0.001$). The relation of DII to hypercreatininuria, hyperoxaluria, and hyperuricosuria was not significant after adjustment for carbohydrate, fiber and protein intake (Table 2).

We also evaluated the association of dietary protein and fiber intake on urinary risk factors (Table 3). After adjustment for covariates, dietary intakes of protein and fiber were slightly related to the decreased odds of hypocitraturia (Protein OR= 0.96, 95%CI: 0.93-0.98; fiber OR= 0.96, 95%CI: 0.94-0.98) and hypercalciuria (Protein OR= 0.97, 95%CI: 0.95-0.99; fiber OR=0.97, 95%CI: 0.95-0.99), but not to hypercreatininuria, hyperoxaluria, and hyperuricosuria.

Discussion

We revealed that, in stone former men, a diet with a high DII is significantly related to the increased odds of having hypercreatininuria, hypercalciuria, hyperuricosuria, and hypocitraturia, but not to hyperoxaluria.

It has been confirmed that kidney stone formers could be susceptible to recurrence in stones formation because of unhealthy dietary patterns [25]. Inconsistent with our finding, a study did not report any significant difference in creatinine across tertiles of DII in subjects with chronic kidney disease [26]. A randomized controlled trial study by Noori et al. [27] on recurrent stone formers showed that a **DASH diet**, which in contrast to a diet with a high DII, is featured by a high intake of whole grains, fruits, low-fat **dairy products** and vegetables, and a low intake of total fat, cholesterol, **saturated fat**, meat, and refined grains, is significantly associated with a decrease in calcium oxalate supersaturation and an increase in citrate excretion. Moreover, another study reported that greater adherence to the Mediterranean **dietary pattern** (characterized by high consumption of fruits and vegetables, fish, **olive oil**, nuts, and legumes; low consumption of **saturated fats**, meat, and sugars; and moderate consumption of wine, is related to the reduced risk for incident kidney stones [28]. The relationship between systemic inflammation and nephrolithiasis has been identified previously [7]. Since both **DASH** and Mediterranean diets **attenuate inflammation** [9 29], the protective effects of these dietary patterns on kidney stones formation may be mediated, at least partly, by reducing systemic inflammation. A cross-sectional conducted on diabetic patients also reported that higher intake of “vegetable and fish” dietary pattern is related to a lower creatinine rates [30]. Vegetables and fish, as components of DII, are identified to have anti-inflammatory effects [31 32]. The DII is a tool to assess the overall impact of a diet on inflammatory potential [22], and is associated with markers of systemic inflammation including such as IL-6 [17], and CRP [19] [...]; IL-6 and CRP are two of the inflammatory biomarkers considered in the calculation of DII [22]. It has been revealed that the DII score is inversely related to the Dietary Approaches to Stop Hypertension Score (DASH), Mediterranean Diet Score, and Healthy Eating Index-2010 [33 34]. Taken together, these findings support that a likely mechanism for the relation of DII scores to hypercreatininuria, hypercalciuria, hyperuricosuria, and hypocitraturia could be explained by the higher systemic inflammation level among people following a pro-inflammatory diet.

Since DII positively depends on protein intake that is also a metabolic risk factor for hypercalciuria, hyperuricosuria, and hypocitraturia, and on contrary, dietary fiber has a negative impact on DII and is a

factor that can reduce calcium absorption, we also adjusted the analysis for protein, carbohydrate, and fiber intake to differentiate the metabolic impact of DII from its pro-inflammatory impact. It was found that DII is related to hypercalciuria and hypocitraturia independent of dietary intake of protein, carbohydrate, and fiber, however, the relationship between DII and hyperuricosuria disappeared, showing that this association may be resulted from metabolic effects of DII. Nevertheless, protein and fiber intake was inversely associated with hypercalciuria and hypercalciuria.

Conclusion

In conclusion, this study found that a diet with high inflammatory property might be unfavorably associated with urinary risk factors of kidney stone formation in men with a history of nephrolithiasis. Additional studies, particularly with prospective cohort design, are necessary to confirm these findings.

Limitation

Several limitations of this study should be considered when interpretation the findings. First, since the participants of the current study were limited to men, our findings may not be generalizable to women; therefore, it is essential to conduct such a study on women too. Third, causation cannot be inferred the cross-sectional design of the present investigation. Finally, the calculation of DII by FFQ has a potential recall bias for the evaluation of dietary intake. Though, the validity and reliability of the questionnaire were established previously.

Abbreviations

IPAQ: international physical activity questionnaires; DII: dietary inflammatory index; PUFAs: polyunsaturated fatty acids; CRP: C- reactive protein; FFQ: food frequency questionnaire; ANOVA: Analysis of variance; OR: Odds ratio; CI: confidence interval; BMI: body mass index;

Declarations

Ethics approval and consent to participate

Ethics approval for the study protocol was granted by The Human Ethics Committee of Tehran University of Medical Sciences (Grant ID: IR.TUMS.VCR.REC1395.1046). All participants signed written informed consent forms.

Consent for publication

Not Applicable.

Availability of data and materials

The data are not publicly available due to containing information that could compromise the privacy of research participants.

Competing interests

All authors declared that they have no competing interests.

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None.

Authors' Contribution

SMKA, designed the research and collected the samples; NSM and SHA wrote the paper; HY and MSY analyzed data; KhM conducted research and had primary responsibility for final content. All authors read and approved the final manuscript.

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Tables

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