Intake of Trace Metals and the Risk of Incident Kidney Stones

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Abbreviations and Acronyms

BMI = body mass index

FFQ = food frequency questionnaire

HPFS = Health Professionals Follow-Up Study

NHS = Nurses' Health Study

Accepted for publication January 16, 2018.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by National Institutes of Health Research Grants DK094910, DK91417, CA186107, CA176726 and CA167552.

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† Financial interest and/or other relationship with BioHealth Italia.

‡ Financial interest and/or other relationship with Allena Pharmaceuticals, AstraZeneca, Exponent, UpToDate and American Society of Nephrology.

§ Equal study contribution.

Purpose: The association between the intake of trace metals and the risk of incident stones has not been longitudinally investigated.

Materials and Methods: We performed a prospective analysis of 193,551 participants in the Health Professionals Follow-up Study, and the Nurses' Health Study I and II. During a followup of 3,316,580 person-years there was a total of 6,576 incident stones. We used multivariate regression models to identify associations of the intake of zinc, iron, copper and manganese with the risk of stones. In a subset of participants with 24-hour urine collections we examined the association between the intake of trace metals and urine composition.

Results: After multivariate adjustment total and dietary intakes of zinc and iron were not significantly associated with incident stones. A higher intake of manganese was associated with a lower risk of stones. The pooled HR of the highest quintile of total manganese intake compared with the lowest intake was 0.82 (95% CI 0.68–0.98, $p = 0.02$). Total but not dietary copper intake was marginally associated with a higher risk of stones (pooled HR 1.14, 95% CI 1.02–1.28, $p = 0.01$). There were no statistically significant associations of the total intake of manganese and copper with urinary supersaturation.

Conclusions: Zinc and iron intake was not associated with a risk of stones. Copper intake may be associated with a higher risk in some individuals. Higher total manganese intake was associated with a lower risk of stones but not with traditional 24-hour urinary composite markers of stone risk. Further research is needed to elucidate the mechanisms by which manganese may reduce kidney stone formation.

Key Words: kidney calculi, zinc, iron, manganese, nutritional status

The role of trace metals in the pathogenesis of kidney stones is unclear. Among them zinc has generated the most interest. Using a *Drosophila* model of ectopic calcification Chi et al found that the mineral concretions that developed after the inhibition of xanthine dehydrogenase were rich in zinc.[1] Furthermore, inhibiting zinc transporter genes in the same model suppressed stone formation, suggesting that zinc may have a critical role in driving the process of heterogeneous nucleation.

Dietary zinc intake was higher in individuals with a self-reported history of kidney stones in the NHANES (National Health and Nutrition Examination Survey).[2] In contrast, a small case-control study in a pediatric population recently showed lower zinc intake in patients with stones.[3]

0022-5347/18/1996-1534/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2018.01.077
Vol. 199, 1534-1539, June 2018
Printed in U.S.A.

Data from longitudinal studies on the association between zinc intake and the risk of kidney stones in adult populations are still lacking.

The intake of other trace metals may affect kidney stone formation. For example, copper might have a modest inhibitory effect on calcium phosphate crystallization.[4] Komleh et al analyzed the serum and urinary concentrations of zinc, copper and manganese in 56 stone formers and 39 healthy controls.[5] The urine concentration of zinc was higher, and copper and manganese urine concentrations were lower among stone formers. Similar studies were performed by Hofbauer[6] and Atakan[7] et al. None of these groups examined the association with dietary intake. Noticeably a recent review concluded that the net lithogenic effects of zinc, copper, iron and manganese are still uncertain.[8]

In this study we analyzed the association between the intake of trace minerals (zinc, copper, iron and manganese) and the risk of a symptomatic first kidney stone in 3 large prospective cohorts. In a subsample of the cohorts we also looked at the cross-sectional association between trace mineral intake and 24-hour urine composition.

METHODS

Study Cohorts

A total of 51,529 male health professionals 40 to 75 years old, including dentists, optometrists, osteopaths, pharmacists, podiatrists and veterinarians, enrolled in the HPFS in 1986. A total of 121,700 female registered nurses 30 to 55 years old enrolled in the NHS I in 1976 and 116,430 female registered nurses 25 to 42 years old enrolled in the NHS II in 1989.

Participants completed and returned an initial questionnaire providing detailed information on diet, medical history and medication. The cohorts are followed by biennial mailed questionnaires, which include inquiries on newly diagnosed diseases such as kidney stones and updated information on diet and supplements every 4 years.

Assessments

Trace Metals and Other Nutrient Intake. Starting in 1986 in HPFS and NHS I, and 1991 in NHS II the participants completed a semiquantitative FFQ asking about the annual average consumption of more than 130 individual foods and 22 beverages. Subsequently a version of this FFQ has been mailed to study participants every 4 years. Nutrient intakes were calculated from the reported frequency of consumption of each specified unit of food and from USDA (United States Department of Agriculture) data on the content of the relevant nutrient in specified portions except for oxalate, which was directly measured in foods by capillary electrophoresis.

The questionnaires collected information on multivitamins and supplements in isolated form. Participants who reported vitamin supplement intake were asked to report the specific brand, amount and frequency of use. This information was used to calculate supplemental trace metal and vitamin intake using a composition database of more than 1,000 multivitamin brands. The FFQs used in the HPFS and NHS cohorts have been validated in subgroups of the cohorts and found to be valid and reliable.[9–11]

Kidney Stones. Participants who reported an incident kidney stone on the main questionnaire were asked to complete an additional questionnaire to determine the date of stone development and associated symptoms. The study primary outcome was an incident kidney stone accompanied by pain or hematuria. The self-reported diagnosis was found to be reliable upon medical record review in a subset of cases with a confirmation rate of 95% in HPFS, 96% in NHS I and 98% in NHS II.[12]

Other Covariates. Information on patient age, weight, height, diabetes history and thiazide use was obtained on the baseline questionnaires and updated every 2 years.

24-Hour Urine Excretion

Urine samples were collected in 3 cycles from the 3 cohorts. For participants who provided more than 3 collections we used the first collection. To reduce the likelihood of over or under collection we excluded participant nonstone formers in the highest and lowest 1% of urine creatinine. Laboratory measurements were made with a system provided by Mission® Pharmacal for the first 2 cycles and by Litholink® for the third cycle.

Statistical Analysis

The study design was prospective with information on exposure collected before the incident kidney stones. Dietary and total (dietary plus supplemental) intakes of trace metals (zinc, iron, copper and manganese) were categorized into quintiles. Dietary exposures and covariates, which were time varying, were updated every 4 years. Analysis incorporated simple time updating, ie each participant was assigned to a quintile based on the most recent FFQ information on those who completed the FFQ.

The person-time of followup was allocated according to exposure status at the start of each followup period. If complete information on diet was missing at the start of a period, the participant was excluded from that period. Participants with a history of cancer, except nonmelanoma skin cancer, or a history of kidney stones at baseline were excluded from analysis. Those in whom cancer developed during followup were censored. Person-time was counted from the date of return of the 1986 HPFS and NHS I questionnaires, and the 1991 NHS II questionnaire to the date of a kidney stone, participant death or the end of followup, whichever was first. The end of followup was 2012 for HPFS and NHS I, and 2011 for NHS II.

Cox proportional hazards regression models were used to calculate HRs and 95% CIs for incident stones for each quintile of exposure. Models were adjusted for age, BMI, diabetes history, thiazide use, supplemental calcium, fluid intake, sodium, animal protein, dietary calcium, potassium, magnesium, fructose, oxalate, total vitamin C, alcohol,