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Intake of Trace Metals and the Risk of Incident Kidney Stones

Pietro Manuel Ferraro^{*,†}, Giovanni Gambaro, Gary C. Curhan^{‡,§}, Eric N. Taylor[§]

Nefrologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli (PMF, GG), Rome, Italy, Channing Division of Network Medicine (ENT) and Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School (GCC), Boston, Massachusetts, and Division of Nephrology and Transplantation, Maine Medical Center (ENT), Portland, Maine

Abstract

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.

Keywords

kidney calculi; zinc; iron; manganese; nutritional status

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*Correspondence: Nefrologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli, 00168, Rome, Italy (pietromanuel.ferraro@unicatt.it).

[§]Equal study contribution.

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 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 Hofbauer⁶ and Atakan⁷ 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 non-stone 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 non-melanoma 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, caffeine, total vitamin D and trace minerals. For each exposure effect modification by age (less than 50 vs 50 years or greater) or BMI (less than 25 vs 25 kg/m² or greater) was tested by including interaction terms in the multivariate adjusted models.

We examined higher levels of zinc intake by dividing the highest quintile into 2 additional categories based on the median intake value of the fifth quintile. For manganese the additional analyses included effect modification by oxalate intake and analysis of dietary and supplemental intakes. Analyses of dietary intake were adjusted for supplemental intakes and vice versa. Estimates of association between intakes of trace metals and risk of stones were pooled by random effects meta-analysis after heterogeneity assessment. The cross-sectional analysis of the association between trace metal intake and 24-hour urine excretion was performed with linear regression models adjusted for all the variables included in the main models plus cohort, stone history, and urine creatinine and sodium. The research protocol for this study was reviewed and approved by the Brigham and Women's Hospital institutional review board.

RESULTS

Overall 193,551 participants were included in analysis and contributed a total of 3,316,580 person-years of followup, during which 6,576 incident kidney stones developed. Supplementary tables 1 to 4 (<http://jurology.com/>) present baseline characteristics. The table and supplementary tables 5 to 10 (<http://jurology.com/>) show the estimated associations of total and dietary intake of trace metals with the risk of incident kidney stones.

After multivariate adjustment the total intake of zinc was not significantly associated with a risk of stones in any cohort (highest vs lowest quintile pooled HR 0.95, 95% CI 0.83–1.10, *p* for trend = 0.87, supplementary table 5, <http://jurology.com/>). Similar results were found for dietary intake (supplementary table 7, <http://jurology.com/>) and after dividing the highest quintile into 2 categories (data not shown).

Total intake of copper was associated with a higher risk of stones in pooled results (pooled HR 1.14, 95% CI 1.02–1.28, *p* for trend = 0.01, see table). However, the association was driven mainly by the NHS I cohort (HR 1.24, 95% CI 0.99–1.56, *p* for trend = 0.04). Additional analysis of deciles performed to look at extreme intakes showed that the highest vs the lowest decile of total copper was also significantly associated with the risk of stones in HPFS (HR 1.38, 95% CI 1.06–1.80, *p* for trend = 0.07). The association with copper was not statistically significant when analyzing dietary intake (supplementary table 7, <http://jurology.com/>). The association between the supplemental intake of copper and the risk of

stones was only significant in NHS I (supplemental intake greater than 2 mg per day vs no supplements HR 1.35, 95% CI 1.02–1.78).

The total intake of iron was not associated with a risk of stones in any cohort (pooled HR 1.05, 95% CI 0.92–1.20, *p* for trend = 0.39, supplementary table 6, <http://jurology.com/>). Similar results were found for the dietary intake (supplementary table 8, <http://jurology.com/>).

The total manganese intake was associated with a lower risk of stones on pooled analyses (pooled HR 0.82, 95% CI 0.68–0.98, *p* for trend = 0.02, see table). However, in NHS II there was no association between total manganese and risk. The dietary intake of manganese was associated with a lower risk of stones in pooled results (pooled HR 0.79, 95% CI 0.71–0.87, *p* for trend <0.001, see table). With regard to the supplemental intake of manganese the distribution was too skewed and the absolute amount was too small to construct quantiles for analysis. We divided supplemental manganese intake into no use, and 0.1 to 2.5 and greater than 2.5 mg per day. In participants with any supplemental manganese intake 2.5 mg per day were approximately the median. The multivariable relative risk when comparing the top category of supplemental manganese with no intake was 0.93 (95% CI 0.81–1.07, *p* = 0.32). However, only about 4% to 5% of participants ingested supplemental manganese greater than 2.5 mg per day.

Interaction terms of age and BMI with trace metals were not statistically significant. For manganese intake there was no significant interaction with oxalate intake. The main contributors of the dietary intake of manganese were tea, coffee, dark bread and cold cereal.

Supplementary tables 10 and 11 (<http://jurology.com/>) show the association of total intake of manganese and copper with 24-hour urine excretion in 5,770 participants with available urine data. After multivariate adjustment higher quintiles of manganese intake were not associated with a specific urine profile except slightly higher oxalate and urine volume. Higher quintiles of copper intake were associated with lower urine uric acid, potassium and magnesium. There were also associations with lower urine citrate and pH, although they were not linear and the associations were not significant for the highest vs the lowest category. Manganese and copper intakes were not associated with lower 24-hour urinary supersaturation of calcium oxalate, calcium phosphate or uric acid.

DISCUSSION

We found no association between zinc intake and the risk of a first symptomatic kidney stone in 3 large prospective cohorts. The association was consistently null for total and dietary intakes adjusted for supplements except for a suggestion of an inverse association in NHS II. However, we had no a priori hypothesis for a differential association in this cohort so that the difference could have been due to chance.

Some previous data suggest that zinc could have a role in the development of kidney stones. Cross-sectional studies showed significantly higher urinary excretion of zinc among calcium stone formers compared with controls¹³ and zinc is also present in calcium stones.¹⁴ An analysis of the NHANES suggested that those with a history of stones have higher dietary

zinc intake than nonstone formers.² However, findings in subsequent studies have not been consistent. A recent case-control study in a pediatric population demonstrated that stone formers had lower dietary zinc intake than controls (8.1 vs 10 mg/day).³ A small randomized, controlled trial in pediatric stone formers showed that there was no effect of oral supplementation with zinc sulfate 1 mg/kg per day for 3 months on the recurrence risk at 9 months.

Regarding other trace metals, we found no association of total and dietary iron intake with the risk of stones. There was a statistically significant association between a higher intake of copper and a higher risk of stones, which was driven predominantly by 1 cohort. Because we observed no association between dietary copper intake and the risk of stones, these findings should be interpreted with caution. Nonetheless, we previously observed cohort specific differences in dietary risk factors for nephrolithiasis.¹⁵ It could be speculated that the higher risk of stones associated with copper intake could be due to its potential effects on oxidative stress status, particularly associated with lower activity of superoxide dismutase.¹⁶

We found a significant association between a higher intake of total manganese and a lower risk of stones, especially in the highest categories of intake. This association was statistically significant in 2 cohorts and it was also present when analyzing dietary intake in all 3 cohorts. Previous studies revealed lower manganese levels in the serum and urine of stone formers compared with nonstone formers,^{5,6} suggesting a protective role against stone formation.

The potential mechanism underlying the association between higher manganese intake and a lower risk of kidney stones is unclear. Manganese is a component of enzymes that combat oxidative stress such as MnSOD (manganese superoxide dismutase). Given the suggestive evidence for a role of oxidative stress in general^{17,18} and MnSOD in particular¹⁹ in kidney stone disease, it might be postulated that a higher manganese intake could lead to more efficient scavenging of reactive oxygen species with a subsequent reduction in the risk of forming stones. Such a hypothesis would be consistent with our finding of minimal differences in commonly measured crystallization promoters or inhibitors in 24-hour urine collections across quintiles of manganese intake.

The strengths of our study include data on 3 large, prospective cohorts with detailed and validated information on dietary intake, medications and lifestyle habits as well as on incident kidney stones and also on 24-hour urine composition in more than 5,700 participants.

Our study also has limitations, including the observational design, the lack of information on the composition of most stones, a predominantly white population, which potentially reduces the generalizability of our findings, and the lack of information on urinary excretion of trace metals, which would have allowed for further speculation on potential mechanisms of association.

CONCLUSIONS

The intake of zinc and iron was not associated with a risk of incident kidney stones. It is possible that a higher copper intake is associated with risk in some individuals. Higher intake of manganese was associated with lower risk but not with lower 24-hour urinary supersaturation of calcium oxalate, calcium phosphate or uric acid. Further research is needed to elucidate the mechanisms by which manganese may decrease kidney stone formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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

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table

Multivariate model of associations of total intake of copper and manganese, and dietary intake of manganese with incident kidney stone risk

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p Value for Trend
<i>Copper*</i>						
HPFS:						
Median mg/day [†]	1.2	1.5	1.7	1.9	3.1	—
No. pts	485	419	354	340	365	—
Age adjusted HR	1.00 (referent)	0.90 (0.79–1.03)	0.79 (0.69–0.90)	0.77 (0.67–0.88)	0.83 (0.72–0.95)	0.03
Multivariate adjusted HR	1.00 (referent)	1.05 (0.91–1.22)	1.04 (0.89–1.22)	1.09 (0.92–1.29)	1.16 (0.95–1.40)	0.14
NHS I:						
Median mg/day [†]	1.1	1.2	1.4	1.6	2.6	—
No. pts	369	321	302	306	301	—
Age adjusted HR	1.00 (referent)	0.85 (0.73–0.99)	0.82 (0.70–0.95)	0.83 (0.71–0.97)	0.86 (0.73–1.00)	0.33
Multivariate adjusted HR	1.00 (referent)	1.02 (0.87–1.20)	1.14 (0.95–1.36)	1.24 (1.02–1.50)	1.24 (0.99–1.56)	0.04
NHS II:						
Median mg/day [†]	1.0	1.1	1.3	1.5	2.7	—
No. pts	731	620	550	538	575	—
Age adjusted HR	1.00 (referent)	0.86 (0.77–0.95)	0.77 (0.69–0.86)	0.76 (0.66–0.84)	0.79 (0.71–0.88)	0.002
Multivariate adjusted HR	1.00 (referent)	0.97 (0.87–1.09)	0.95 (0.83–1.08)	1.03 (0.89–1.19)	1.08 (0.91–1.28)	0.30
Adjusted pooled estimate HR:						
Age	1.00 (referent)	0.87 (0.81–0.93)	0.78 (0.73–0.85)	0.78 (0.72–0.84)	0.82 (0.76–0.88)	<0.001
Multivariate	1.00 (referent)	1.01 (0.93–1.09)	1.03 (0.93–1.14)	1.10 (0.99–1.22)	1.14 (1.02–1.28)	0.01
<i>Manganese*</i>						
HPFS:						
Median mg/day [†]	1.8	2.3	2.7	3.2	4.7	—
No. pts	496	422	383	349	313	—
Age adjusted HR	1.00 (referent)	0.84 (0.73–0.96)	0.78 (0.68–0.89)	0.72 (0.63–0.83)	0.64 (0.56–0.74)	<0.001
Multivariate adjusted HR	1.00 (referent)	0.92 (0.80–1.06)	0.92 (0.78–1.08)	0.89 (0.74–1.07)	0.78 (0.63–0.97)	0.07
NHS I:						
Median mg/day [†]	1.7	2.2	2.6	3.1	4.8	—
No. pts	392	358	299	287	263	—
Age adjusted HR	1.00 (referent)	0.89 (0.77–1.03)	0.74 (0.64–0.86)	0.72 (0.61–0.84)	0.67 (0.58–0.79)	<0.001

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p Value for Trend
Multivariate adjusted HR	1.00 (referent)	1.00 (0.86–1.17)	0.86 (0.72–1.03)	0.82 (0.67–1.01)	0.70 (0.55–0.89)	0.002
NHS II:						
Median mg/day [†]	2.2	2.8	3.4	4.1	5.7	–
No. pts	725	675	565	530	519	–
Age adjusted HR	1.00 (referent)	0.93 (0.84–1.03)	0.78 (0.70–0.87)	0.73 (0.65–0.82)	0.72 (0.64–0.80)	<0.001
Multivariate adjusted HR	1.00 (referent)	1.06 (0.95–1.19)	0.96 (0.84–1.10)	0.94 (0.81–1.09)	0.95 (0.80–1.13)	0.36
Pooled estimates:						
Age adjusted HR	1.00 (referent)	0.89 (0.83–0.96)	0.77 (0.71–0.83)	0.73 (0.68–0.78)	0.68 (0.63–0.74)	<0.001
Multivariate adjusted HR	1.00 (referent)	1.00(0.92–1.09)	0.92(0.85–1.01)	0.89 (0.83–0.97)	0.82 (0.68–0.98)	0.02
<i>Dietary manganese[‡]</i>						
HPFS:						
Median mg/day [†]	1.8	2.2	2.6	3.0	4.0	–
No. pts	475	464	392	341	291	–
Age adjusted HR	1.00 (referent)	0.96 (0.84–1.09)	0.81 (0.70–0.92)	0.73 (0.63–0.83)	0.63 (0.55–0.73)	<0.001
Multivariate adjusted HR	1.00 (referent)	1.02 (0.89–1.18)	0.92 (0.79–1.08)	0.89 (0.75–1.05)	0.84 (0.69–1.03)	0.08
NHS I:						
Median mg/day [†]	1.7	2.1	2.4	2.9	3.7	–
No. pts	408	353	302	289	247	–
Age adjusted HR	1.00 (referent)	0.84 (0.73–0.97)	0.72 (0.62–0.83)	0.69 (0.59–0.80)	0.61 (0.52–0.71)	<0.001
Multivariate adjusted HR	1.00 (referent)	0.92 (0.79–1.08)	0.84 (0.71–1.00)	0.86 (0.71–1.02)	0.79 (0.64–0.97)	0.03
NHS II:						
Median mg/day [†]	2.2	2.7	3.2	3.8	4.8	–
No. pts	747	691	607	541	428	–
Age adjusted HR	1.00 (referent)	0.92 (0.83–1.02)	0.81 (0.73–0.90)	0.72 (0.64–0.81)	0.57 (0.51–0.65)	<0.001
Multivariate adjusted HR	1.00 (referent)	1.04 (0.93–1.16)	0.96 (0.85–1.09)	0.90 (0.78–1.03)	0.75 (0.64–0.88)	<0.001
Pooled estimates:						
Age adjusted HR	1.00 (referent)	0.91 (0.85–0.98)	0.78 (0.73–0.84)	0.71 (0.67–0.77)	0.60 (0.55–0.65)	<0.001
Multivariate adjusted HR	1.00 (referent)	1.00 (0.93–1.08)	0.92 (0.85–1.00)	0.88 (0.82–0.95)	0.79 (0.71–0.87)	<0.001

* Adjusted for age, BMI, diabetes history, thiazide use and supplemental calcium; intake of fluid, salt, animal protein, dietary calcium, potassium, magnesium, fructose, oxalate, total vitamin C, alcohol, caffeine and total vitamin D; and total zinc, iron and manganese intake.

[†] First period.

[‡]Adjusted for age, BMI, history of diabetes, thiazide use and supplemental calcium; intake of fluid, salt, animal protein, dietary calcium, potassium, magnesium, fructose, oxalate, total vitamin C, alcohol, caffeine, total vitamin D and supplemental manganese; and total zinc, copper and iron intake.

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