Kidney Medicine

Insulin Resistance in Hypercalciuric Calcium Kidney Stone Patients

Megan Prochaska, Gloria Adeola, Noah Vetter, Raghavendra G. Mirmira, Fredric Coe, and Elaine Worcester

Rational & Objective: Diabetes and uric acid kidney stones are strongly associated. Patients with calcium kidney stones also have higher risk of developing diabetes compared with nonkidney stone patients yet this has not been further investigated. We aimed to characterize insulin resistance in calcium kidney stone patients.

Study Design: Observational.

Setting & Population: This study was performed in the University of Chicago Clinical Research Center. Kidney stone patients (N = 42) were selected for having idiopathic hypercalciuria and calcium stones with no other medical conditions, and controls (N = 27) were healthy.

Exposures: All participants presented to the Clinical Research Center in a fasting state and at least 2 timed fasting blood and urine collections were collected before a fixed breakfast. Six additional timed blood and urine collections were performed after breakfast.

Outcomes: We compared fasting and fed indices of insulin resistance between the groups.

Analytic Approach: We used *t* tests and multivariable linear regression models. A sensitivity analysis removing all patients who had ever been on a thiazide diuretic was also performed.

Results: In separate multivariable linear models, kidney stone patients had higher fasting serum insulin levels (24 (3-46 pmol/L), $P = 0.03$) and higher homeostatic model of insulin resistance (HOMA-IR) (1.0 (0.2-1.8), $P = 0.02$). In separate multivariable linear models, kidney stone patients had higher fed serum glucose levels (10 (2-18 mg/dL), $P = 0.01$). Results were similar in a sensitivity analysis removing all patients who had ever been on a thiazide diuretic. There were no differences in urine composition based on HOMA-IR levels.

Limitations: Single institution. Small sample size limited subanalyses by different calcium stone types.

Conclusions: Calcium kidney stone patients without diabetes or other medical conditions demonstrated signs of insulin resistance compared with healthy matched controls.

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Diabetes and higher glycemic indices are important clinical risk factors for developing kidney stones.[1-5] In one study the multivariable adjusted odds of kidney stones was 1.63 (1.23-2.16) for those who had type 2 diabetes (T2D).[4] In another study, higher fasting blood glucose and glycated hemoglobin (HbA1c) levels were associated with higher risk of kidney stones in men even at levels in the normal reference range (blood glucose 90-99 mg/dL) or prediabetic range (HbA1c 6.0% to 6.4%).[5] One large cohort study showed the opposite association is also true: history of kidney stones is associated with subsequently higher risk of diabetes, even when controlling for thiazide diuretic use,[1] which may increase the risk of T2D.[6] In none of these studies were the investigators able to separate uric acid from calcium stones. Uric acid stones are linked directly to diabetes and insulin resistance through reduced urine pH arising, in part, from abnormalities of renal acid excretion.[7-9]

Taken together, these studies suggest that many patients presenting with stones have unsuspected insulin resistance, a known risk factor for cardiovascular disease[10] and may benefit from selective early intervention. In support of this, multiple studies have found higher risk of hypertension,[11] cardiovascular disease,[12-14] stroke,[13,15] and chronic kidney disease[16,17] in kidney stone patients. However, once again, there is the problem of uric acid stones, which have strong links to cardiovascular disease as well as insulin resistance.[8]

To date, no study has documented whether insulin resistance is a feature of fully characterized calcium stone patients. To provide this missing information, we compared fasting and fed indices of glucose metabolism and insulin resistance between healthy controls and calcium-based kidney stone patients without diabetes or systemic cause of stone using individuals previously reported in a different context.[18,19]

METHODS

Participants with calcium kidney stones and hypercalciuria were recruited from the kidney stone clinics at the University of Chicago and Indiana University. These participants have been studied for different aspects of mineral metabolism relative to the pathophysiology of idiopathic hypercalciuria[18,19] but information about glucose metabolism in this cohort has not been previously reported. There were 42 calcium kidney stone participants and 27 healthy controls included in this study. Kidney stone patients formed calcium oxalate or calcium phosphate stones and were selected for having idiopathic hypercalciuria (>200 mg/day)[20] without other metabolic derangements.

PLAIN-LANGUAGE SUMMARY

Diabetes is strongly associated with kidney stones, particularly uric acid kidney stones. However, patients who form calcium kidney stones may also have an increased risk of developing diabetes, but this has not been further explored. We collected markers of insulin resistance in otherwise healthy patients with calcium kidney stones and healthy control volunteers to evaluate for early signs of insulin resistance in patients with calcium kidney stones. Compared to healthy control participants, we found that patients with calcium kidney stones are more likely to have insulin resistance. Follow-up research is needed to determine the mechanisms contributing to insulin resistance in these patients. Earlier screening for insulin resistance may be beneficial for patients with calcium kidney stones.

Participants were excluded if they had diagnosed diabetes, history of intestinal surgery, or hypertension requiring more than a thiazide. Control participants had no personal or family history of kidney stones. Participants who had previously been on thiazides were included in the primary analysis. A sensitivity analysis excluding anyone who had ever been on a thiazide diuretic, even if only for a few weeks, was also performed. This study was approved by the University of Chicago Institutional Review Board (Protocol Numbers 12882A and 09-164B).

Study Protocol

The study protocol has been described elsewhere.[18,19] In brief, this study occurred in the University of Chicago Clinical Research Center (CRC). Before the study day each participant met with the CRC dietitian and was provided instructions to follow a prestudy diet for 5 days that was similar to the study diet. The study diet mirrored contemporary US diet recommendations and specified 2,000 mg per day of sodium and 1,200 mg per day of calcium. Medications that may affect mineral metabolism, including thiazide diuretics, calcium and vitamin D supplements, multivitamins, and alkali supplements, were held for 1 week.

On the study day participants presented to the CRC in a fasting state. Two or 3 fasting blood samples with matching urines were collected every 1-hour and additional urines with matching bloods were collected every half-hour for 2 hours and every hour for 2 more hours after a fixed study breakfast for a total of 6 postprandial blood samples. The high-carbohydrate study breakfast was developed in collaboration with the CRC dietitian and consisted of typical breakfast items (cereal, coffee cake, orange juice) with set micro- and macronutrients levels (calorie levels 70% carbohydrate, 20% fat, and 10% protein). Both kidney stone and control participants received 1 of 3 caloric levels per day (1,800, 2,100, or 2,400 kcal/day) based on an individual's estimated energy needs.[21]

Laboratory Measurements

We measured serum creatinine, insulin, C-peptide, potassium, calcium, ultrafilterable calcium, and phosphorus levels as previously described.[22-24] Serum glucose levels were measured in the CRC using YSI 2300 Stat Plus analyzer. Glucagon like peptide-1 (GLP-1) measurements were performed using ELISA (Alpco, Salem, NH). Glucagon measurements were performed at LabCorp using enzyme immunoassay. Not all participants had GLP-1 or glucagon levels measured as these were added to the protocol after some participants had already completed it. In each urine sample, we measured volume, pH, and calcium, sodium, creatinine, citrate, potassium, ammonia, and oxalate levels using methods described elsewhere.[22,23] All blood and urine samples were analyzed at the time of the study.

Statistical Analysis

Mean fasting and fed values for all serum and urine variables were calculated for each individual. Homeostatic model of insulin resistance (HOMA-IR) was calculated by multiplying mean fasting glucose (mmol/L) by mean fasting insulin (mU/L) and dividing by the constant 22.5.[25,26] Fractional excretion of calcium was calculated conventionally using ultrafilterable calcium. Notched box plots with fasting and fed values by kidney stone versus control participants were generated for serum glucose, change in serum glucose (fed minus fasting), insulin, and HOMA-IR. Two population t tests and χ^2 test were used to compare participant characteristics and mean fasting and fed and serum and urine values between kidney stone and control participants. Paired t tests were used to compare within group differences in urine and serum values from fasting to fed. A scatter plot with univariate regression lines for body mass index (BMI) versus HOMA-IR was created and presented by kidney stone patients versus control participants.

In separate multivariable linear regression models, the individual associations between being a kidney stone patient and serum glucose, insulin, C-peptide, GLP-1, glucagon, and HOMA-IR levels (all continuous) were examined. Individual multivariable linear regression models predicting serum glucose, insulin, C-peptide, and HOMA-IR each controlled for age, BMI (both continuous) and sex. Because of smaller sample sizes, the multivariable model predicting GLP-1 levels only controlled for sex and BMI (continuous), and the multivariable model predicting glucagon levels only controlled for age and BMI (both continuous).

A sensitivity analysis was performed excluding the 21 kidney stone participants who had ever been on a thiazide diuretic, even if briefly. All above descriptive statistics, statistical analyses, and multivariable linear regression models were then performed. All of the statistical analyses were done using SAS software 9.4 (SAS Institute Inc, Cary, NC).

Table 1. Mean Fasting and Fed Characteristics of Patients Who Form Calcium Stones and Controls (N = 69)

	Fasting			Fed		
	Controls (N = 27)	Stone-forming patients (N = 42)	*P* value	Controls (N = 27)	Stone-forming patients (N = 42)	*P* value
Age (y)	41 (12)	48 (12)	0.02	-	-	-
Body mass index (kg/m^2)	26 (6)	27 (4)	0.48	-	-	-
Sex, male, N (%)	14 (52%)	26 (62%)	0.46	-	-	-
Thiazide, N (%)	0 (0%)	21 (50%)	<0.001	-	-	-
Systolic BP (mm Hg)[a]	114 (13)	116 (13)	0.67	118 (12)	118 (14)	0.99
Diastolic BP (mm Hg)[a]	69 (9)	69 (8)	0.95	70 (9)	69 (9)	0.61
MAP (mm Hg)[a]	84 (10)	85 (9)	0.87	86 (9)	85 (11)	0.75

Data presented as mean (standard deviation) unless otherwise noted.
P values compare controls versus stone-forming patients within food period (t-test or χ^2 test, where appropriate).
Within group comparisons (paired t-test comparing fasting versus fed) represented in bold ($P < 0.001$) and italics ($P < 0.05$).
Abbreviations: BP, blood pressure; MAP, mean arterial pressure.
[a]N = 19 for fasting controls, N = 31 for fasting stone-forming patients, N = 21 for fed controls, and N = 38 for fed stone-forming patients.

RESULTS

Participant Characteristics

Kidney stone patients were older than controls but otherwise similar in BMI, sex, and blood pressure, the latter under both fasting and fed conditions (Table 1).

Univariate Analyses of Key Fasting and Fed Serum Values

Compared with controls, kidney stone patients had higher fasting serum insulin and HOMA-IR levels (Table 2, Fig 1 lower left panel, and Fig 2 left panel). HOMA-IR was markedly elevated (>3, significant insulin resistance) more frequently in stone-forming patients than controls (Table 2). This difference persisted among subjects never exposed to thiazide (Table S1). Fasting serum glucose levels were higher in stone-forming patients but the difference was marginally significant. Although the fraction of subjects with fasting glucose levels greater than 100 mg/dL was higher in stone-forming patients the difference was not significant (Table 2). Among only those subjects never exposed to thiazides, the difference was significant (Table S1). Fed glucose levels were higher in stone-forming patients but fed insulin levels were not different (Table 2, Fig 1 right upper and lower panels).

Table 2. Mean Fasting and Fed Serum Values in Patients Who Form Calcium Stones and Controls (N = 69)

	Fasting			Fed		
	Controls (N = 27)	Stone-forming patients (N = 42)	*P* value	Controls (N = 27)	Stone-forming patients (N = 42)	*P* value
HOMA-IR	1.6 (0.9)	2.7 (2.1)	0.006	-	-	-
Fasting glucose >100 mg/dL, N (%)	3 (11%)	13 (31%)	0.08	-	-	-
HOMA-IR >3, N (%)	2 (7%)	14 (33%)	0.02	-	-	-
Glucose (mg/dL)	92 (7)	96 (10)	0.05	106 (13)[a,d]	117 (16)[d]	0.005
Insulin (pmol/L)	42 (20)	67 (55)	0.01	357 (313)[d]	445 (333)[d]	0.28
C-peptide (pmol/L)	677 (276)	806 (423)	0.13	2,315 (1,082)[d]	2,673 (1,327)[d]	0.25
Glucagon (pg/mL)[b]	58 (30)	64 (19)	0.52	66 (29)[e]	71 (20)	0.58
GLP-1 (pmol/L)[c]	7.7 (10.7)	6.8 (11.3)	0.83	8.4 (9.8)	12 (13.6)[e]	0.47
Potassium (mmol/L)	4.1 (0.4)	4.0 (0.2)	0.24	4.1 (0.3)	4.0 (0.2)	0.31
Calcium (mmol/L)	9.3 (0.3)	9.3 (0.4)	0.71	9.4 (0.3)[d]	9.5 (0.5)[d]	0.29
Phosphorus (mmol/L)	3.6 (0.6)	3.2 (0.5)	0.003	3.4 (0.5)[e]	3.0 (0.4)[d]	<0.001
Creatinine (mg/dL)	0.9 (0.2)	0.9 (0.2)	0.52	0.9 (0.2)	0.9 (0.2)	0.35
FE calcium (percentage)	1.5 (0.5)	3.0 (1.0)	<0.001	2.8 (0.9)[d]	4.9 (1.8)[d]	<0.001

Data presented as mean (standard deviation) unless otherwise noted.
P values compare controls versus stone-forming patients within food period (*t*-test or χ^2 test, where appropriate).
Abbreviations: BP, blood pressure; FE, fractional excretion; GLP-1, glucagon like peptide-1; HOMA-IR, homeostatic model of insulin resistance; MAP, mean arterial pressure.
[a]N = 26.
[b]N = 17 for controls, N=15 stone-forming patients.
[c]N = 15 for controls, N=14 stone-forming patients.
[d]Within group comparisons (paired t-test comparing fasting versus fed) are represented ($P < 0.001$).
[e]Within group comparisons (paired t-test comparing fasting versus fed) are represented ($P < 0.05$).

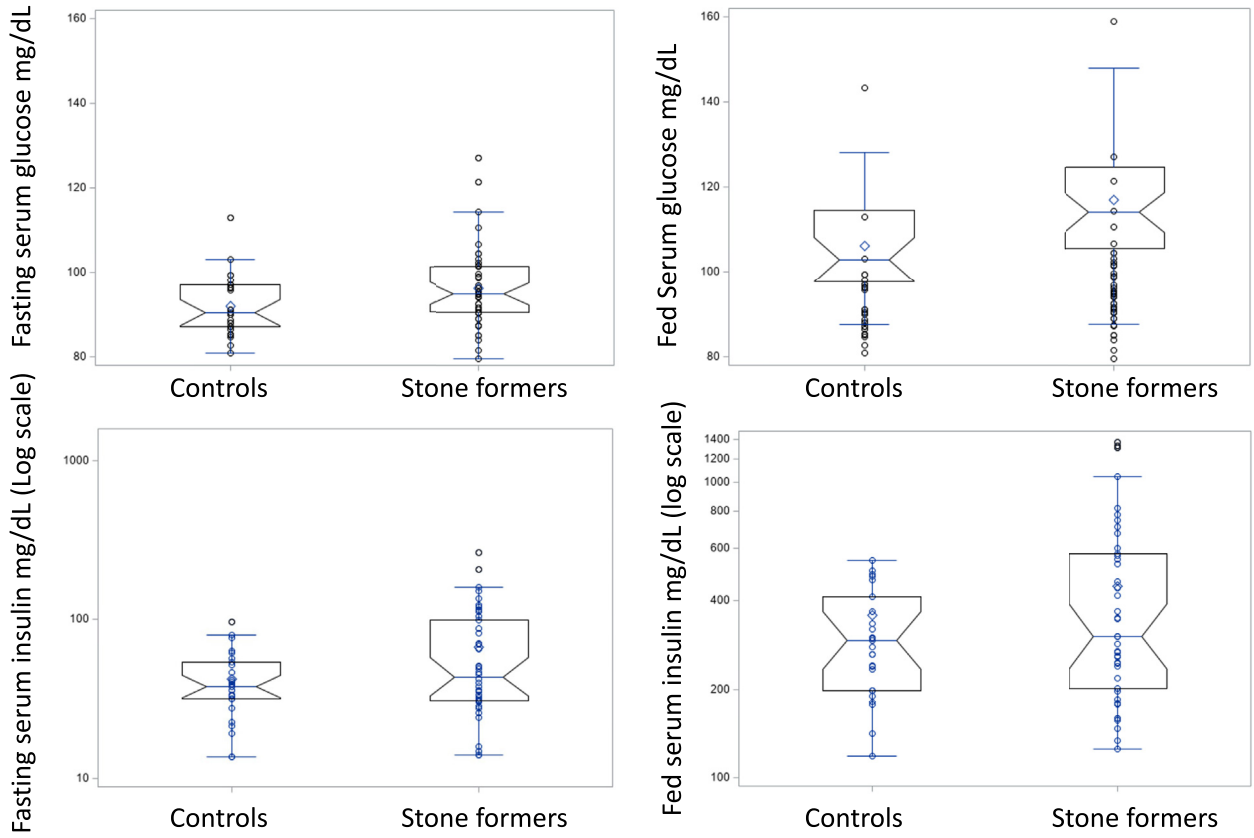

Figure 1. N = 42 patients who form calcium stones (SF), N = 27 controls. Top left: Notched boxplot of fasting serum glucose levels in controls and SF. Top right: Notched boxplot of fed serum glucose levels in controls and SF. Bottom left: Notched boxplot of fasting serum insulin levels in controls and SF. Bottom right: Notched boxplot of fed serum insulin levels in controls and SF. Open dots represent individuals. Open diamond represents group mean. Notches represent 95% nonparametric confidence intervals.

There were no fasting or fed differences in serum glucagon, GLP-1, potassium, calcium, or creatinine levels between the 2 groups (Table 2). Of note, serum phosphorus levels were lower in stone-forming patients. As expected, fractional excretion of calcium was higher in kidney stone patients compared with controls because we selected for hypercalciuria (Table 2). Results were similar when limited to the 21 kidney stone patients not on thiazides (Table S1).

Also as expected, serum glucose, insulin, and C-peptide levels increased with food in both groups (Table 2, Fig 2 right panel). However, glucagon levels increased only in controls, and GLP-1 levels only increased in stone-forming patients. Of interest, serum calcium levels increased, and serum phosphorus levels decreased in both groups (Table 2).

Multivariable Analyses of Key Fasting and Fed Serum Values

In multivariable models controlling for age, sex, and BMI, fasting serum insulin, HOMA-IR, and fed serum glucose levels remained significantly higher in kidney stone patients compared with controls (Table 3). There were no differences in fasting serum glucose, C-peptide, GLP-1, or glucagon levels between kidney stone patients and controls (Table 3). Results were similar when models were limited to the 21 kidney stone patients not on thiazides (Table S2). Compared with controls, the multivariable adjusted difference between fed and fasting glucose was larger in stone-forming patients (7mg/dL (95% confidence intervals 1 to 12 mg/dL)) (not shown).

HOMA-IR values are known to vary with BMI[27,28] and the regression of HOMA-IR on BMI is significant among stone-forming patients and controls (Fig 3). The 2 regression slopes did not differ significantly (stone-forming patients: 0.2 [0.09 to 0.3] versus controls: 0.09 [0.04 to 0.1]), although the 95% confidence limits barely overlap.

Urine

Based on selection, kidney stone patients were hypercalciuric (Tables 2 and S3). There were no other differences between kidney stone patients and controls for any of the measured urine parameters of potential interest for this study (Table S3). Serum HOMA-IR levels had no relationship to urine citrate levels, urine ammonia levels, urine pH or fractional excretion of calcium (not shown).

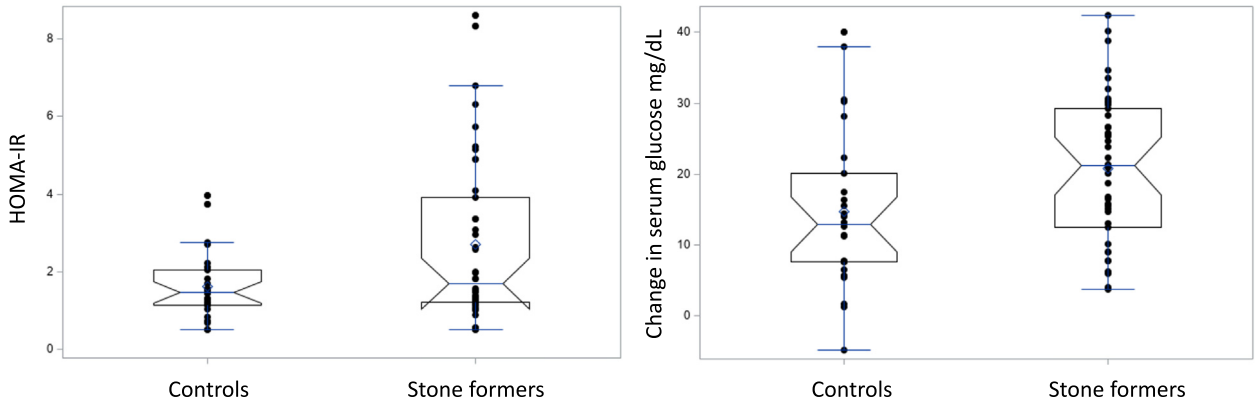

Figure 2. N = 42 patients who form calcium stones (SF), N = 27 controls. Left panel: Notched boxplot of homeostatic model of insulin resistance (HOMA-IR) levels in controls and SF. Optimal HOMA-IR level is <2. HOMA-IR level 2 to <3 indicates early insulin resistance. HOMA-IR level >3 represents significant insulin resistance. Right panel: Notched boxplot of change in serum glucose levels (Fed levels minus fasting levels) by controls and SF. Comparing change in controls 15 (11) mg/dL versus change in SF 21 (11) mg/dL, $P = 0.03$. Dots represent individuals. Open diamond represents group mean. Notches represent 95% nonparametric confidence intervals.

DISCUSSION

This study offers evidence that hypercalciuric calcium stone-forming patients have more insulin resistance compared with well-matched healthy control subjects. Compared with controls, HOMA-IR and fasting insulin levels are higher and serum glucose levels are borderline higher among the stone-forming patients. In the fed state, serum glucose levels are higher and the fasting-to-fed change in serum glucose is greater for stone-forming patients when compared with controls. The prevalence of clearly abnormal values for HOMA-IR (>3, significant insulin resistance) was also higher in stone-forming patients. These abnormalities persisted when accounting for age, sex, and BMI in multivariable models. Of note, the BMI did not differ between the 2 groups. Abnormalities in serum glucose and insulin levels and HOMA-IR values did not correlate with any of the detailed serum and urine stone risk factors that we quantified in these studies.

We were able to dissociate our findings from prior use of thiazide. Because stone-forming patients are often

Table 3. Multivariable Differences in Serum Parameters in Stone-Forming Patients Compared to Controls (N = 69)

	MV adjusted mean difference (95% CI) for stone-forming patients	*P* value
Fasting		
Glucose (mg/dL)	3 (−1 to 8)	0.14
Insulin (pmol/L)	24 (3-46)	0.03
HOMA-IR	1.0 (0.2-1.8)	0.02
C-peptide (pmol/L)	81 (−94 to 255)	0.35
GLP-1 (pmol/L)[a]	−1 (−9 to 6)	0.73
Glucagon (pg/mL)[b]	12 (−7 to 32)	0.21
Fed		
Glucose (mg/dL)[c]	10 (2-18)	0.01
Insulin (pmol/L)	72 (−93 to 238)	0.39
C-peptide (pmol/L)	208 (−406 to 823)	0.37
GLP-1 (pmol/L)[a,b]	3 (−6 to 12)	0.50
Glucagon (pg/mL)[b]	6 (−14 to 27)	0.53

Multivariable models for glucose, insulin, HOMA-IR, and C-peptide controlled for age, sex, and body mass index. Glucagon like peptide-1 multivariable model controlled for sex and body mass index. Glucagon multivariable model controls for age and body mass index. Glucagon like peptide-1 and glucagon models included fewer covariates given the smaller sample size.
Abbreviations: CI, Confidence intervals, HOMA-IR, homeostatic model of insulin resistance, GLP-1, glucagon-like peptide-1.
[a]N = 29.
[b]N = 32.
[c]N = 68 as one participant is missing fed glucose levels.

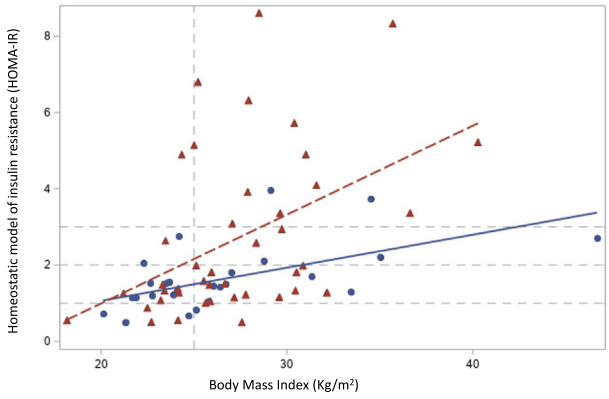

Figure 3. N = 42 patients who form calcium stones (SF), N = 27 controls. Homeostatic model of insulin resistance (HOMA-IR) levels by body mass index (BMI) and presented by controls and SF. Controls with blue circles and SF in red triangles. Univariate linear regression lines stratified by SF (red dotted, slope 0.2 (0.09 to 0.4), $P = 0.002$) and controls (blue solid, 0.09 (0.04 to 0.1), $P = 0.002$) are shown. Horizontal dotted lines represent HOMA-IR levels of 1, 2 (<2 "Optimal"), and 3 ("significant insulin resistance"). Vertical dotted line represents BMI 25 kg/m^2.

treated with thiazide type diuretics, we completed a sensitivity analysis rigorously excluding everyone who had ever had treatment with that drug class (Tables S1 and S2). Despite the limitation of patient numbers, the abnormality of HOMA-IR remained significant. This supports the idea that insulin resistance is an intrinsic health risk factor in this group of hypercalciuric calcium stone patients compared with well-matched controls.

Our findings are consistent with those of prior studies. In a large epidemiologic study, the risk of new onset diabetes was higher for kidney stone patients compared with patients who did not form kidney stones. In that study multivariable adjusted relative risk for kidney stone-forming patients to develop diabetes was 1.33 (1.18 to 1.50) in older women, 1.48 (1.14 to 1.91) in younger women, and 1.49 (1.29 to 1.72) in men compared with nonkidney stone-forming patients.[1] The analysis of this study included use of thiazide but did not include data on stone type. In another study, HOMA-IR and insulin levels were elevated in women with a self-reported prior history of kidney stones compared with women without stones.[3] This study also did not have data on stone type, present data on thiazide use, or include important covariates like BMI in multivariable models. Our study accounted for these clinical variables and provides an estimate of the prevalence of insulin resistance in a group of hypercalciuric calcium stone-forming patients.

We did not find any differences in excretion of common urine kidney stone risk factors by HOMA-IR. This is consistent with prior work showing minimal effect of insulin on urine calcium.[29] This differs from previous studies that have described lower urine citrate levels and pH in diabetic kidney stone patients. However, some of these may have been uric acid stone-forming patients, in whom acid-base abnormalities are well known and related to diabetes and insulin resistance.[7,9,30] One prior study of nondiabetic calcium-based kidney stone patients found lower urine citrate levels and higher HOMA-IR levels but no other changes in urine composition.[30] We were unable to confirm that finding in our study. However, there was a noticeable scatter of high HOMA-IR values within their calcium-based kidney stone population which, lacking a control group, is difficult to interpret further.[30]

Taken together, this work establishes in a highly defined calcium stone-forming population what has been observed in an epidemiologic study of much larger size but less resolution of detail. It would appear that calcium stone forming and insulin resistance are related to each other. The direction of causality remains to be delineated. It is possible that inflammation is part of the underlying link as inflammation is strongly associated with insulin resistance[31,32] and is recognized as having a role in calcium kidney stone formation,[33-35] but more study is needed.

Perhaps the most clinically significant aspect of our work arises from the prevalence of very abnormal HOMA-IR (>3, significant insulin resistance) in our small series of highly studied calcium stone-forming patients: 33%. Given that we studied a very common phenotype,[36] hypercalciuric idiopathic stone-forming patients, if our fraction with abnormal HOMA-IR values is at all representative, then clinicians must expect to find this abnormality not infrequently in their management of stone disease.

Given this, insulin resistance may account for, in part, the well-established increase in cardiovascular and metabolic disease in stone-forming patients which includes higher risk of hypertension,[11] cardiovascular disease,[12-14] stroke,[13,15] and chronic kidney disease.[16,17] This reasoning suggests that management of stone-forming patients should include some estimates of insulin responsiveness beyond a routine fasting blood sugar (eg, fasting glucose and insulin measured together). Further studies should be done to substantiate these results.

Our study has limitations. This study is small and single center. Despite the small sample size, we found a difference between kidney stone patients and controls, but we did not have large enough sample sizes to make further comparisons between calcium oxalate and calcium phosphate stone-forming patients. We do not have waist circumference measurements or lipid levels and did not collect GLP-1 and glucagon levels for all participants.

In conclusion, idiopathic hypercalciuric calcium kidney stone patients have higher levels of HOMA-IR, fasting serum insulin, and fed serum glucose compared with healthy controls when controlling for age, sex, BMI and accounting for thiazide use. This likely represents high prevalence of insulin resistance in hypercalciuric calcium kidney stone patients which may contribute to their well-described risk of metabolic syndrome and poor cardiovascular outcomes. Additional work to better understand underlying mechanisms is needed.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Table S1: Mean Fasting and Fed Values in Stone-Forming Patients and Controls Who Have Never been on a Thiazide (N = 48).

Table S2: Multivariable Differences in Serum Parameters in Stone-Forming Patients Compared With Controls for Participants Who had Never Been on a Thiazide (Total N = 48, Stone-Forming Patients N = 21, Controls N = 27).

Table S3: Mean Fasting and Fed Urinary Values by Stone-Forming Patients and Controls (N = 69).

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REFERENCES

1. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int*. 2005;68(3):1230-1235.
2. Kabeya Y, Kato K, Tomita M, et al. Associations of insulin resistance and glycemic control with the risk of kidney stones. *Intern Med*. 2012;51(7):699-705.
3. Ando R, Suzuki S, Nagaya T, et al. Impact of insulin resistance, insulin and adiponectin on kidney stones in the Japanese population. *Int J Urol*. 2011;18(2):131-138.
4. Weinberg AE, Patel CJ, Chertow GM, Leppert JT. Diabetic severity and risk of kidney stone disease. *Eur Urol*. 2014;65(1):242-247.
5. Kim S, Chang Y, Jung HS, et al. Glycemic status, insulin resistance, and the risk of nephrolithiasis: A cohort study. *Am J Kidney Dis*. 2020;76(5):658-668.e1.
6. Punzi HA, Punzi CF. Antihypertensive and lipid-lowering heart attack trial study, Trinity Hypertension Research Institute. Metabolic issues in the Antihypertensive and Lipid-Lowering Heart Attack Trial Study. *Curr Hypertens Rep*. 2004;6(2):106-110.
7. Cameron MA, Maalouf NM, Adams-Huet B, Moe OW, Sakhaee K. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. *J Am Soc Nephrol*. 2006;17(5):1422-1428.
8. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K. Low urine pH: A novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol*. 2007;2(5):883-888.
9. Pak CYC, Sakhaee K, Moe O, et al. Biochemical profile of stone-forming patients with diabetes mellitus. *Urology*. 2003;61(3):523-527.
10. Kosmas CE, Bousvarou MD, Kostara CE, Papakonstantinou EJ, Salamou E, Guzman E. Insulin resistance and cardiovascular disease. *J Int Med Res*. 2023;51(3):3000605231164548.
11. Madore F, Stampfer M, Willett W, Speizer F, Curhan G. Nephrolithiasis and risk of hypertension in women. *Am J Kidney Dis*. 1998;32(5):802-807.
12. Ferraro PM, Taylor EN, Eisner BH, et al. History of kidney stones and the risk of coronary heart disease. *JAMA*. 2013;310(4):408.
13. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and cardiovascular events: a cohort study. *Clin J Am Soc Nephrol*. 2014;9(3):506-512.
14. Rule AD, Roger VL, Melton LJ, et al. Kidney stones associate with increased risk for myocardial infarction. *J Am Soc Nepgrol*. 2010;21(10):1641-1644.
15. Yuan M, Zhou HY, Hu F, et al. Association between kidney stones and risk of developing stroke: a meta-analysis. *Neurol Sci*. 2021;42(11):4521-4529.
16. Rule AD, Bergstralh EJ, Melton LJ, Li X, Weaver AL, Lieske JC. Kidney stones and the risk for chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4(4):804-811.
17. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. *BMJ*. 2012;345:e5287.
18. Worcester EM, Gillen DL, Evan AP, et al. Evidence that postprandial reduction of renal calcium reabsorption mediates hypercalciuria of patients with calcium nephrolithiasis. *Am J Physiol Ren Physiol*. 2007;292(1):F66-F75.
19. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. Evidence for disordered acid-base handling in calcium stone-forming patients. *Am J Physiol Ren Physiol*. 2020;318(2):F363-F374.
20. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. *Kidney Int*. 2008;73(4):489-496.
21. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr*. 1985;39(Suppl 1):5-41.
22. Worcester EM, Coe FL, Evan AP, et al. Evidence for increased postprandial distal nephron calcium delivery in hypercalciuric stone-forming patients. *Am J Physiol Ren Physiol*. 2008;295(5):F1286-F1294.
23. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. Mechanism for higher urine pH in normal women compared with men. *Am J Physiol Ren Physiol*. 2018;314(4):F623-F629.
24. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. Evidence for increased renal tubule and parathyroid gland sensitivity to serum calcium in human idiopathic hypercalciuria. *Am J Physiol Ren Physiol*. 2013;305(6):F853-F860.
25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419.
26. Matli B, Schulz A, Koeck T, et al. Distribution of HOMA-IR in a population-based cohort and proposal for reference intervals. *Clin Chem Lab Med*. 2021;59(11):1844-1851.
27. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev*. 2018;98(4):2133-2223.
28. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. *Nat Med*. 2017;23(7):804-814.
29. Yoon V, Adams-Huet B, Sakhaee K, Maalouf NM. Hyperinsulinemia and urinary calcium excretion in calcium stone formers with idiopathic hypercalciuria. *J Clin Endocrinol Metab*. 2013;98(6):2589-2594. doi:10.1210/jc.2013-1301
30. Cupisti A, Meola M, D'Alessandro C, et al. Insulin resistance and low urinary citrate excretion in calcium stone formers. *Biomed Pharmacother*. 2007;61(1):86-90.
31. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006;116(7):1793-1801.
32. Lee YS, Olefsky J. Chronic tissue inflammation and metabolic disease. *Genes Dev*. 2021;35(5-6):307-328.
33. Thongboonkerd V, Yasui T, Khan SR. Editorial: Immunity and inflammatory response in kidney stone disease. *Front Immunol*. 2021;12:795559.
34. Taguchi K, Okada A, Unno R, Hamamoto S, Yasui T. Macrophage function in calcium oxalate kidney stone formation: A systematic review of literature. *Front Immunol*. 2021;12:673690.
35. Canela VH, Bowen WS, Ferreira RM, et al. A spatially anchored transcriptomic atlas of the human kidney papilla identifies significant immune injury in patients with stone disease. *Nat Commun*. 2023;14(1):4140.
36. Lieske JC, Rule AD, Krambeck AE, et al. Stone composition as a function of age and sex. *Clin J Am Soc Nephrol*. 2014;9(12):2141-2146.