Type 2 Diabetes Increases the Risk for Uric Acid Stones

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An increased prevalence of nephrolithiasis has been reported in patients with diabetes. Because insulin resistance, characteristic of the metabolic syndrome and type 2 diabetes, results in lower urine pH through impaired kidney ammoniagenesis and because a low urine pH is the main factor of uric acid (UA) stone formation, it was hypothesized that type 2 diabetes should favor the formation of UA stones. Therefore, the distribution of the main stone components was analyzed in a series of 2464 calculi from 272 (11%) patients with type 2 diabetes and 2192 without type 2 diabetes. The proportion of UA stones was 35.7% in patients with type 2 diabetes and 11.3% in patients without type 2 diabetes ($P < 0.0001$). Reciprocally, the proportion of patients with type 2 diabetes was significantly higher among UA than among calcium stone formers (27.8 *versus* 6.9%; $P < 0.0001$). Stepwise regression analysis identified type 2 diabetes as the strongest factor that was independently associated with the risk for UA stones (odds ratio 6.9; 95% confidence interval 5.5 to 8.8). The proper influence of type 2 diabetes was the most apparent in women and in patients in the lowest age and body mass index classes. In conclusion, in view of the strong association between type 2 diabetes and UA stone formation, it is proposed that UA nephrolithiasis may be added to the conditions that potentially are associated with insulin resistance. Accordingly, it is suggested that patients with UA stones, especially if overweight, should be screened for the presence of type 2 diabetes or components of the metabolic syndrome.

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Incidence of urinary stone disease rose considerably in recent decades in all industrialized countries (1,2), as did the incidence of obesity, the metabolic syndrome, and type 2 diabetes (3–6). These epidemiologic changes took place in parallel with marked modifications in dietary habits and lifestyle that occurred in all Western and westernized populations, characterized by a high calorie intake coupled with reduced physical activity (7–9). This temporal parallelism suggested that an association might exist among diabetes, obesity, and urinary stone disease. Two recent studies revealed an increased prevalence of nephrolithiasis in patients with diabetes as compared with patients without diabetes (10,11), but in these studies, the chemical type of nephrolithiasis was not identified. Therefore, it was not defined whether calcium (Ca) or uric acid (UA) stones or both contributed to the increased prevalence of urinary stone disease in patients with diabetes, as alterations in urine biochemistry associated with obesity and type 2 diabetes may favor the formation of UA as well as of Ca stones (12–15).

Insulin resistance, which constitutes the fundamental metabolic disorder that is associated with the metabolic syndrome and type 2 diabetes (16,17), results in defective renal ammoniagenesis and low urine pH (18,19) and therefore may be expected to favor the production of UA stones, because a low urine pH is the major lithogenic factor in idiopathic UA nephrolithiasis (20–23). Pak *et al.* (24) found the proportion of UA stones to be especially high (33.9%) among stone formers with type 2 diabetes. Nevertheless, because all of them had a very high body weight, the respective influence of obesity and type 2 diabetes *per se* could not be delineated. Indeed, the prevalence of UA stones was reported to be higher in obese than in lean individuals in a study of Ekeruo *et al.* (25) and in a recent study from our group (26).

Taking advantage of the large number of patients who had calculi and were referred for analysis to our laboratory, we analyzed the respective influence of type 2 diabetes and of body size on the distribution of UA and Ca stones in a large series of calculi from patients whose body weight and height together with diabetes status were available. We hypothesized that the proportion of UA stones would be higher in stone formers with type 2 diabetes than without type 2 diabetes.

Materials and Methods

Study Protocol

From January 1, 1990, to December 31, 2004, 40,718 calculi were referred for analysis to the Laboratoire CRISTAL. All calculi were analyzed according to our protocol published elsewhere (27,28). In short, morphologic examination of both surface and section was followed by sequential Fourier transform infrared spectroscopic analysis. The relative proportions of the various stone components were quantified by analysis of a global powder of the sample. Calculi were classified on the basis of their main component (*i.e.*, accounting for at least half of the stone content). Calcium oxalate mono- and dihydrate, together with calcium phosphate, were grouped into the single category of Ca stones, and anhydrous and dihydrate forms of UA were grouped into the category of UA stones. Included in the study were

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calculi from patients for whom information on diabetes status, body height, and body weight had been provided and who had idiopathic Ca or UA nephrolithiasis. Excluded from the study were struvite and cystine stones, whose occurrence depends on specific factors that are not known to be influenced by diabetes or body size. Only patients with type 2 diabetes were considered (*i.e.*, patients who were older than 35 yr at onset of hyperglycemia or diagnosis of diabetes and not initially treated with insulin). Finally, the study material consisted of calculi from 2464 patients (1760 men, 704 women), including 272 patients with type 2 diabetes and 2192 patients without type 2 diabetes.

The body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters). BMI values were stratified into three classes according to the World Health Organization definitions: Normal (BMI < 25 kg/m^2), overweight (25 to 29.9 kg/m^2), or obese ($\geq$30 kg/m^2). Patients were also identified as first-stone formers or recurrent stone formers, the latter being defined as patients who experienced at least two separate stone episodes.

In addition, we analyzed blood and urine lithogenic parameters in a subset of 252 patients who were followed at our stone clinic, 25 of whom had type 2 diabetes and 227 of whom did not. All these patients were evaluated as outpatients while consuming their usual diet. None received drugs that could alter urinary pH or urate metabolism for at least 2 wk before blood and urine sampling. None of the 25 patients who had type 2 diabetes and underwent laboratory evaluation at our institution received any oral hypoglycemic agent before or during this evaluation. The fractional excretion of urate (FeUA) was calculated as the ratio of UA to creatinine clearance using 24-h urine creatinine and UA excretion and the corresponding fasting serum creatinine and UA concentrations.

Statistical Analyses

Results are given as means ± SEM. Categorical comparisons were performed using the χ^2 test. Numeric variables were compared using *t* test or ANOVA. Correlations between parameters were performed using Pearson and Spearman tests. Multivariate logistic regression analysis was used to determine the odds ratios (OR) for having UA stones according to diabetes status, BMI, age, and gender. Data analysis was performed with the NCSS statistical package (J. Hintz, Gainesville, FL).

Results

Overall, 272 (11%) patients had type 2 diabetes, whereas 2192 (89%) did not. Table 1 compares the characteristics of patients with and without type 2 diabetes. The male-to-female ratio (2.73:2.47) did not differ between the two groups. In contrast, there were marked differences with respect to age, BMI, stone composition, and proportion of recurrent stone formers between the two groups. Overall, the mean age of patients with type 2 diabetes exceeded that of patients without type 2 diabetes by nearly 12 yr (59.4 ± 11.3 *versus* 47.8 ± 14.5 yr; $P < 0.0001$). Stone formers who were younger than 50 yr were three times more frequent among patients without type 2 diabetes, whereas stone formers who were $\geq$70 yr of age where two times frequent among patients with type 2 diabetes. The mean BMI value was strikingly higher in patients with type 2 diabetes than in patients without type 2 diabetes (29.9 ± 6.1 *versus* 25.1 ± 4.1 kg/m^2; $P < 0.0001$), and 80% of patients with type 2 diabetes were overweight or obese, as compared with only 38% of patients without type 2 diabetes ($P < 0.0001$). The relative proportion of Ca stones was significantly lower in patients with than without type 2 diabetes, whereas the proportion of UA stones was three times higher in the former than in the latter ($P < 0.0001$). The proportion of recurrent stone formers was significantly higher (nearly two-fold) in patients with than without type 2 diabetes, and this was apparent especially for UA nephrolithiasis.

Influence of Diabetes Status in Men and Women

The distribution of Ca and UA stones in male and female stone formers, with respect to diabetes status, together with their respec-

Table 1. Characteristics of stone formers both with and without diabetes

	With Diabetes	Without Diabetes	*P*
No (% of the whole series)	272 (11)	2192 (89)	
Male/female (gender ratio)	199/73 (2.73)	1561/631 (2.47)	NS
Age (yr; mean ± SEM)	59.4 ± 11.3	47.8 ± 14.5	<0.00001
<50 (%)	20.6	57.8	<0.00001
50 to 69.9 (%)	62.9	34.0	<0.00001
≥70 (%)	16.5	8.2	<0.0001
BMI (mean ± SEM)	29.9 ± 6.1	25.1 ± 4.1	<0.00001
<25 (%)	19.9	62.1	<0.00001
25 to 29.9 (%)	36.4	27.6	<0.00001
≥30 (%)	43.7	10.3	<0.00001
No. of stones (%)			
Ca stones	175 (64.3)	1945 (88.7)	<0.00001
UA stones	97 (35.7)	247 (11.3)	<0.00001
Recurrent stones (%)			
all calculi	52.3	28.3	<0.00001
Ca stones	45.8	27.8	<0.00001
UA stones	64.4[b]	32.6	<0.00001

[a]BMI, body mass index; Ca, calcium; UA, uric acid.
[b]$P < 0.01$ UA *versus* calcium stones.

Table 2. Distribution of Ca and UA stones with respect to diabetes status in male and female stone formers[a]

	With Diabetes (n = 272)			Without Diabetes (n = 2192)		
	Men (n = 199)	Women (n = 73)	All (n = 272)	Men (n = 1561)	Women (n = 631)	All (n = 2192)
UA stones						
n (%)	66 (33.2)	31 (42.5)	97 (35.7)	187 (11.9)[b]	60 (9.5)[b]	247 (11.3)[b]
age (yr)	61.4 ± 11.9	59.7 ± 10.9	60.9 ± 11.6	59.7 ± 13.8	59.6 ± 14.9	59.7 ± 14.0
BMI (kg/m^2)	30.2 ± 6.0	33.2 ± 6.7	31.2 ± 6.3	27.1 ± 5.0[b]	27.1 ± 6.5[b]	27.1 ± 5.4[b]
Ca stones						
n (%)	133 (66.8)	42 (57.5)	175 (64.3)	1374 (88.1)[b]	571 (90.5)[b]	1945 (88.7)[b]
age (yr)	59.3 ± 10.6	56.4 ± 12.2	58.6 ± 11.1	46.5 ± 13.6[b,c]	45.9 ± 14.5[b,c]	46.3 ± 13.9[b,c]
BMI (kg/m^2)	28.7 ± 5.2	30.9 ± 7.3	29.3 ± 5.9[d]	24.9 ± 3.5[b,c]	24.4 ± 4.8[b,c]	24.8 ± 3.9[b,c]

[a]Results are mean ± SD.
[b]$P < 0.0001$ between patients with and without diabetes.
[c]$P < 0.0001$, [d]$P < 0.05$ between UA and Ca stone formers.

tive age and BMI is given in Table 2. Overall, the proportion of Ca stones was significantly lower in patients with than without type 2 diabetes, both in women (57.5 *versus* 90.5%) and in men (66.8 *versus* 88.1%). Conversely, the proportion of UA stones was strikingly higher in patients with than without type 2 diabetes both in men (33.2 *versus* 11.9%) and in women (42.5 *versus* 9.5%). The mean age of Ca stone formers was significantly higher in patients with than without type 2 diabetes, both in men and in women, whereas the mean age of UA stone formers did not differ with diabetes status in either gender.

Respective Influence of Diabetes and Body Size

Table 3 depicts the distribution of Ca and UA stones in the three BMI classes among patients with and without type 2 diabetes, together with the age of patients in the respective groups, both genders being considered together. Among patients with type 2 diabetes, the proportion of UA calculi rose gradually with BMI, from 27.8% in the normal-BMI group to 40.3% in the obese group. The same was true among patients without type 2 diabetes, with the proportion of UA stones rising from 8.1% in the normal-BMI group to 25.2% in the obese group. Thus, the relative proportion of UA stones rose with BMI both in patients with and without type 2 diabetes but was consistently higher in the former than in the latter. Of note, the influence of diabetes was the more marked in patients with normal BMI and was less apparent as BMI rose. Indeed, UA stones were 3.4 times more frequent in patients who both did and did not have type 2 diabetes and whose BMI was <25 kg/m^2 and only 1.6 times in patients whose BMI was ≥30 kg/m^2.

Respective Influence of Diabetes and Age

The proportion of UA stones rose significantly with age in both patients with and without type 2 diabetes, but the effect of age was less marked in the former than in the latter, as UA stones were four times more frequent in patients who did than did not have type 2 diabetes and were younger than 50 yr and only 1.4 times in patients who were ≥70 yr of age. In both patients with and without type 2 diabetes, the BMI of patients was higher in UA than in Ca stone formers in the age classes

Table 3. Distribution of Ca and UA stones with respect to BMI in stone formers with and without diabetes[a]

	BMI (kg/m^2)					
	With Diabetes (n = 272)			Without Diabetes (n = 2192)		
	<25 (n = 54)	25 to 29.9 (n = 99)	≥30 (n = 119)	<25 (n = 1362)	25 to 29.9 (n = 604)	≥30 (n = 226)
UA stones (%)						
n (%)	15 (27.8)	34 (34.3)	48 (40.3)	111 (8.1)[b]	79 (13.1)[b]	57 (25.2)[c]
age (yr)	65.1 ± 10.0	63.8 ± 11.1	57.5 ± 11.6	63.8 ± 14.8	58.6 ± 12.5[d]	53.0 ± 11.7[d]
Ca stones (%)						
n (%)	39 (72.2)	65 (65.7)	71 (59.7)	1251 (91.9)[b]	525 (86.9)[b]	169 (74.8)[b]
age (yr)	58.6 ± 14.8	59.3 ± 10.7	58.0 ± 9.0	45.3 ± 14.2[b,e]	47.4 ± 12.8[b,e]	50.5 ± 14.1[b]

[a]Results are mean ± SD.
[b]$P < 0.0001$, [c]$P < 0.01$, [d]$P < 0.05$ between patients with and without diabetes.
[e]$P < 0.0001$ between UA and Ca stones.

Table 4. Clinical and laboratory data in stone formers (25 with diabetes and 227 without diabetes) with UA or Ca calculi[a]

	With Diabetes (n = 25)		Without Diabetes (n = 227)	
	UA	Ca	UA	Ca
Clinical data				
no. of patients	10	15	26	201
men/women	9/1	11/4	20/6	143/58
age at first stone episode (yr)	51.5 ± 10.5	46.1 ± 11.4	53.1 ± 8.6	32.8 ± 12.3[b,f]
age at referral (yr)	56.7 ± 7.0	53.4 ± 10.4	58.0 ± 6.1	42.2 ± 12.8[b,f]
weight (kg)	88.1 ± 10.9	89.0 ± 14.0	78.7 ± 10.2[g]	69.6 ± 13.1[c,f]
BMI (kg/m^2)	28.7 ± 3.8	30.0 ± 4.7	26.5 ± 3.5	23.7 ± 3.6[c,f]
SBP (mmHg)	170 ± 23	162 ± 13	155 ± 17[g]	134 ± 17[b,f]
DBP (mmHg)	93 ± 14	92 ± 7	87 ± 7	77 ± 9[b,f]
Serum biochemistry				
glucose (mmol/L)	9.1 ± 2.9	7.8 ± 1.1	5.4 ± 0.6[f]	5.2 ± 0.5[e,f]
calcium (mmol/L)	2.40 ± 0.09	2.35 ± 0.06	2.36 ± 0.08	2.33 ± 0.09
phosphate (mmol/L)	1.14 ± 0.16	0.94 ± 0.15[d]	0.99 ± 0.17[g]	1.00 ± 0.18
magnesium (mmol/L)	0.81 ± 0.06	0.77 ± 0.05	0.83 ± 0.06	0.81 ± 0.10
UA (μmol/L)	348 ± 71	360 ± 99	376 ± 80	307 ± 67[b,h]
bicarbonate (mmol/L)	27.4 ± 1.9	27.1 ± 1.5	27.5 ± 2.3	27.3 ± 2.2
creatinine (μmol/L)	98 ± 16	91 ± 17	99 ± 19	90 ± 13[c]
Urinary parameters				
volume (L/d)	2.29 ± 0.8	2.11 ± 0.61	1.85 ± 0.50[g]	1.72 ± 0.57[g]
UA (mmol/d)	5.38 ± 0.91	4.26 ± 1.26[e]	3.66 ± 0.96[f]	3.89 ± 1.20
FeUA (%)	9.4 ± 2.3	6.9 ± 2.6[e]	5.8 ± 1.6[f]	8.1 ± 1.9[f,g]
pH	5.07 ± 0.27	5.52 ± 0.39[d]	5.13 ± 0.23	5.91 ± 0.35[b,f]
calcium (mmol/d)	5.54 ± 3.23	8.52 ± 2.67[e]	5.02 ± 2.48	7.51 ± 3.31[b]
phosphate (mmol/d)	35.2 ± 7.9	33.6 ± 12.6	31.2 ± 8.8	30.1 ± 10.5
oxalate (mmol/d)	0.55 ± 0.19	0.52 ± 0.15	0.46 ± 0.18	0.43 ± 0.16[g]
citrate (mmol/d)	5.46 ± 2.41	3.98 ± 1.44	3.72 ± 1.81[g]	2.90 ± 1.35[d,h]
magnesium (mmol/d)	4.27 ± 2.11	4.62 ± 2.14	3.96 ± 1.39	4.45 ± 1.64

[a]Data are mean ± SD. DBP, diastolic BP; FeUA, fractional excretion of urate; SBP, systolic BP.
[b]$P < 0.0001$, [c]$P < 0.001$, [d]$P < 0.01$, [e]$P < 0.05$ between UA and Ca stone formers within groups with and without diabetes.
[f]$P < 0.0001$, [g]$P < 0.05$, [h]$P < 0.01$ between patients who have or do not have diabetes and are UA or Ca stone formers.

<50 and 50 to 69.9 yr, whereas it did not differ in those who were aged ≥70 yr (data not shown).

Laboratory Data in 252 Stone Formers

Among the 252 patients who underwent laboratory evaluation at our institution, 25 (9.9%) had type 2 diabetes, whereas 227 (90.1%) did not. These proportions are comparable to those observed in the whole series. The distribution of UA and Ca stones among patients with and without type 2 diabetes, together with the corresponding anthropometric, clinical, and laboratory parameters, is shown in Table 4.

Within the group with type 2 diabetes, age, BMI, systolic (SBP) and diastolic BP (DBP), and uricemia did not differ between UA and Ca stone formers. In contrast, daily urinary UA excretion, FeUA, and serum phosphate were higher and urine pH and daily Ca excretion were lower in UA than in Ca stone formers. Within the group without type 2 diabetes, age of patients, BMI, SBP, DBP, serum uric acid, and citraturia were higher and Ca excretion, FeUA, and urine pH were lower in UA than in Ca stone formers.

Correlations between these parameters differed in patients with and without type 2 diabetes. Among patients with type 2 diabetes, there was a negative association between urine pH and serum glucose ($r = -0.42$, $P = 0.046$), serum phosphate ($r = -0.44$, $P = 0.032$), and daily UA excretion ($r = -0.5$, $P = 0.013$) but no correlation between urine pH and FeUA. In contrast, among patients without type 2 diabetes, there was a significant positive association between urine pH and FeUA ($r = 0.22$, $P = 0.0006$) and a negative correlation between urine pH on the one hand and BMI, SBP, DBP, serum UA, and fasting glucose values on the other hand, suggesting that presence of the metabolic syndrome, reflected by the clustering of high BMI, hypertension, and impaired glucose tolerance, was associated with low urine pH.

Multivariate Analysis

Logistic regression analysis was used to determine the relative contribution of diabetes, BMI, age, and gender on the risk for UA stone formation. Indeed, because the proportion of Ca stones necessarily was the complement of the proportion of UA

Table 5. Stepwise regression analysis: OR of having UA calculi according to diabetes status, BMI, age, and gender[a]

	OR (95% CI)	*P*
Model 1		
whole series ($n = 2464$)		
diabetes (yes)	6.9 (5.5 to 8.8)	<0.00001
BMI (per 1 kg/m^2)	1.05 (1.03 to 1.07)	<0.00001
gender (male)	1.29 (1.00 to 1.69)	0.05
age (per 1 yr)	0.97 (0.96 to 0.98)	<0.0001
Model 2		
patients with BMI <25 ($n = 1416$)		
diabetes	24.2 (15.5 to 37.7)	<0.00001
gender (male)	1.71 (1.09 to 2.67)	0.017
age (per 1 yr)	0.98 (0.97 to 0.99)	<0.0001
Model 3		
patients with BMI ≥25 ($n = 1048$)		
diabetes	4.43 (3.35 to 5.85)	<0.00001

[a]CI, confidence interval; OR, odds ratio.

stones and because the most salient finding was the strikingly higher proportion of UA stones in patients with type 2 diabetes when compared with patients without type 2 diabetes, analysis was focused on factors that contribute to the risk for UA stones (Table 5). By univariate analysis, increasing age, presence of diabetes, increasing BMI, and male gender were positively and significantly associated with the risk for UA stones. By multivariate analysis in the whole series (model 1), only presence of diabetes, increasing BMI, and male gender still were independent significant risk factors, with diabetes having the strongest influence. Switch of the effect of age from "aggravating" to "protective" probably reflects the association of older age with increased prevalence of diabetes and higher BMI. Among patients within the normal-BMI range (model 2), diabetes and male gender both were independently associated with the risk for having UA stones, whereas in overweight/obese patients (model 3), only diabetes was a significant risk factor.

Discussion

The aim of our study was to evaluate the distribution of stone components in stone formers with *versus* without type 2 diabetes, with the hypothesis that type 2 diabetes may be associated with an increased risk for formation of UA stones. Our findings confirm this hypothesis on an epidemiologic basis in showing for the first time that the proportion of UA stones is strikingly higher in stone formers with than without type 2 diabetes and that type 2 diabetes constitutes a strong independent factor of UA nephrolithiasis, with overweight/obesity acting as an additional risk factor. Reciprocally, our data show that the prevalence of type 2 diabetes is more than three times higher among UA stone formers than among Ca stone formers.

Two epidemiologic studies showed an association between diabetes and urolithiasis. In a cross-sectional study, Meydan *et al.* (10) observed a prevalence of stone disease of 21% in patients with diabetes, as compared with 8% in patients without diabetes, but the BMI of patients was not considered and the chemical type of stones was not ascertained. In a prospective epidemiologic study that involved three large cohorts in the United States, the Nurses' Health Studies I and II (older and younger women) and the health Professionals Follow-Up study (men), Taylor *et al.* (11) observed a higher prevalence of a history of kidney stones at baseline in both genders and a higher incidence of stone episodes in women during follow-up in patients with *versus* without diabetes. The influence of diabetes on the risk for nephrolithiasis was independent of age and BMI, but the chemical type of stone disease was not recorded. Therefore, although the prevalence of urinary stone disease was shown to be increased globally in patients with diabetes, it was not defined which type of stones was preferentially formed in patients with diabetes, either Ca or UA stones or both.

Two studies recently provided arguments in support of a preferential relationship between type 2 diabetes and UA stone formation. Sakhaee *et al.* (18) first showed that 21 patients with pure UA nephrolithiasis were overweight and hypertriglyceridemic, with 33% of them having overt diabetes and 23.8% having glucose intolerance. Pak *et al.* (24) specifically tested the hypothesis that patients with type 2 diabetes may exhibit a high prevalence of UA stones. They observed that 20 (33.9%) of 59 stone-forming patients with type 2 diabetes had UA stones, as compared with only 8.5% of 493 stone formers without diabetes, and suggested that insulin resistance, the characteristic feature of type 2 diabetes, could be involved in the low urine pH observed in UA stone formers with diabetes. Later, Abate *et al.* (19) afforded demonstrative evidence that insulin resistance at the level of the kidney induces defective ammoniagenesis and low urine pH, patients with recurrent UA nephrolithiasis being severely insulin resistant. Despite such metabolic studies that clearly suggest a close relationship between type 2 diabetes and UA stone formation, studies that evaluated the association

of UA nephrolithiasis and type 2 diabetes on an epidemiologic basis were lacking.

Taking advantage of the large number of patients who had stones and were referred to our laboratory, we used such an approach to assess the distribution of Ca and UA stones with respect to the diabetes status and BMI of patients in a large population of stone formers. Our data afford the first epidemiologic evidence that type 2 diabetes favors the production of UA calculi, because the proportion of UA stones was more than three times higher in stone formers with than without type 2 diabetes.

Several pathophysiologic arguments may explain the propensity of stone formers with type 2 diabetes to produce UA stones. A permanently low urine pH is the key factor in UA nephrolithiasis (18,20–23). Insulin resistance, the central metabolic derangement in type 2 diabetes (17), and it precursor state, the metabolic syndrome (16), manifest in the kidney in inducing a defective ammoniagenesis, which itself results in the production of an acidic urine (18,19). In addition, insulin has been shown to enhance a parallel UA and sodium reabsorption in the proximal convoluted tubule, resulting in hyperuricemia and decreased UA and sodium excretion (29–31). Hyperinsulinemia seems to induce hyperuricemia, decreased FeUA, and hypertension. Also, hyperglycemia, by influencing proximal tubular reabsorption of glucose and sodium, may alter the tubular transport of UA.

FeUA was shown to be decreased in overweight pure UA stone formers without diabetes in the studies of Sakhaee *et al.* (18,23,24), whereas it was similar in UA stone formers with overt type 2 diabetes and in Ca stone formers whether they had diabetes or not (24). Similarly, in our series, FeUA values were found to be the lowest among the subgroup of patients who had UA nephrolithiasis without diabetes, who also were overweight and hypertensive, whereas FeUA did not differ between UA stone formers with type 2 diabetes and Ca stone formers, either with diabetes or not. Of note, urine pH was low in all UA stone formers but was not uniformly low in all stone formers with diabetes, as it was observed only in 40% of them. Therefore, there seems to be a heterogeneity within patients with diabetes as to the presence of an acidic urine. In addition, in patients with diabetes, there was no positive correlation between urine pH and FeUA, which is at variance with the group without diabetes.

Indeed, patients with type 2 diabetes often are overweight, and fat accumulation is a cause of insulin resistance through the excessive generation of proinflammatory cytokines and the defective production of the insulin-sensitizing adiponectin by the inflated mass of adipocytes (17,32–34). Thus, obesity by itself induces insulin resistance with its consequences on renal tubular functions. Maalouf *et al.* (35) recently showed, in a study of 4800 stone formers with a wide range of body size, a strong inverse association between body weight and urinary pH. Conversely, obese individuals often have excessive dietary intakes (7–9), which lead to increased excretion of lithogenic solutes (13,14). High purine consumption and the high acid ash content from animal proteins result in hypocitraturia and lowered urine pH. All these factors favor both Ca and UA stone formation (22). The variable urinary citrate excretion in UA stone formers, as observed in our series and by others (18), may reflect the combined influence of diabetes and dietary factors. Thus, obesity may add to the renal effects of diabetes to aggravate impaired ammoniagenesis and urine pH lowering. In support of this, in our cohort, patients who had diabetes and were in the obese BMI range had a higher proportion of UA stones than those with a normal BMI.

An increasing prevalence of UA stones with aging has been reported by several groups (36,37) and in previous studies from our laboratory (26,38). This influence of age was confirmed in our study. The proportion of UA stones rose both in patients with and without diabetes; this was apparent especially in patients who were ≥70 yr of age. Here also, insulin resistance may be a contributing factor. Indeed, older individuals have been shown to exhibit a reduced ammoniagenesis, resulting in low urine pH (39,40). This alteration in tubular function is likely to result from the age-associated decline in mitochondrial function, which induces insulin resistance (41). Glucose tolerance has been shown to decline with aging (42), and an increased prevalence of the metabolic syndrome with age has been reported in large epidemiologic studies (4,43).

With respect to gender, Taylor *et al.* (11) observed that women had a stronger association of diabetes with the risk for prevalent kidney stones than did men and that only women exhibited a higher risk for incident stones with diabetes, but the type of stones was not defined. In our series, the overrepresentation of UA calculi in association with diabetes also was more apparent in women than in men, a finding that contrasts with the lower prevalence of urolithiasis in general and UA urolithiasis in particular in women than in men (33,38).

The association between type 2 diabetes and UA nephrolithiasis probably has wider implications than just UA stone formation. The association among hypertension, hyperuricemia, and atherothrombotic cardiovascular events has been pointed out repeatedly (34,44–46). In view of the clustering of hyperuricemia, hypertension, and high BMI in our UA stone formers, as also observed by others (18,23,24), we suggest that UA nephrolithiasis should be considered a possible manifestation of insulin resistance in patients who are overweight and have type 2 diabetes rather than simply an easily treatable form of urinary stone disease.

From a practical point of view, patients who receive a diagnosis of UA nephrolithiasis, especially if overweight and/or hypertensive, should be screened for the other components of the metabolic syndrome, such as hypertriglyceridemia and glucose intolerance, in accordance with current guidelines (47,48). Early detection and treatment of these risk factors may help to prevent or delay the progression toward type 2 diabetes and atherosclerotic complications (17).

Conclusion

Our data provide epidemiologic evidence that type 2 diabetes is significantly associated with an increased risk for UA stone formation, because the proportion of UA stones is strikingly higher in stone formers with than without diabetes. These findings suggest that UA nephrolithiasis should be considered

as possibly reflecting a state of insulin resistance rather than simply UA stone formation. Accordingly, onset of UA nephrolithiasis in a patient should prompt a check for type 2 diabetes and the components of the metabolic syndrome, especially in overweight patients.

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