Type-2 Diabetes and Kidney Stones: Impact of Diabetes Medications and Glycemic Control

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OBJECTIVE To evaluate the impact of diabetic medications and glycemic control on the urine pH, 24-hour urine stone risk profile, and stone composition.

PATIENTS AND METHODS We retrospectively reviewed our database searching for type-2 diabetic patients with kidney stones from July 2002 to January 2013. Patients were divided in 2 groups according to their diabetic medications: insulin vs oral antihyperglycemics. Patients were compared based on their urine collections and stone composition. A linear regression was done to assess which variables could predict a low urine pH. In a subgroup analysis, patients on thiazolidinediones (ie, pioglitazone) were compared with patients on other oral antihyperglycemics.

RESULTS We analyzed 1831 type-2 diabetic patients with stone disease; 375 (20.5%) were included in the insulin group and 1456 (79.5%) in the antihyperglycemics group. Linear regression revealed male gender ($P = .011$) and insulin therapy ($P < .001$) as protective factors of low urine pH, whereas HbA1c level ($P < .001$) was inversely related to the urine pH (odds ratio, −0.066; 95% confidence interval, −0.096 to −0.036; $P < .001$). There were no significant differences in other 24-h urine stone risk parameters or stone composition between the groups. There were also no significant differences in the subgroup analysis.

CONCLUSION Urine pH is inversely related to HbA1c level. Insulin therapy is associated with higher urine pH than oral antihyperglycemic agents despite higher HbA1c suggesting that insulin may modify urine pH independent of glycemic control. UROLOGY 84: 544–548, 2014. © 2014 Elsevier Inc.

Nephrolithiasis prevalence has been increasing[1] and many risk factors have been related to this painful and costly disease. Geographical and weather conditions,[2,3] race and ethnicity,[4] dietary issues,[5] and more recently, the metabolic syndrome[6] are some of the explanations for this rise in the lifetime risk of kidney stones. The metabolic syndrome has been linked to an increased risk of hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia.[7,8] Diabetes mellitus (DM), which is one of leading components of the metabolic syndrome, is advocated as important cause of some of these urine derangements.

Several articles have shown a higher prevalence of kidney stones in diabetic patients.[9,10] The pathophysiology underlying this increased risk of stones with DM is thought to be impaired ammoniagenesis, higher acid excretion, and consequent lower urine pH.[7,8] This underlying modification in the urine can result in a higher incidence of urinary calculi, particularly uric acid stones.[11] Moreover, the severity of the diabetes is thought to correlate with a higher kidney stone risk.[12]

We hypothesized that diabetic medications (insulin vs oral antihyperglycemics) may influence urine pH, and consequently, the risk of stone formation. In this study, we aimed to evaluate the impact of diabetes medications and glycemic control on the urine pH, 24-hour urine stone risk profile, and stone composition. We also hypothesized that patients on thiazolidinediones (ie, pioglitazone) would have higher urine pH and lower risk of uric acid stones as it has been reported that these drugs may decrease insulin resistance and thus improve ammoniagenesis and increase urine pH.[13-17]

PATIENTS AND METHODS

Study Design

After institutional review board Approval, we retrospectively reviewed our database searching for diabetic patients who also

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Table 1. Demographic data, HbA1c level, and urine pH from insulin and oral antihyperglycemics groups

Data	Insulin (n = 375), Median (Mean ± Standard Deviation)	Oral Antihyperglycemics (n = 1456), Median (Mean ± Standard Deviation)	*P* Value
Age (y)	61.2 (58.9 ± 14.0)	60.1 (60.1 ± 11.4)	.127
Gender (Male)	53.6%	62.6%	<.001
BMI (kg/m^2)	31.2 (33.2 ± 9.0)	32.1 (33.3 ± 7.1)	.905
HbA1c (%)	7 (7.5 ± 1.8)	6.7 (6.9 ± 1.3)	<.001
Urine pH	6 (5.9 ± 0.8)	5.5 (5.7 ± 0.8)	<.001

BMI, body mass index.

had the diagnosis of kidney stones from July 2002 to January 2013. Our database is composed of patients with a diagnosis of urolithiasis—this includes patients with symptomatic calculi presenting to the emergency room or urology clinic as well as patients noted to have asymptomatic calculi on imaging studies. This was a cross-sectional study; all subjects included in this study were patients who had pre-existing DM diagnosed before the kidney stone disease, and the time interval between onset of diabetes and diagnosis of stone disease was not available for analysis. Only type-2 diabetic patients were included in this analysis. Data recorded comprised age, gender, body mass index (BMI), glycosylated hemoglobin level (HbA1c), all diabetes-related medications (insulin or oral antihyperglycemics), all stone-related medications (ie, allopurinol, potassium citrate, vitamin B6, thiazide), urine pH, 24-hour urine stone risk profiles, and stone composition. For patients with multiple urine collections, the first baseline collection was used, before the initiation of dietary or medical intervention.

Patients on potassium citrate were excluded from urine pH analysis. Urinary pH was measured by dipstick or pH meter on spot urine. Stone composition was obtained from samples that were obtained at the time of an interventional procedure (shockwave lithotripsy, ureteroscopy, or percutaneous nephrolithotomy) or after spontaneous passage. Stone analysis was done using infrared spectrometry and stones were classified according to their majority component (>50%) into calcium oxalate, calcium phosphate, uric acid or struvite (ammonium magnesium phosphate).

Patients were divided in 2 groups according to their diabetic medications: insulin vs oral antihyperglycemics. Those patients treated with both classes of medications at the time of stone diagnosis and baseline 24-hour urine metabolic evaluation were excluded from this analysis. Groups were compared for age, gender, BMI, HbA1c level, urine pH, 24-hour urine analysis (volume, sodium, potassium, calcium, oxalate, uric acid, and citrate), and stone composition. Then, in a subgroup analysis we compared patients on thiazolidinediones (ie, pioglitazone) to patients on others oral antihyperglycemics.

Statistical Analysis

Results were expressed in proportion and mean and standard deviation. Mann Whitney test or Students *t* test were used to compare continuous variables, whereas Fischer exact test was used to compare categorical variables between the groups. A multivariate analysis including age, gender, BMI, and HbA1c level was done to assess urine pH differences between the groups. Then, a linear regression was performed to assess which variables (diabetes medications, age, gender, BMI, and HbA1c level) could predict a low urine pH. Thereafter, groups were compared based on their urine collections and stone composition. Statistical analysis was performed with SPSS, version 20.0 (SPSS Inc., Chicago, IL) and significance level was set at $P < .05$.

RESULTS

We analyzed the records from 1831 type-2 diabetic patients with kidney stone disease (60.7% male). Mean age was 59.8 ± 12.0 years and mean BMI was 33.2 ± 7.6 kg/m^2. These patients were divided in 2 groups, 375 (20.5%) in the insulin group and 1456 (79.5%) in the oral antihyperglycemics group. On univariate analysis, patients in the insulin group had a lower proportion of males (53.6% vs 62.6%; $P < .001$) and higher mean HbA1c (7.5% vs 6.9%; $P < .001$) and urine pH levels (5.9 vs 5.7; $P < .001$; Table 1).

After a multivariate analysis controlling for all the other parameters (BMI, age, gender, HbA1c), the urine pH level remained significantly different between the groups ($P < .001$). A linear regression searching for predictive factors of low urinary pH revealed male gender ($P = .011$) and insulin ($P < .001$) as protective factors, whereas HbA1c level ($P < .001$) was inversely related to the urine pH. For each point added in the HbA1c level, the urine pH decreased by 0.066 (odds ratio [OR], −0.066; 95% confidence interval [CI], −0.096 to −0.036; $P < .001$). There were no significant differences in the 24-urine stone risk profiles or stone composition between the groups (Table 2).

In the subgroup analysis, there were no significant differences between patients who were receiving thiazolidinediones compared to other oral antihyperglycemics (Table 3). Patients on thiazolidinediones presented with similar mean urine pH to those patients on others oral antihyperglycemics (5.7 vs 5.7; $P = .67$). There were also no differences in the 24-hour urine stone risk profile or stone composition between the groups (Table 4).

We evaluated the proportion of patients in each group who had a urine pH ≤5.5. The percentage of patients with a pH ≤5.5 was 45.6% in the insulin group, compared with 57.4% in the oral antihyperglycemics group ($P < .001$). The percentage of patients with a urine pH ≤5.5 if on thiazolidinediones was 57.3% compared with 57.2%% for other oral hyperglycemics ($P = 1.00$).

COMMENT

In this study, we found that male patients on insulin therapy have a higher urine pH when compared with other type-2 diabetic patients with stones. Furthermore, we showed a significant negative correlation between HbA1c and urine pH. These findings may be important when counseling diabetic patients who also have kidney stones about their treatment options. As such, we