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RESEARCH ARTICLE

Kidney stones in patients with type 2 diabetes mellitus. Metabolic risk factors

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ABSTRACT

Background: In the past few decades, the prevalence of kidney stones in Western countries has increased in parallel with the growing overweight/obesity and type 2 diabetes mellitus rates. An increased insulin resistance in these patients explains, in part, the rising prevalence of uric acid stones.

Aim: The Aim of this retrospective study was to evaluate the metabolic abnormalities in type 2 diabetic and non-diabetic patients with kidney stones.

Methods: A total of 104 diabetic patients (age: 57.8 ± 11 years) and 130 non-diabetics (age: 52.1 ± 6.7 years) with kidney stones were selected.

Results: Higher rates of body mass index, hypertension, urinary tract infection, gout and hyperuricemia were observed in diabetic patients as compared to the non-diabetics, while similar rates were found for their family history of kidney stones. Metabolic abnormalities were detected in 95.2% and 81.5% of diabetics and non-diabetics, respectively. Idiopathic hypercalciuria was the most frequent abnormality in both groups, although as a simple abnormality, in diabetic patients, unduly acidic urine was the more common.

Conclusions: unduly acidic urine is the most frequent single abnormalities in patients with diabetes mellitus and is in part responsible for the greater number of uric acid stones.

Keywords: Metabolic risk factors; kidney stone; type 2 diabetes

Introduction

Nephrolithiasis is one of the most common urological conditions[1,2].

The prevalence and incidence of kidney stones in many regions of the world has continued to increase in the past 15 to 20 years[3], and is a highly prevalent disease, with rates ranging from 7 to 13% in North America, 5-9% in Europe, and 1-5% in Asia[4]. A recent update of the National Health and Nutrition Examination Survey (NANHES) from 2015-2018 in 10,521 participants over 20 years of age, the prevalence of renal lithiasis was 11% (95% CI 10.1-12.0). The 12-month incidence was 2,1 % (95% CI 1.5-2.7), or 2054 stones per 100,000 adults. Significant relationships have been found between stone incidence and subject age, body mass index, race and history of hypertension[5].

Also, diabetics have almost 3 times more renal lithiasis than non-diabetic individuals (21% vs 8%)[6].Taylor studied the association between obesity, weight gain and risk of renal lithiasis in 3 large cohort studies, Nurses' Health Study I and II (NHS I and NHS II) and Health Professional Follow-up Study (HPFS), where they were able to observe as the risk of stone formation increases as the body mass index (BMI) increases and in those subjects with a BMI > 30 the risk was significantly higher in relation to subjects with normal BMI[7]. Worcester et al observed that after passage of a first stone, the risk of recurrence is 40% at 5 years and 75% at 20 years[8]. It is important to note that between 25-30% of patients with renal lithiasis have a family history of kidney stones, which demonstrates the important role of heredity in stone formation[9,10]. The high prevalence of urinary calculi has a significant impact on health systems due to the costs of diagnosing and treating the stones[11].

Renal lithiasis is due to an imbalance between the amount of inhibitors (citrate, magnesium) and promoters (calcium, uric acid, phosphates, oxalates and cystine) of crystallization in the urine; different alterations in the chemical composition of the urine can create a favorable environment for the formation of kidney stones. Other risk factors that must be assessed in patients with renal lithiasis are urinary volume and pH. An acidic urinary pH favors the precipitation of uric acid crystals and an alkaline pH of calcium phosphate. The stones composition varies according to the country analyzed. A multicenter study that included 10 countries, from Europe, Asia and America, found 59% of calcium oxalate stones, 3% calcium phosphate, 9% pure uric acid, 13% calcium oxalate and phosphate, 8% oxalate and uric acid and 5% struvite[12].

Kidney stones are currently considered as a systemic condition that is not only limited to the kidney and urinary tract[13], but is also significantly related to diabetes mellitus (DM), obesity, hypertension (HT), metabolic syndrome and chronic kidney disease (CKD), all of which are cardiovascular risk factors[13,14]. Several studies have shown a higher prevalence of renal lithiasis in patients with diabetes mellitus compared to patients without diabetes[15,16]. The pathophysiological explanations for the increased risk of renal lithiasis diabetics have largely focused on insulin resistance (IR)[17,18] that decreases, both ammonia synthesis and transport, leading to abnormal urine acidification and low urinary pH[15]. Therefore, this can be expected to favor

the production of uric acid stones (UA), as low urine pH is the main lithogenic factor in UA nephrolithiasis[19]. On the other hand, diabetes patients also form calcium oxalate stones, linked in part to hyperinsulinemia associated with insulin resistance that favors increased calcium excretion[20,22]. The objective of this study was to evaluate metabolic risk factors in kidney stones patients with type 2 diabetes and compare them, with a population with non-diabetic renal lithiasis.

Methods

STUDY DESIGN AND POPULATION

We conducted a retrospective cross-sectional study in patients with kidney stones (KS) and type 2 diabetes mellitus from all over the country from 2015 to 2021. All patients completed a form with their personal and family medical history. Almost all of the patients were Caucasian like the majority of the Argentine population living in large cities. From our database of studies of patients with KS, 104 with type 2 diabetes mellitus and 130 with renal lithiasis without diabetes were selected as control, matched by sex and age. As this is a retrospective cross-sectional study, we couldn´t know with precision the time of evolution of the kidney stones or diabetes in each patient.

The diagnosis of type 2 diabetes mellitus was established based on fasting plasma glucose levels ≥ 126 mg/dL or glycosylated hemoglobin (A1c) levels ≥ 6.5% or receiving oral antidiabetic drugs or insulin (American Diabetes Association criteria). Among diabetic patients, 81 were taking oral antidiabetics, 20 were receiving insulin, 2 were receiving oral antidiabetics plus insulin and 1 was controlled by diet alone. Renal lithiasis was diagnosed either based on confirmation of X-rays, ultrasound or computed tomography or by spontaneous or surgical removal of kidney stones. All patients were evaluated at least one month after the symptomatic event or no more than 12 months since the last episode of renal lithiasis; none of them should have a urinary tract infection. Patients with creatinine clearance levels (CrCl) <60 ml/min (corrected for 1.73 m2 BSA), as well as those with prolonged immobilization or receiving drugs that affect mineral metabolism, such as corticosteroids, diuretics or anticonvulsants, were excluded. All patients with KS were evaluated following an outpatient protocol whereby they were asked to continue their usual diet and fluid intake. To reduce bias, two 24-hour urine samples (periods A and B) were obtained and kept refrigerated in additive-free plastic containers. Urine pH (upH) was measured in freshly emitted urine, by pH electrode, when the patient arrived at the laboratory. If it was < 5.5, another determination was repeated in fresh urine and if it persisted, a urine saturation test was performed. A fasting blood sample was collected from all patients. The techniques used for the different blood and urine determinations were: both serum creatinine and urine (Jaffe) and phosphate (UV) were measured using an automated analyzer (Spectrum CCX Abbot Labs US).Serum calcium was measured by ion-specific electrode (ISE) tests with an automated 6 Synchron CX3 analyzer (Beckman, Beckman Instruments, Inc. Brea, California, USA). The same method was used for the determination of calcium in urine in an acidified aliquot. Serum ionic calcium was

measured by ISE (Roche Instrument Diagnostic 4 AVL) tests without pH correction (normal value 4.5–5.2 mg/dL). Sodium and potassium levels in blood and urine were measured with an automated CX3 analyzer. Urine magnesium with the Synchron Systems (Calmagite) reagent using the Synchron CX4 automated analyzer. Uric acid levels were measured using the reaction of uricase in alkalized aliquots to prevent precipitation. Urine oxalate was measured in an acidified aliquot using an enzyme assay (Trinity Biotech, Co. Bray, Wicklow, Ireland). A pH electrode was used to measure urine pH in a fasting urine sample. Urine citrate was determined by an enzyme assay using reagents from Sigma-Aldrich Corp. (St. Louis, Missouri, USA). The determination of cystine in urine samples was performed by the Brand chemical reaction. Serum intact parathyroid hormone was measured by IRMA in patients with suspected primary hyperparathyroidism (HPTP). Since our protocol did not include tubular acidification tests, renal tubular acidosis was not included as part of the study and the cases found were diagnosed during the follow-up period.

Idiopathic hypercalciuria (IH) was defined as urinary calcium levels > 300 mg/24 h for men and > 220 mg/24 h for women or > 4 mg/kg per day for either sex. Hyperuricosuria (HU) uric acid excretion was > 750 mg/24 h and > 700 mg/24 h for men and women, respectively, or > 600 mg/L urine. Unduly acidic urine (UAU) when urine pH was < 5.5 on at least two different measurements on the same day. Hypocitraturia (HC) < 350 mg/24 h. Hypomagnesuria (HM) < 60 mg/24 h, hyperoxaluria (HOx) > 45 mg/24 h. Cystinuria (CIS) was defined as values > 250 mg/24 h. Low urine volume (LUV) was considered at values < 1000 mL/24 h. Patients without biochemical disorders that could justify the occurrence of renal lithiasis were classified as "no metabolic abnormalities" (NMA). Of the 104 kidney stone formers with diabetes mellitus, their composition was determined in 33 (32%) using an optical crystallography with polarized light (since our institution does not have other more precise biochemical techniques) and in 27 (21%) of non-diabetic patients with renal lithiasis.

Statistical analysis (Student's T-test, Chi square test, proportionality and Pearson test) was performed using the CSS Statisc Software program (StatSoft Inc., Tulsa, OK, US). A $p < 0.05$ was considered statistically significant

Results

The main demographic characteristics of patients with renal lithiasis and type 2 diabetes and non-diabetics are shown in Table 1.

Table 1 shows the demographic characteristics of diabetic and non-diabetic patients with kidney stones.

Kidney stones	Type 2 diabetes n = 104	Non-diabetics n = 130	p
Age (years)	57.8 ± 11	52.1 ± 6.7	NS
Gender (male, female)	M:61, F:43	M:66, F:64	------
Height (m)	1.68 ± 0.1	1.66 ± 0.1	NS
Weight (kg)	90 ± 17	76.4 ± 15	< 0.01
BMI (weight/height^2)	32 ± 5	27.5 ± 4.5	< 0.01

Predominance was observed in male patients with diabetes mellitus, with a male-to-female ratio of 1.4:1. Although height measurements were similar, both weight and body mass index (BMI) were higher in diabetic patients. In patients with type 2 diabetes: arterial hypertension (HT), urinary tract infection, gout, hyperuricemia and a family history of renal lithiasis, first or second degree, were observed in 61%, 40.2%, 18.4% and 25.5% of cases, respectively; while in non-diabetic patients, these were observed in 33%, 22.2%, 12.5% and 25%, respectively. Of the 33 kidney stones analyzed in type 2 diabetes, 19 (58%) corresponded to calcium oxalate, 9 (27%) to uric acid and 5 (15%) to mixed stones (calcium oxalate/uric acid). In the 27 kidney stones analyzed from non-diabetic patients, 5 (18.5%) were uric acid and 22 (81.5%) were calcium salts (oxalate, phosphate). Urinary pH was lower in patients with type 2 diabetes than in non-diabetics (5.4 ± 04 vs. 6.0 ± 0.4, p< 0.001). This difference grew with increasing BMI in patients with type 2 diabetes and remained unchanged in non-diabetics. Urine volume and calcium and uric acid urine were similar between the two groups. However, a slight, non-statistically significant increase in natriuria was observed in type 2 diabetes compared to non-diabetics patients. Biochemical abnormalities were found in 95.2% (n = 99) of diabetic and 81.5% (n = 106) of non-diabetic patients. No metabolic abnormalities were found in 4.8% of patients with type 2 diabetes and 18.5% of non-diabetic patients. Among patients with metabolic abnormalities, single alteration were recognized in 47.5% (n = 47) of diabetic and 77% (n = 82) of non-diabetic patients. Table 2, shows single metabolic abnormalities in both groups.

Table 2 Single metabolic abnormality in both groups

Metabolic Abnormalities	Non-diabetics n = 82/106 (77%)	Type 2 diabetes n = 47/99 (47.5%)	p
UAU	4 (3.8%)	19 (19.1%)	<0.01
HU	11 (10.4%)	12 (12.3%)	NS
IH	47 (44.3%)	9 (9.0%)	<0.001
HM	4 (3.8%)	3 (3.0%)	NS
HC	7 (6.6%)	3 (3.0%)	0.01
HPTP	3 (2.8%)	1 (1.1%)	NS
HOx	4 (3.8%)	0	
CIS	2 (1.9%)	0	

UAU unduly acidic urine; HU Hyperuricosuria; IH Idiopathic hypercalciuria;HM IHpomagnesuria HC Hypocitraturia; HPTP Primary hyperparathyroidism,HOx Hyperoxaluria; CIS Cystinuria

UAU and HU were found more frequently in diabetic patients; while idiopathic hypercalciuria and HU were more common in non-diabetics.

The combined metabolic abnormalities were more frequent in diabetic patients, as shown in Table 3

Table 3 Combined metabolic abnormalities in both groups

Metabolic Abnormalities	Non-diabetics n = 24/106 (22.6%)	Type 2 diabetes n = 52/99 (52.5%)	p
IH + HU	9 (8.75%)	7 (7.07%)	NS
IH + HM	2 (1.9%)	7 (7.07%)	NS
IH + HC	2 (1.9%)	1 (1.01%)	NS
IH + HOx	1 (0.95%)	1 (1.01%)	NS
HC+HM	2 (1.9%)	2 (2.02%)	NS
HC + HU	1 (0.95%)	3 (3.03%)	NS
UAU + HOx	1 (0.95%)	1 (1.01%)	NS
Other	6 (5.7%)	30 (30. 28%)	<0.01
Total	**23%**	**52.5%**	**<0.01**

IH Idiopathic hypercalciuria; HU Hyperuricosuria; HM Hypomagnesuria; HC Hypocitraturia;HOx Hyperoxaluria; UAU excessively acidic urine

Only the most frequent combinations are mentioned, given the large number of associations. As shown in Figure 1, when analyzing the total metabolic abnormalities (single and combined) in type 2 diabetes, IH was the most common abnormality, although the prevalence was lower than in non-diabetic patients. In addition to IH, the most important

differences included the higher proportion of UAU, hyperuricosuria and the lower incidence of hypocitraturia compared to non-diabetics patients.

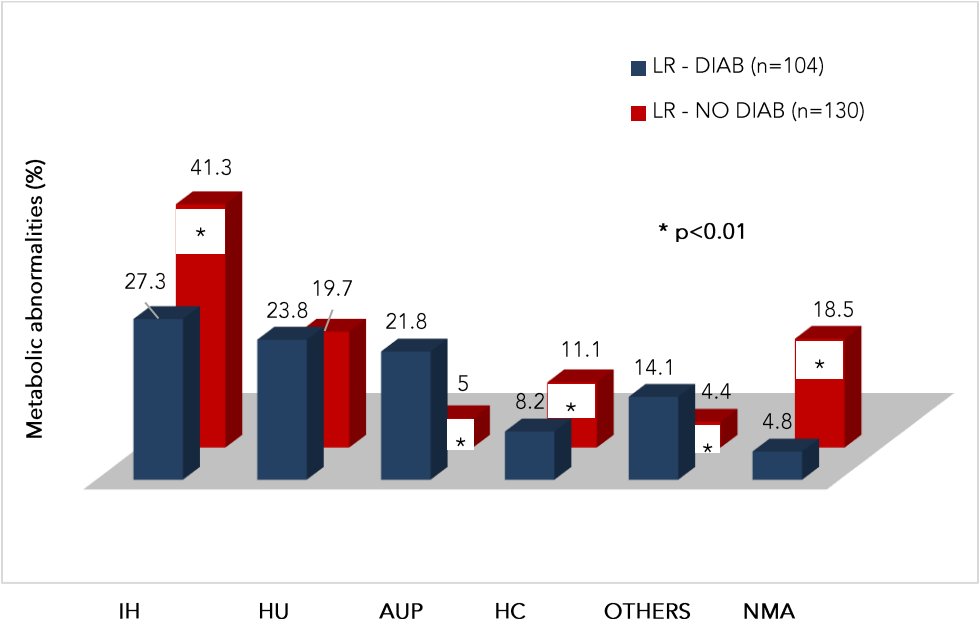

Fig1: Metabolic abnormalities (single and combined) in both groups

Low urinary volumes were observed in 7% (n = 9) of non-diabetics and 3.9% (n = 5) of patients with type 2 diabetes.

Discussion

Type 2 diabetes is remarkably associated with increased risk with kidney stone disease[23]. In this sense, Meydan et al[15] have described renal lithiasis in 21% of 286 diabetic patients compared to 8% in 111 non-diabetic individuals, almost 3 times more, and the rate of recurrence were significantly higher in the diabetics compared to the controls. A prospective study by Taylor et al[14] that included 289,900 individuals (men and women of different ages) found an increased risk of renal lithiasis in diabetic patients of up to 68% in young women (25-43 years of age), 38% in older women (30-55 years) and 31% in men, compared to non-diabetic individuals, matched by age and sex. On the other hand, a study by Daudon et al[24] in Paris, found in 2464 patients with KS that 11% were diabetic, a value higher than the 7.2% observed by our group in 252 lithiasis patients (unpublished data).

In our study, the male/female ratio was 1.4:1, similar to the 1.6:1 ratio described by Weinberg et al[25], and lower than the 2.2:1 described in 666 diabetic patients with renal lithiasis[23]. The age of the patients was higher in the diabetics than in the controls, although it did not reach statistical significance, while the weight and the BMI were significantly higher than in the lithiasic controls. Also, we observed higher HT and history of urinary tract infections in diabetic patients than in non-diabetics. The presence of a family history of first or second-degree renal lithiasis was the same in both groups and similar to that described in a previous series of our group in non-diabetic patients with nephrolithiasis[26]. In relation to the composition of kidney stones in diabetic patients, Pak et al[17] found uric acid stones in 34% of cases, as

opposed to 6.2% in non-diabetic individuals with renal lithiasis. These data are consistent with the analysis of 2464 patients with renal lithiasis of uric acid, of which 35.7% were diabetics and 11.3% non-diabetics[24]. In our study, we were only able to analyze 33 stones in type 2 diabetes and 27 without diabetes. Uric acid stones predominated in patients with diabetes than in non-diabetics, 27% vs 18.5%. Although this percentage is lower than that described above, it is higher than the 16.5% found after analyzing 8885 stones from non-diabetic patients in Argentina[27]. With regard to urinary pH, diabetic patients had lower upH than non-diabetic and this decreased significantly with increasing BMI. Our study finds a significant decrease in urinary pH, $p<0.001$ in diabetic lithiasis vs controls. These data are consistent with those found by Maalouf et al[28] in 4883 patients with renal lithiasis who showed an inverse relationship between upH and body weight. The reduction of upH, characteristic of overweight, obesity and diabetes mellitus[14,28,29] has been associated with insulin resistance[30-32]. Excessive urinary acidity of uric acid stone-formers, is associated with increased net acid excretion and reduced excretion of ammonia, which normally acts as a buffer for urine acidity[33]. Some researchers have suggested defects in enzymes that metabolize glutamine into ammonia and α-ketoglutarate, such as glutaminase and/or glutamate dehydrogenase[34,35]. Although acid upH is the central cause of uric acid stone formation in diabetic patients, also the lower citrate excretion linked to tubular defects[20] and hypercalciuria associated with compensatory hyperinsulinemia due to insulin resistance[21], would explain the formation of calcium salts stones. Our study found no difference in uric acid and calcium excretion or low urinary volume, but an increase in natriuresis was observed with respect to non-diabetics. Metabolic abnormalities were found in 95.2% and 81.5% of diabetic and non-diabetic patients respectively.

Single metabolic abnormalities were observed in 47.5% and 77% of diabetic and non-diabetic patients. The single most frequent metabolic disturbance in diabetic patients was unduly acidic urine, while idiopathic hypercalciuria was the most common metabolic abnormality in non-diabetic patients. Hyperuricosuria was the second most common abnormality found in both groups of patients. While hypocitraturia was less frequent in diabetic patients, hypomagnesuria was similar between the two groups. We did not find cases of cystinuria or hyperoxaluria, and oxalate excretion was similar in diabetic and non-diabetic stones.

The combined abnormalities were more frequent (52.5%) in diabetic than non-diabetic patients (23%), with IH + HU being the most frequent in both groups.

Limitations of the study: increased number of patients with KS in both diabetics and non-diabetics, to increase the statistical strength of the study. Low number of kidney stones for analysis in both group of patients. In addition, in our institution we do not have more precise techniques, such as X-ray diffraction or infrared spectrometry for the analysis of stones.

Conclusions

The combined metabolic alterations in patients with diabetes and renal lithiasis were greater than the single alterations. As single abnormality, unduly acidic urine is the most

frequent metabolic diagnosis in lithiasic patients with type 2 diabetes, whereas idiopathic hypercalciuria is in non-diabetic kidney stone patients. This acid urinary pH favors the presence of uric acid stones found in patients with diabetes.The other two abnormalities most frequently in lithiasic diabetic patients are hypercalciuria and hyperuricosuria. While in non-diabetics, hypercalciuria is followed by hyperuricosuria and hypocitraturia. Kidney stones in patients with type 2 diabetes predominates in men, and is most commonly associated with high blood pressure, urinary tract infections, gout, and hyperuricemia. Patients with kidney stones and type 2 diabetes are diagnosed at an older age and have a higher BMI.

Conflict of Interest Statement:

The authors declare that they have no conflict of interest.

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