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SUGAR AND STONES: DOES DIABETES MELLITUS INFLUENCE THE MANAGEMENT AND OUTCOMES OF PATIENTS TREATED SURGICALLY FOR UROLITHIASIS IN THE UNITED KINGDOM?

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ABSTRACT

Introduction

Urolithiasis is a common urological problem in the United Kingdom. 6% of the adult population were diagnosed with diabetes in England in 2013. Researchers suggest the association of diabetes with stone formation, recurrence, and morbidity. This study aimed to compare the prevalence of risk factors like metabolic syndrome, urinary tract infections, age, gender and ethnicity among diabetics versus non-diabetics and to determine how diabetes affects the biochemical and surgical outcomes of urolithiasis.

Methods

There were182 patients treated surgically for urolithiasis between January 2010 and December 2012 were retrospectively analyzed. Information was cross-referenced with electronic notes to produce biochemical and surgical data.

Results

A total of 31 (17%) patients had type 2 diabetes. The mean age of diabetics was significantly higher than non-diabetics by nearly 12 years (p-value < 0.001). Hypertension, hyperlipidaemia, obesity and UTIs were more prevalent among diabetics (p-value < 0.001, < 0.001, 0.01, 0.009 respectively). Diabetics had significantly bigger mean stones size (p-value=0.008) and are at higher risk of stone recurrence at 1 year (p-value =0.04) than non-diabetics. Stone recurrence was not significant at 3 and 5 years between the two groups. Diabetics significantly had higher urinary oxalate, and nearly statistically significant lower phosphate levels (p-value=0.007, 0.076 respectively).

Conclusions
Diabetics were significantly older and associated with metabolic syndrome. UTIs were more prevalent among diabetics which put them at risk of postoperative complications. Diabetics are at higher risk of stone recurrence at 1 year compare to non-diabetics. Biochemical urinary findings are important as they can guide the management of recurrent stone formers.

Keywords: *urolithiasis, metabolic syndrome, diabetes, stone recurrence, stone formation, complications*

Urolithiasis is a highly prevalent disease, with rates varying from 1% to 20% worldwide.[1–4] The annual incidence is 1–2 cases per 1000 people. Previously published results from the Office for National Statistics have shown that the prevalence of urinary tract stones in England in 2010 was 0.16% with an estimated population of 54 million. Over the past five years, admissions to hospital with urinary tract stones related symptoms have increased by almost 4.4%.[5] Using Hospital Episodes Statistics online data tool (http://www.hesonline.nhs.uk), emergency and elective urolithiasis admissions to hospitals and associated interventions have significantly increased. The lifetime prevalence of urinary stones was estimated at 14%. This has changed the trend in England to surgically treat more proportion of patients present with urolithiasis which overall increased the total number of interventions and procedures performed over seven years from 28,624 to 42,068.

Many factors, such as metabolic syndrome have been recognized to increase the potential risks of individuals to develop urinary tract stones. Identifying those factors will help clinicians to provide the essential work up and necessary investigations required for those who at risk to prevent stone growth, formation, and recurrence.

Diabetes increases the risk of urolithiasis though its metabolic effect on urine parameters. 21% of diabetics are at risk of urinary stone disease compare to 8% non-diabetics.[6] Through insulin resistance, the production and the transport of ammonia in the renal tubular lumen decreases which can result in urine acidification, lower urine pH and lower urinary citrate were found to correlate with stone formation.[7,8] Low urinary pH in type two diabetes plays a major role in promoting more uric acid precipitation in the urine, converting the soluble urate salt into insoluble uric acid.[9] This will increase stone formation, especially the incidence of uric acid stones compared to those who are not diabetics.

The prevalence of the disease in adults globally was estimated to range from 7.2 to 11.4%. In the United Kingdom, as part of the Quality and Outcomes Framework (QOF) general practices do register the number of people diagnosed with diabetes, and therefore, prevalence figures are available. In 2013,[10], the prevalence of diabetes in the adult population in the United Kingdom was estimated at 6.0% (Table 1).

According to (QOF) report in 2014-2015, In England, the prevalence rate has increased slightly to 6.4.[11] The South of England region has the lowest prevalence of all regions at 5.8% compared to almost 7.5% in the West Midlands.

This study aims to investigate the influence of diabetes mellitus on the surgical outcomes of patients treated for urinary stone disease; our main objectives are:

1. To determine the prevalence of diabetes and metabolic syndrome among patients treated with surgery for urolithiasis in a small population in Britain.
2. To provide evaluation and comparison of several factors associated with urolithiasis like Age, Gender, and Ethnicity; among diabetics versus non-diabetics.
3. To provide a comparison of pre, peri and postoperative factors related to surgical interventions for

TABLE 1 Prevalence of Diabetes in the Adult UK Population

Country	Prevalence	Number of People
England	6.0%	2,703,044
Northern Ireland	5.3%	79,072
Scotland	5.2%	252,599
Wales	6.7%	173,299

urolithiasis among diabetics and non-diabetics such as:

- Serum and urinary metabolic profile.
- Stone size, clearance, and recurrence.
- Urinary tract infections, surgical complications and the length of hospital stay.

METHODS

Patient Selection

Patients were identified and selected from an existing database of a single urological surgeon who specialized in stones management and endourology. Patients were selected retrospectively, and the researchers who were selecting the patients were blind to the data outcome of those patients. All patients in the database who were treated surgically for urolithiasis over three years between January 2010 and December 2012 were included in the analysis. 182 patients were identified who were surgically managed for urinary tract stones at Sandwell and West Birmingham NHS Hospitals.

Inclusion Criteria

In this study, we included only adult patients 18+ who have had confirmed diagnosis of urinary tract stones treated endoscopically with either retrograde intrarenal surgery (RIRS) or percutaneous nephrolithotomy (PCNL) over three years period.

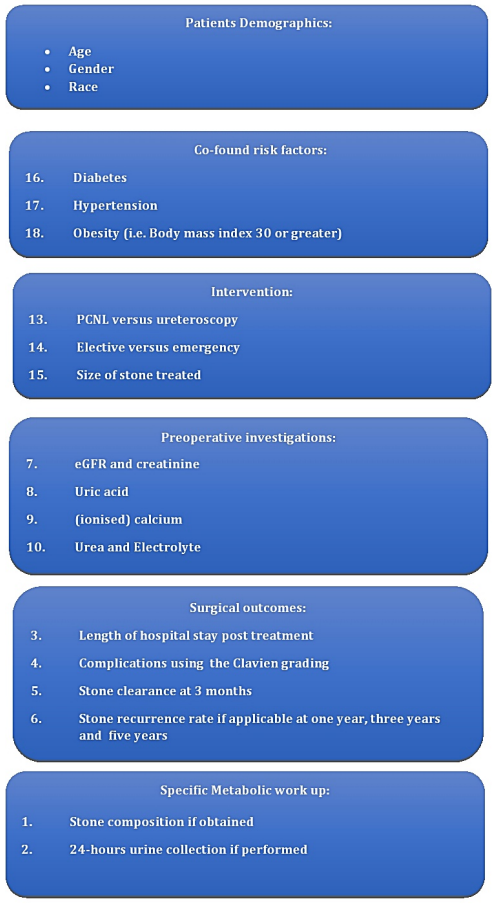
Exclusion Criteria

Patients who have received surgical treatment for other urological diseases other than urolithiasis were excluded. Patients who have been not treated with RIRS or PCNL during the three years and received other treatment modalities for urinary stones with either Shockwave lithotripsy, open or laparoscopic surgery only were not selected.

Data Collection

Using the EAU guidelines from 2017[1] different variables were identified to be analyzed. A proforma was used to help collect our data. The variables were sorted in terms of how they would impact on patient and at what point they would be relevant. Figure 1 demonstrates how the variables were sorted. Electronic notes were searched to try and find the relevant data.

FIG. 1 Information collected in the study.



RESULTS

Patients Demographics

Age

There were 31 (17%) patients had type two diabetes, whereas 151 (83%) did not. The mean age of diabetic patients was significantly higher than patients without diabetes by nearly 12 years (64 versus 52 years old, p-value =< 0.001).

Diabetics and non-diabetics individuals were further stratified by age group (Figure 2). This has clearly defined that adult patients (less than 40 years old) treated surgically for urolithiasis were predominantly non-diabetics. Similarly, from the age group of (40 to 60), 71 (47%) non-diabetics were surgically treated compared to (38%) 12 diabetics. Diabetes among urolithiasis patients was found to be more prevalent

in those who are older than 60 years (61% versus 30% non-diabetics).

Gender

Figure 3. demonstrates the differences in gender in both the diabetic versus nondiabetic cohort. Out of 31 Patients who have diabetes, 20 (65%) were males compared to 11 (35%) female patients. Gender was not significantly associated with the prevalence of urinary tract stones among diabetics and non-diabetics (p-value = 0.866). In our study, the male to female ratio was (1.7:1).

Ethnicity

Among this ethnically diverse cohort, Caucasians were the most predominant (n=122, 67%) followed by Asians (n= 46, 25%) and then Afro-Caribbeans (n=14, 8%). Furthermore, we have analyzed the prevalence of diabetes mellitus among those ethnic groups (Figure 4).

Analysis of the above results did not show any statistically significant difference in ethnicities between diabetics and non-diabetic urolithiasis patients (p-value= 0.672).

FIG. 2 Representing the number of diabetics and non-diabetics respondents by age groups.

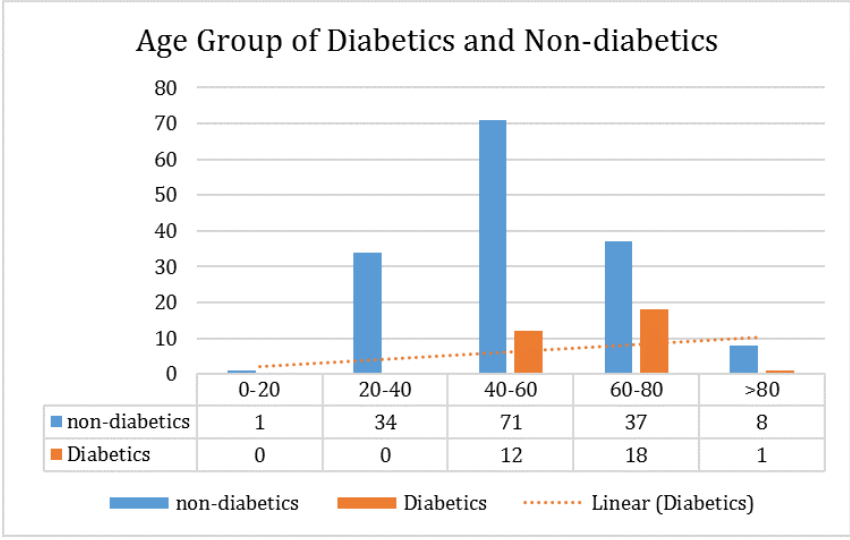


FIG. 3 Representing diabetic and non-diabetic patients by gender.

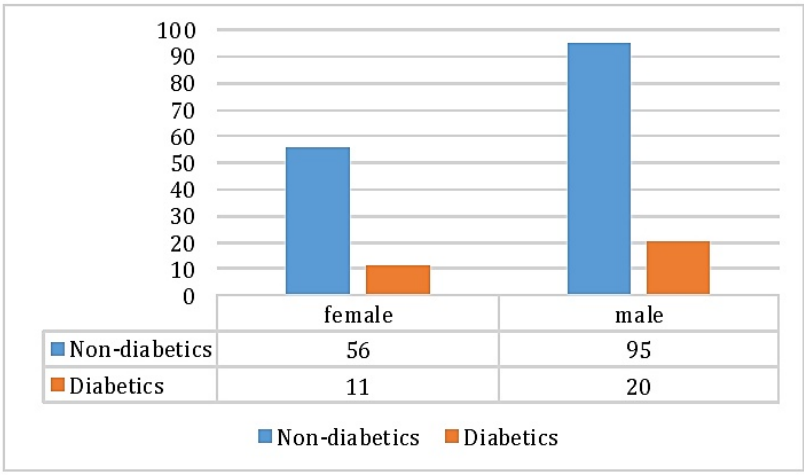


FIG. 4 Representing diabetic and non-diabetic patients by ethnicity.

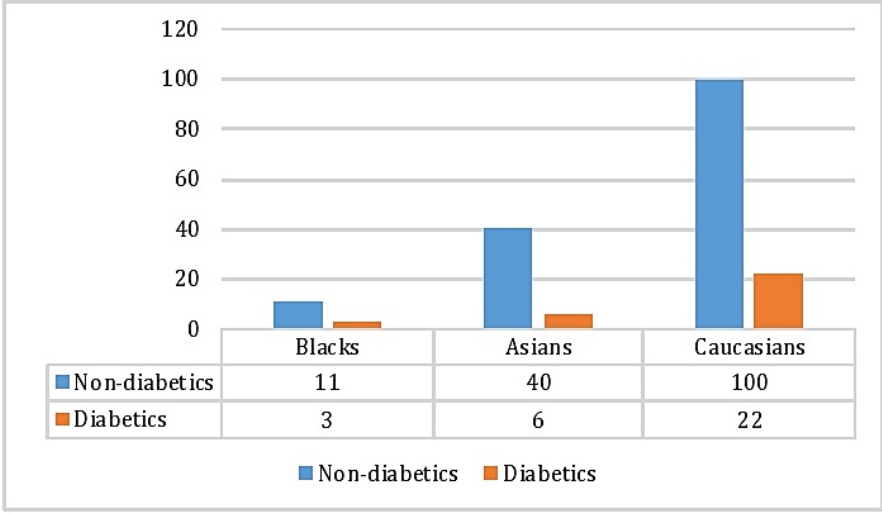


TABLE 2 Representing Various Variables of Risk Factors of Stone Formation

	Non-Diabetics (83%, n=151)	Diabetics (17%, n=31)	p-value
Hypertension	37%, n=51	84%, n=26	< 0.001
Hyperlipidaemia	23%, n=34	84%, n=26	< 0.001
Obesity	9%, n=14	35% n=11	0.01
Known recurrent stone formers	15%, n=23	16%, n=5	0.925

Risks Factors

Univariate analysis of confounding risk factors, including metabolic syndrome and the previous history of renal stones formation was used. Our results have shown that metabolic syndrome components were more prevalent among diabetics group (hypertension 84%, hyperlipidemia 84% and obesity 35%) compare to non-diabetics who underwent surgical stone treatment (Table 2).

Surgical Intervention

Operative details of 182 patients who were treated by a single urological surgeon in our institute over three years' period were shown in (Figure 5). Only two surgical approaches were included in the analysis. Ureteroscopy was the common procedure performed; represented (83%) of which ten cases were performed as an emergency.

Kidney or ureteral stones treated were either solitary, multiple or staghorn calculus. The mean stone size in diabetic patients was found to be significantly bigger (p-value= 0.008) than stones obtained from non-diabetic patients (Table 3).

Preoperative Investigations

Routine preoperative investigations for patients who managed surgically for their urolithiasis were evaluated in both diabetics and non-diabetics. Variables which were especially related to urinary stones work up were then analyzed (Table 4).

Diabetes was associated significantly with lower eGFR, which could represent a higher prevalence of chronic kidney disease, especially among those with a history of urinary tract stones compare to non-diabetics.

Urinary tract infections were significantly higher among diabetics. All identified UTIs were treated

preoperatively with appropriate antibiotics according to hospital policy. Figure 6 shows common organisms that were identified during preoperative screening.

Immediate Surgical Outcomes

Six patients had postoperative surgical complications, of which three occurred in diabetics. The nature of these surgical complications demonstrated in Table 5.

The mean length of hospital stay among diabetics was 2.8 days. This was longer compared to non-diabetics group (2.0 days); however, it was not statistically significant (p-value=0.17).

Stone Recurrence and Clearance

No visible stones on X-ray KUB or insignificant residual fragments (less than 4 mm) after surgical treatment was defined as stone clearance. At three months, available data on diabetics and non-diabetics group has shown; 13 diabetic patients had stone clearance at 3 months (42%) compared to 109 non-diabetics (72%), (p-value= 0.89).

Data of stone recurrence were difficult to obtain as most patients were discharged once stones have been completely treated, and they considered stone

FIG. 5 Analysis of surgical approach in diabetic and non-diabetic patients.

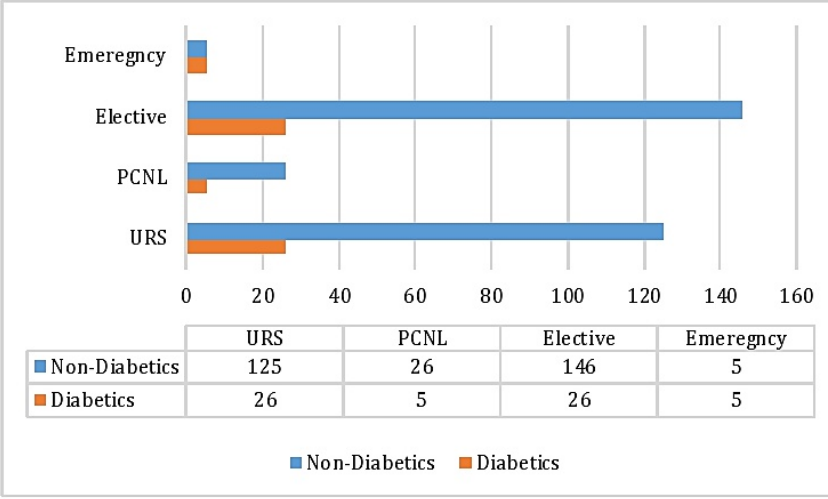


TABLE 3 Representing Stone Size Treated among Diabetics and Non-Diabetics

	Range of Stone Size	Mean of Stone Size
Non-diabetics	1-40 mm	7.0 mm
Diabetics	3-25 mm	7.5 mm

TABLE 4 Representing Basic Preoperative Serum and Urine Workup

	Normal Values	Non-Diabetics Mean	Diabetics Mean	p-value
Creatinine	44-90 umol/L	91	95	0.44
eGFR	>90 ml/min	73.8	65.7	0.049
Uric Acid	<420 umol/L	324	370	0.12
Ionised Calcium	2.2-2.6 mmol/L	4.7	2.35	0.32
Positive Midstream Urine	Negative culture	N=24(16%)	N=13(42%)	0.009

FIG. 6 Analysis of positive urine cultures results in infections.

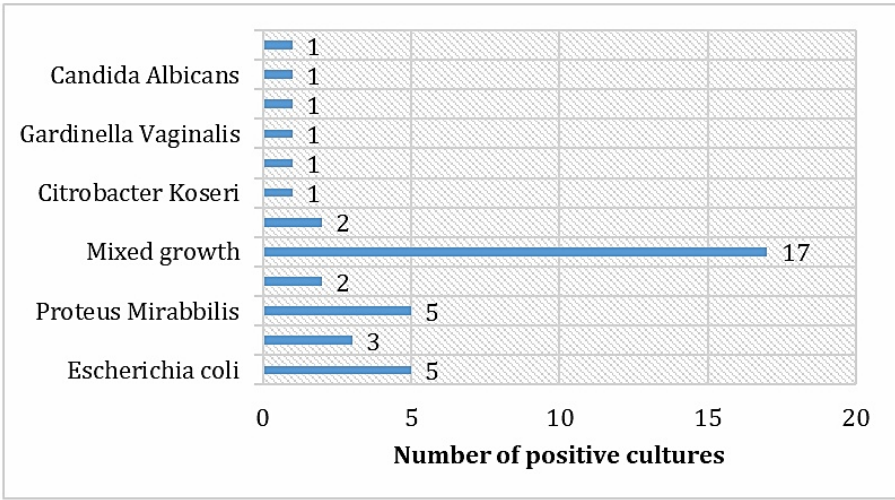


TABLE 5 Modified Clavien-Dindo Classification of Surgical Complications

	Non-Diabetic	Diabetics
Grade 2	1	1
Grade3	1	2
Grade4	1	0

free. Table 6 has shown a detailed analysis of diabetics and non-diabetics periodic follow-ups at one, three and five years to identify stone recurrence. Diabetics are significantly at higher risk of stone recurrence at 1 year compared to non-diabetics (p=0.04). Our three and five years' data did not demonstrate any significant differences in stone recurrence rate among diabetics compared to non-diabetic individuals treated surgically for urinary tract stones.

Stone Biochemical Profile

Biochemical records of 73 stones were evaluated (n=13 in diabetics) versus (n=60 in non-diabetics). Data on stone compositions in each group were further analyzed. (Figure 7 and Figure 8).

Our results revealed that stones predominantly contained calcium oxalate monohydrate, and calcium oxalate dihydrate was commonly found among our cohort. The proportion of stones that contained these two components didn't differ between diabetics and non-diabetics groups (p value= 0.96, p value= 0.36 respectively). Carbonate apatite stones were significantly higher in the non-diabetes cohort (p-value =0.024). Diabetics were found to have a higher prevalence of urate stones (19%) versus (3%) in non-diabetics. However, it was not statistically significant (p-value= 0.11). Other stone types such as; Calcium Phosphate, Struvite (Magnesium ammonium phosphate) and Cystine were only found in non-diabetic patients.

Urine Biochemical Profile

The 24-hours urinary collection data were available on 83 patients in our study. Urinary parameters of 17 diabetics (55%) and 66 non-diabetics (44%) were further evaluated and statistically analyzed (Table 7), expect urinary pH as it's not formally measured. 24-hours urinary phosphate was significantly lower among diabetic patients compared to non-diabetics. Similarly, oxaluria was significantly more prevalent in diabetics than non-diabetics. Other parameters did not differ statistically between the two groups.

TABLES 6 The Trend for Stone Recurrence among the Diabetic and Non-diabetic Individuals

	Follow Up at One Year, (p-value= 0.04)		
	Number of patients had follow up	Patients with recurrence	Patients without recurrence
Non-diabetics	N=85	N=11, (13%)	74 (87%)
diabetics	N=14	N=6 (46%)	8 (54%)

	Follow Up at Three Years, (p-value= 0.5)		
	Number of patients had follow up	Patients with recurrence	Patients without recurrence
Non-diabetics	N=84	N=17, (20%)	N=67, (80%)
diabetics	N=9	N=3, (33%)	N=6, (67%)

	Follow Up at Five Years, (p-value= 0.5)		
	Number of patients had follow up	Patients with recurrence	Patients without recurrence
Non-diabetics	N=78	N=10, (13%)	N=68, (87%)
diabetics	N=10	N=3, (30%)	N=7, (70%)

TABLE 7 Analysis of 24-Hours Urinary Biochemical Parameters

	Non-Diabetics Means	**Diabetics Means**	**p-value**
Total volume (Litre/day)	1.9	1.8	0.56
Uric acid (mmol/24hr)	3.14	2.8	0.48
Calcium(mmol/24hr)	5.59	4.78	0.54
Phosphate(mmol/24hr)	26	19.9	0.076
Oxalate (mmol/24hr)	0.32	0.42	0.007
Citrate(mmol/24hr)	2.35	3.4	0.26
Magnesium (mmol/24hr)	3.81	3.16	0.31

FIG. 7 Analysis of stones composition in non-diabetics.

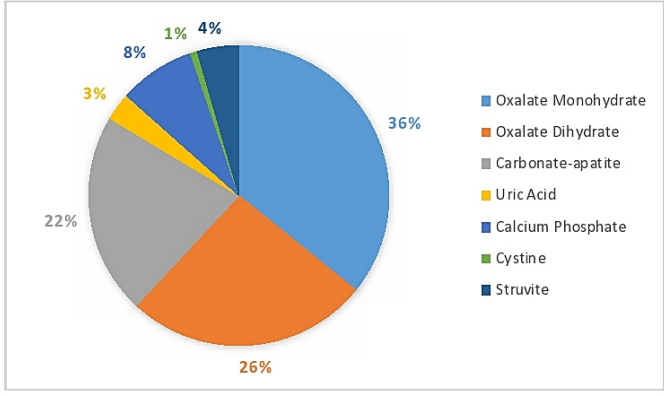
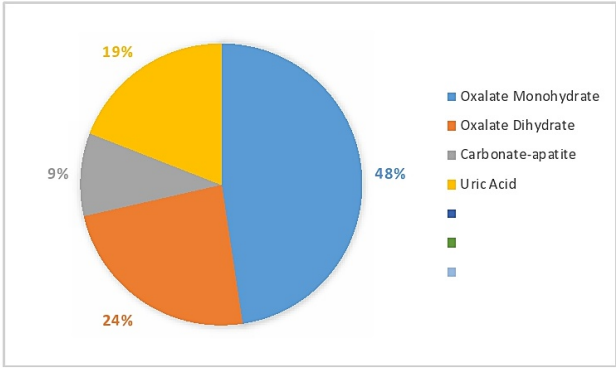


FIG. 8 Analysis of stones composition in diabetics.



DISCUSSION

Patients Demographics and Baseline Characteristics

This study found that diabetes mellitus was positively prevalent among patients with urolithiasis (17%) compared to the national figure of 6% (adult aged 17 years or older) with diagnosed diabetes in England in 2013.[12] Nationally, almost a quarter of people areunaware of their diagnosis with type two diabetes; as a result, the diagnosed population understate the true prevalence.[13] When these undiagnosed people are considered, the true prevalence in England then can be estimated.

Age

The study results have shown that diabetics with urinary tract stones were older compared to the non-diabetics' cohort. This was observed among previously published international studies which have confirmed that the prevalence of urolithiasis and diabetes mellitus increased with age in many countries like Germany, Italy, Greece, Turkey, Iran and United States.[3,14–19] In the United Kingdom prevalence of diabetes increased sharply with age in those aged 0–29 (0.33%), 30–59 (3.37%) and 60+ years (13.92%). From our study, older diabetes (more than 60 years) are at higher risk of urolithiasis compare to non-diabetics. This could also be explained by the increased aging population in the United Kingdom.

Gender

Historically, urinary tract stones affect men, two to three times more than women. In the National Health and Nutrition Examination Survey (NHANES), 2007-2010[3] analyzed data of 12,110 patients and showed the prevalence of urinary tract stones was 10.6% among males compared with 7.1% among women. In our study, 115 (63%) of the cohort were males. Of those, 20 (10%) were diabetics. However, there was no significant statistical difference in the same gender group between diabetics and non-diabetics (p-value=0.86). In regards to the association of diabetes with gender in the United Kingdom, and epidemiological statistical study has also shown diabetes mellitus affects more men than women (56% Vs 44% respectively.[20]

Ethnicity

An epidemiological study conducted nationally has revealed a higher prevalence of diabetes mellitus among ethnic minority groups in the United Kingdom. In an ethnically diverse city in Britain like Manchester, the prevalence of diabetes mellitus was 20% in Caucasians, 22% in African-Caribbeans, and 33% in Asians.[21] Comparatively, in North Birmingham, the prevalence of diabetes mellitus was 40.6% in Caucasians and 53.3% in the ethnic minority population.[22]

A population-based, cross-sectional study involving 15,364 from the United States National Health and Nutrition Examination Survey revealed that the

prevalence of kidney stone disease was 5.9% among Caucasians compared to 1.7% in African/Caribbeans decent.[23]

Risk Factors

The known shared links between these metabolic disorders are insulin resistance. Due to altered renal acid-base metabolism, increased urinary excretion of calcium, oxalate, and uric acid lead to increased risk of calcium and uric acid-containing urinary tract stones.[24]

In a study examining body mass index and its urolithiasis risk, it showed that obesity and weight gain were associated with an increased risk of kidney stone formation,[25] the relative risk for men with a BMI of 30 or greater versus those with a BMI of 21 to 22.9 was 1.33 (95% CI, 1.08-1.63; p-value <.001). The relative risks for the same categories of BMI in older and younger women were 1.90 (95% CI, 1.61-2.25; p-value <.001) and 2.09 (95% CI, 1.77-2.48; p-value <.001).[26]

A previously published study of 132 patients compared biochemical urinary parameters related to stone formation between known hypertensive and normotensive individuals for five years. These revealed urinary parameters were higher in both hypertensive males and females compared to the normotensive group.[27] In hypertensive males, analysis results showed calcium levels were (263) vs. (199 mg/day in normotensive), magnesium (100 vs. 85 mg/day), uric acid (707 vs. 586 mg/day), and oxalate (34.8 vs. 26.5 mg/day). In hypertensive females results were; calcium (212 vs. 154 mg/day), phosphate (696 vs. 614 mg/day), and oxalate (26.2 vs. 21.7 mg/day).

A case-control study to examine the relationship between different types of stones and lipid profile parameters.[28] The study enrolled 49 patients (35 males and 14 females) who had been diagnosed with urolithiasis and underwent open surgery or percutaneous surgery for stone disease. It showed statistical differences between mixed calcium oxalate monohydrate and calcium oxalate dihydrate stone formers and the controls in terms of levels of cholesterol (p-value < 0.01), and levels of triglycerides (p-value < 0.01). There were significant differences between uric acid stone formers and controls in the case of cholesterol levels (p-value < 0.05), and triglyceride levels (p-value < 0.01). This explains that other components of metabolic syndrome, such as hypercholesterolemia, and hyperlipidemia are highly prevalent among patients with urolithiasis and associated with various types of stone formation.

Surgical Approach

Our results confirmed the findings of greater stone size among diabetics compared to non-diabetics (p-value=0.008). Previous literature has confirmed the association of metabolic syndrome and the risk of urolithiasis, and more researchers have studied the correlation between metabolic syndrome and diabetes with differences in stone burden.[29] Their results showed that the stone burden was greater among patients suffering from metabolic syndrome and diabetes compared to non-diabetics (17.6 mm vs 6.3 mm, p-value=0.002) which both lead to multiple urinary metabolic changes caused by insulin resistance that can increase stone formation.

The stone burden in addition to other factors such as high BMI and medical comorbidities is essential and helpful for urologists who plan to treat such patients surgically as these factors could predict the operation type, duration and success rate.

Role of Preoperative Investigations

Chronic Kidney Disease (CKD)

Diabetes is a major systemic microvascular disease that could cause chronic kidney disease (diabetic nephropathy). Likewise, urolithiasis is a well-known disease that could initiate renal damage. This study results revealed that kidney functions were deranged and the estimated glomerular filtration rate was significantly lower among the diabetic group (p-value < 0.05). A systematic literature review of a total of 71 studies from 30 different countries with sample sizes ranging from 505 to 211,132 was performed.[30] It was shown that the annual incidence of CKD stage 1 and stage 2 (microalbuminuria) and CKD stage 3 and stage 4 (macroalbuminuria) is around 2–3% in type one diabetes, and around 8% in type two diabetes. The incidence of developing eGFR < 60 mL/min/1.73 m2 is around 2–4% per year.

Similar findings were observed in a prospective study of more than 5000 individuals in the United

Kingdom to determine the progression of CKD in type two diabetes.[31]

The risk of renal damage could increase to almost twice if associated with urinary stones in addition to existing diabetes mellitus. This result either due to obstruction, associated infections or surgical related injuries caused by repeated interventions. Many published studies have shown that urolithiasis may play an important role in the development of chronic kidney disease,[32–34] especially among those who suffer from frequent urinary tract infections, struvite stones, anatomical abnormalities, and urinary diversions.[35]

Urinary Tract Infections

We have shown that urinary tract infections were more predominant among diabetics with urinary tract stones (41%, p-value <0.05) compared to non-diabetics. An observational study conducted in the United Kingdom among patients followed up for one year using a general practice research database. This confirmed that the incidence of urinary tract infection was (46.9 per 1000 patients per year) among diabetics and (29.9 per 1000 per year) for non-diabetics.[36]

Meydan et al. have studied risks associated with urinary stone disease such as diabetes. It was found that diabetic individuals (21%) were at higher risk of urolithiasis compared to non-diabetics (8%). Associated urinary tract infections were significantly higher among diabetics (8%) compared to non-diabetics group (1%), p-value < 0.05.[37] Those findings suggest that patients with diabetes and urolithiasis treated surgically at higher risks of infections, postoperative complications and increased morbidity.[38–41]

Surgical Complications

Ureteroscopy and Percutaneous nephrolithotomy are continuing to be popular, safe and effective procedures for treating urinary tract stones in the United Kingdom and worldwide. As in any other surgical approach, risk factors for potential intra and postoperative complications should be identified to avoid potential risks of morbidity and mortality among those who underwent treatment for urolithiasis.

The increase in complications, length of hospitalization and morbidity were also observed among patients with metabolic syndrome and diabetes who underwent surgical treatment for urinary stones disease compared to the control group.[42] In a large PCNL study involved 5803 patients, incidence of postoperative fever of more than 38.5 Degree Celsius required further treatment was significantly associated with diabetes (OR = 1.38, CI [1.05–1.81]).[43] Diabetes was considered as a strong predictor of the risk of frequent positive urine cultures in this cohort which were estimated at (16.2%). Elderly patients with medical comorbidities like diabetes are at a significant risk of sepsis (6.56%) compared to those who were younger (1.3%).[44] This explains that old age, diabetes, and medical comorbidities do affect surgical outcomes and increase the length of hospital stay.[44]

Stone Compositions

Prevalence of metabolic syndrome and diabetes have a significant link to a higher incidence of stones formation through several urinary metabolic alterations related to low urinary pH, hyperuricosuria and low urinary volume.[45] Uric acid stone former were found to have a higher prevalence of diabetes, obesity and higher serum uric acid level compared to others.[46] This was also observed in a large stone cohort in United states population which found diabetics had a significantly greater proportion of uric acid in their stones (50.2% vs 13.5% in non-diabetics, P < 0.001).[47]

Component of metabolic syndrome like diabetes independently associated with differences in stones composition of 590 kidney stones removed surgically by either PCNL or by ureterorenoscopy over five years in another American population.[48] The statistical analysis showed diabetes was independently associated with a higher proportion of uric acid stones and less significant relationship with calcium contained stone-like phosphate and oxalate.

Our study did confirm similar findings, as more diabetics have had higher urate stone compared to non-diabetics and less calcium oxalate dihydrate contained stones. Both results were not significant compared to non-diabetics. These findings suggest that there are other factors associated with type two diabetes or insulin resistance that are responsible for stone formation.

Twenty-Four Hours Urinary Collection

Secondary to its metabolic effect on urine biochemical components through insulin resistance and

abnormal ammonia metabolism, diabetes associated with higher urinary excretions of uric acid, oxalate and lower pH which could predict future stone recurrence among diabetics population.[47]

From our results, we have shown that diabetics did have significantly higher urinary oxalate secretion than non-diabetics (p-value=0.007) which in line with the previously published study.

We have also found that diabetics had lower urate and nearly significant lower urinary phosphate than non-diabetics (p-value=0.48), (p-value=0.076) respectively. Only a few studies have shown the relationship between metabolic regulations of urinary phosphate and its biochemical effect on urine crystallization and stones formation.[24] Urine phosphate excretion correlates with sodium and protein ingestion, but it hasn't yet fully studied or understood how it clinically increases or prevents the risk of calcium oxalate or calcium phosphate stones.[49]

A total of 1117 patients in the United States were examined retrospectively as part of a large study of patients with urolithiasis. Twenty-four hours of urinary collection data were analyzed in both diabetics and non-diabetics population. (16%) Diagnosed with diabetes at the time of urine analysis.[47] Results confirmed that diabetics have significant higher oxalate, uric acid, citrate and lower calcium and phosphate (p-value = <0.05) compare to non-diabetics. Fram et al.[50] found that in an ethnically diverse inner city in America treated for urinary stone disease (n=955), diabetics (28%) had significantly lower urinary phosphate (p-value = 0.004) compared to non-diabetics group. Eisner et al.[51] retrospectively reviewed a database of 462 stone-forming patients, of which 9.9% had type two diabetes mellitus. Diabetics excreted nearly significant more daily oxalate compared to non-diabetics (p-value= 0.09) and significantly lower daily urinary phosphate level compared to the control (p-value= 0.002).

Stone Clearance and Recurrence

Out of 182 patients treated surgically for urolithiasis, (42%) diabetics and (72%), non-diabetics were completely stone-free by three months (p-value= 0.89). The rest of the patients who were not stones free at three months follow-up were either managed conservatively or had further interventions in the long-term. However, those data were not fully analyzed in this study.

Generally, once stones are treated and patients considered to be asymptomatic, they will be discharged from the hospital back to their local general practitioner with the view of further referral if they become symptomatic with urolithiasis. Therefore, data of periodic follow-ups for the whole cohort were difficult to obtain. Data of one, three and five years follow-ups did show that diabetics are significantly at higher risk of stone recurrence at one year compare to non-diabetics (p-value=0.04). Our three and five years' data did not demonstrate any significant differences in stone recurrence rate between the two groups.

A total of 332 stone formers (253 males, 79 females) and 949 control were evaluated in a retrospective study (52). Obesity was found to be highly prevalent (p-value <0.05) among male stone formers and consider to be a risk of calcium stones recurrence compared to the control group. A systematic review of 21 randomized controlled trials conducted to quantify risks and predictors of stone recurrence in calcium stone formers, Analysis of 2168 participants over 3.2 years follow-up showed that previous stone history was a main risk factor of the overall recurrence rate. From our results, recurrent stone history was not significant between diabetics and non-diabetics (p-Value= 0.925).[53]

A retrospective analysis was conducted among 321 patients with a history of urolithiasis to determine the impact of lipid profile on stone recurrence between 2004 and 2009.[54] A median follow-up of 35.0 months has shown that 109 patients (34%) had a stone recurrence. Stone recurrence was more common in the hyperlipidemia group compared with the control group (45.9% versus 29.7%; p-value = 0.005).

Diabetes increases the risk of stone formation, as has previously described in our study. Other risk factors associated with diabetes such as hyperlipidemia and obesity showed to increase the risk of stone recurrence among stone formers patients. Those risk factors were significantly prevalent in the diabetes cohort included in our study. However, the association between diabetes and the risk of stone recurrence among different stone formers need to be further evaluated in prospective studies and randomized controlled trials.

CONCLUSIONS

To our knowledge, this is the first study that was carried out to examine risk factors, surgical outcomes and biochemical abnormalities associated with diabetes mellitus among surgically treated patients with urinary tract stones among a population in a British inner city.

From this study:

- We found that (17%) of our cohort were diabetics with urolithiasis who required surgical intervention with either RIRS or PCNL.
- The diabetics were older and significantly associated with metabolic syndrome disease, which increases the risk of urolithiasis.
- Chronic kidney disease and UTIs were more prevalent among diabetics. Such factors need to be identified and appropriately managed preoperatively.
- The stone burden was significantly higher in the diabetics group compared to non-diabetics.
- Diabetics are significantly at higher risk of stone recurrence at one year compare to non-diabetics (p=0.04). The three and five years' data did not demonstrate any significant differences in stone recurrence rate between the two groups.
- Diabetics were significantly associated with higher urinary oxalate, and approach statistical significance in having lower urinary phosphate levels. Those findings are important as they can influence dietary counselling, medical management and stone prevention.

REFERENCES

1. Turk C, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Urolithiasis. Eur Assoc Urol [Internet]. 2015;69(3):475–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26344917
2. Prezioso D, Illiano E, Piccinocchi G, Cricelli C, Piccinocchi R, Saita A, et al. Urolithiasis in Italy: An epidemiological study. Arch Ital di Urol e Androl 2014;86(2):99–102.
3. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. Eur Urol 2012;62(1):160–5.
4. Seklehner S, Laudano M a, Chughtai B, Jamzadeh A, Del Pizzo JJ, Engelhardt PF, et al. Trends in the utilization of percutaneous and open nephrolithotomy in the treatment of renal calculi. J Endourol [Internet] 2013;27(8):984–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23590666
5. Heers H, Turney BW. Trends in urological stone disease: a 5-year update of hospital episode statistics. BJU Int 2016;118(5):785–9.
6. Meydan N, Barutca S, Caliskan S, Camsari T, Meydan N, Barutca S, et al. Urin Stone Dis Diabet Mel 2016;5599(August).
7. Li H, Klett DE, Littleton R, Elder JS, Sammon JD. Role of insulin resistance in uric acid nephrolithiasis. World J Nephrol 2014;3(4):237–42.
8. Cupisti A, Meola M, D'Alessandro C, Bernabini G, Pasquali E, Carpi A, et al. Insulin resistance and low urinary citrate excretion in calcium stone formers. Biomed Pharmacother 2007;61(1):86–90.
9. Coe FL, Strauss AL, Tembe V, Le Dun S. Uric acid saturation in calcium nephrolithiasis. Kidney Int [Internet] 1980;17(5):662–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7401461
10. Diabetes UK. Diabetes-key-stats-guidelines-April2014-1. Diabetes UK [Internet] 2014;(3):1–21. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:DIABETES+:+FACTS+AND+STATS#5
11. Health and Social Care Information Centre. Quality and Outcomes Framework – Prevalence, Achievements and Exceptions Report QOF Data Quality Statement and Frequently Asked Questions. 2014-15. 2015;(October).
12. Mary E. Adult Obesity and Type 2 Diabetes About Public Health England. Public Heal Engl 2014;1–39.
13. Holman N, Forouhi NG, Goyder E, Wild SH. The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: Estimates of total diabetes prevalence for England, 2010-2030. Diabet Med 2011;28(5):575–82.
14. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health and Nutrition Examination Survey 1999-2002. Diabetes Care 2006; 29(6):1263–8.
15. Amato M, Lusini ML, Nelli F. Epidemiology of nephrolithiasis today. In: Urologia Internationalis 2004; 1–5.

16. Hesse A, Brändle E, Wilbert D, Köhrmann KU, Alken P. Study on the Prevalence and Incidence of Urolithiasis in Germany Comparing the Years 1979 vs. 2000. Eur Urol 2003;44(6):709–13.
17. Akinci M, Esen T, Tellaloglu S. Urinary stone disease in Turkey: an updated epidemiological study. Eur Urol 1991;20(3):200–3.
18. Stamatiou KN, Karanasiou VI, Lacroix RE, Kavouras NG, Papadimitriou VT, Chlopsios C, et al. Prevalence of urolithiasis in rural Thebes, Greece. Rural Remote Health 2006;6(4):610.
19. Safarinejad MR. Adult urolithiasis in a population-based study in Iran: Prevalence, incidence, and associated risk factors. Urol Res 2007;35(2):73–82.
20. Diabetes UK. Facts and Stats [Internet]. https://www.diabetes.org.uk/About_us/What-we-say/Statistics/ (Accessed: 13/07/2016). 2015. Available from: https://www.diabetes.org.uk/About_us/What-we-say/Statistics/
21. Riste L, Khan F, Cruickshank K. High prevalence of type 2 diabetes in all ethnic groups, including europeans, in a British inner city: Relative poverty, history, inactivity, or 21st century Europe? Diabetes Care 2001;24(8):1377–83.
22. Prevalence and risk Care processes Structured education Treatment targets.
23. Stamatelou K, Francis M, Jones C, Nyberg L, Curhan G. Time trends in reported prevalence of kidney ston . . . [Kidney Int. 2003] - PubMed - NCBI. Kidney Int [Internet] 2003;63:1817–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed?term=time trend in reported prevalence of kidney stones in US
24. Shafiee M. Urinary Composition and Stone Formation. Univ Toronto. 2010;23(85–88):165–9.
25. Siener R, Glatz S, Nicolay C, Hesse A. The role of overweight and obesity in calcium oxalate stone formation. Obes Res [Internet] 2004;12(1):106–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14742848%5Cnhttp://onlinelibrary.wiley.com/store/10.1038/oby.2004.14/asset/oby.2004.14.pdf?v=1&t=ils0mmfg&s=35747f86e3015a1cbb7a0c3ff28e5285bf2a76be
26. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA [Internet] 2005;293(4):455–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15671430
27. Borghi L, Meschi T, Guerra A, Briganti A, Schianchi T, Allegri F, et al. Essential arterial hypertension and stone disease. Kidney Int 1999;55(6):2397–406.
28. Inci M, Demirtas A, Sarli B, Akinsal E, Baydilli N. Association between body mass index, lipid profiles, and types of urinary stones. Ren Fail [Internet] 2012;34(July):1140–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22889148
29. Tran TY, Flynn M, O'Bell J, Pareek G. Calculated insulin resistance correlates with stone-forming urinary metabolic changes and greater stone burden in high-risk stone patients. Clin Nephrol [Internet] 2016; Available from: http://www.ncbi.nlm.nih.gov/pubmed/27125629
30. Koye DN, Shaw JE, Reid CM, Atkins RC, Reutens AT, Magliano DJ. Incidence of chronic kidney disease among people with diabetes: a systematic review of observational studies. Diabet Med [Internet] 2017;1–15. Available from: http://doi.wiley.com/10.1111/dme.13324
31. Adler a I, Stevens RJ, Manley SE, Bilous RW, Cull C a, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225–32.
32. Worcester EM, Parks JH, Evan AP, Coe FL. Renal function in patients with nephrolithiasis. J Urol [Internet] 2006;176(August):600–3; discussion 603. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16813897
33. Vupputuri S, Soucie JM, McClellan W, Sandler DP. History of kidney stones as a possible risk factor for chronic kidney disease. Ann Epidemiol 2004;222–8.
34. Gambaro G, Favaro S, D'Angelo A. Risk for renal failure in nephrolithiasis. Am J Kidney Dis 2001;37(1523–6838 (Electronic)):233–43.
35. Gambaro G, Favaro S, D'Angelo A. Risk for renal failure in nephrolithiasis. Am J Kidney Dis [Internet] 2001;37(2):233–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11157364
36. Hirji I, Guo Z, Andersson SW, Hammar N, Gomez-Caminero A. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). JDiabetes Complicat 2012;26(1873–460X (Electronic)):513–6.
37. Meydan N, Barutca S, Caliskan S, Camsari T. Urinary stone disease in diabetes mellitus. Scand J Urol Nephrol 2003;37(1):64–70.

38. Wei W, Leng J, Shao H, Wang W. Diabetes, a risk factor for both infectious and major complications after percutaneous nephrolithotomy. Int J Clin Exp Med 2015;8(9):16620–6.
39. Lojanapiwat B. Infective complication following percutaneous nephrolithotomy. Urol Sci [Internet] 2016;27(1):8–12. Available from: http://dx.doi.org/10.1016/j.urols.2015.04.007
40. Mitsuzuka K, Nakano O, Takahashi N, Satoh M. Identification of factors associated with postoperative febrile urinary tract infection after ureteroscopy for urinary stones. Urolithiasis 2015;44(3):257–62.
41. Ronald A, Ludwig E. Urinary tract infections in adults with diabetes. In: Int J Antimicrob Agents 2001;287–92.
42. Nalbant I, Ozturk U, Sener NC, Dede O, Bayraktar AM, Imamoglu MA. The comparison of standard and tubeless percutaneous nephrolithotomy procedures. Int Braz J Urol. 2012;38(6):795–800.
43. Gutierrez J, Smith A, Geavlete P, Shah H, Kural AR, de Sio M, et al. Urinary tract infections and post-operative fever in percutaneous nephrolithotomy. World J Urol 2013;31(5):1135–40.
44. Nakamon T, Kitirattrakarn P, Lojanapiwat B. Outcomes of percutaneous nephrolithotomy: Comparison of elderly and younger patients. Int Braz J Urol 2013;39(5):692–701.
45. Pak CYC, Sakhaee K, Moe O, Preminger GM, Poindexter JR, Peterson RD, et al. Biochemical profile of stone-forming patients with diabetes mellitus. Urology 2003;61(3):523–7.
46. Viers BR, Lieske JC, Vrtiska TJ, Herrera Hernandez LP, Vaughan LE, Mehta RA, et al. Endoscopic and Histologic Findings in a Cohort of Uric Acid and Calcium Oxalate Stone Formers. Urology 2015;85(4):771–6.
47. Hartman C, Friedlander JI, Moreira DM, Elsamra SE, Smith AD, Okeke Z. Differences in 24-hour urine composition between stone patients with and without diabetes mellitus. BJU Int [Internet] 2014;1–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24823472
48. Kadlec AO, Greco K, Fridirici ZC, Hart ST, Vellos T, Turk TM. Metabolic syndrome and urinary stone composition: What factors matter most? Urology 2012;80(4):805–10.
49. Whalley NA, Martins MC, Van Dyk RC, Meyers AM. Lithogenic risk factors in normal black volunteers, and black and white recurrent stone formers. BJU Int 1999;84(3):243–8.
50. E.B. F, S. M, J.M. S. The Effect of Disease Severity on 24-Hour Urine Parameters in Kidney Stone Patients with Type 2 Diabetes. Urology [Internet] 2016;87:52–9. Available from: http://www.elsevier.com/locate/urology%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=20151008277
51. Eisner BH, Porten SP, Bechis SK, Stoller ML. Diabetic Kidney Stone Formers Excrete More Oxalate and Have Lower Urine pH Than Nondiabetic Stone Formers. J Urol 2010;183(6):2244–8.
52. Kin M. No Title. (December 1995).
53. Ferraro PM, Curhan GC, D'Addessi A, Gambaro G. Risk of recurrence of idiopathic calcium kidney stones: analysis of data from the literature. J Nephrol 2016;
54. Kang HW, Seo SP, Kim WT, Kim YJ, Yun SJ, Lee SC, et al. Hypertriglyceridemia is associated with increased risk for stone recurrence in patients with urolithiasis. Urology 2014;84(4):766–71.