CASE REPORT

What is the relationship between type 2 diabetes mellitus and urolithiasis?

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Abstract: *Aim:* Despite the high incidence of urolithiasis in general population, the exact underlying pathology is unknown. Possible association between urolithiasis and parameters of physical health were assesed in the presented study .
Material and methods: The study was performed at an Internal Medicine out patient unit during routine check ups. Patients between the ages of 20 and 70 years were studied to prevent debility induced weight loss in elderly. Patients with devastating illnesses were excluded to avoid their possible effects on weight. Cases with urolithiasis were collected in one group, and age and sex-matched cases without urolithiasis were collected in other group.
Results: Eighty cases with urolithiasis and 120 cases without were studied. Mean age of urolithiasis cases was 49.0 years, and 52.5 % of them were female. Mean weight of the urolithiasis cases was 76.0 kg, whereas it was 80.8 kg in the group without urolithiasis (*p=0.013*). The prevalence of type 2 diabetes mellitus (DM) was significantly higher in the urolithiasis group with unknown reasons (17.5 % vs 7.5 %, *p<0.01*). There was no significant difference as for the height, body mass index, prevalence of hypertension, and mean values of low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride between the groups.
Conclusion: In spite of several terrible effects of excess weight on health, we could not detect any association with urolithiasis, but there is a highly significant association between urolithiasis and type 2 DM, and it may have hundreds of mechanisms with variable priorities, which must be explained with further studies *(Tab. 1, Ref. 21).* Full Text in free PDF *www.bmj.sk.*
Key words: urolithiasis, type 2 diabetes mellitus, excess weight, hypertension.

Urolithiasis is a common pathology in the general population, and lifetime risk of nephrolithiasis is 12–15 % for a white man and 5–6 % for a white woman with an up to 50 % of lifetime recurrence ratio (1). Even we detected the rate of urolithiasis as 13.7 % and 15.2 % in women and men in a previous study, respectively (2). Approximately 80 % of the stones are composed of calcium oxalate (CaOx) and calcium phosphate (CaP), and CaOx is the main constituent of them. Beside that, 10 % of struvite (magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme urease) and 9 % of uric acid stones are seen. Majority of the CaOx stone formers suffer from no systemic disease (3), and minority of the patients have primary hyperparathyroidism or some other disorders of calcium metabolism, hyperoxaluria secondary to bowel disease (enteric hyperoxaluria), or genetic disorders of oxalate metabolism (primary hyperoxaluria). In the study, we tried to assess any association between urolithiasis and parameters of physical health including body weight, height, body mass index (BMI), diabetes mellitus (DM), hypertension (HT), and lipid profiles.

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Material and methods

The study was performed at the Internal Medicine out-patient unot of the Mustafa Kemal University during routine check ups between August 2008 and January 2009. Patients between the ages of 20 to 70 years were enrolled into the study to prevent debility induced weight loss in elderly. Their medical histories including HT, DM, dyslipidemia, already used medications, and performed operations were obtained, and a routine check up procedure including fasting plasma glucose (FPG), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), an abdominal X-ray in supine position, and an abdominal ultrasonography were performed. An additional intravenous pyelography (IVP) was performed just in suspected cases from presenting urolithiasis as a result of the urinalysis, abdominal X-ray and abdominal ultrasonography, since uric acid stones are not easily seen on X-rays whereas they are seen as filling defects on IVP. So urolithiasis was diagnosed either by a medical history or as a result of current laboratory findings. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. BMI of each case was calculated by the measurements of the same physician instead of verbal expressions. Weight in kilograms is divided by height in

Tab. 1. Characteristic features of the study cases.

Variables	Cases with urolithiasis	Cases without urolithiasis	p-value
Number	80	120	
Female ratio	42 (52.5%)	63 (52.5%)	>0.05
Mean age (years)	49.0±10.8 (20-70)	48.7±10.1 (20−70)	>0.05
Mean body weight (kg)	76.0±13.2	80.8±12.9	0.013
Mean height (cm)	162.8±10.0	164.6±10.7	>0.05
Mean BMI* [kg/m(2)]	28.5±5.2	29.6±4.9	>0.05
Prevalence of DM†	17.5% (14)	7.5% (9)	<0.01
Prevalence of HT‡	13.7% (11)	15.0% (18)	>0.05
Mean LDL-C§ (mg/dL)	132.7±39.6 (3.4±1.0 mmol/l)	134.7±30.2 (3.4±0.7 mmol/l)	>0.05
Mean HDL-C• (mg/dL)	44.1±9.3 (1.1±0.2 mmol/l)	45.8±10.4 (1.1±0.2 mmol/l)	>0.05
Mean TG** (mg/dL)	157.4±76.9 (1.7±0.8 mmol/l)	155.7±75.7 (1.7±0.8 mmol/l)	>0.05

*Body mass index †Diabetes mellitus ‡Hypertension §Low density lipoprotein cholesterol •High density lipoprotein cholesterol **Triglyceride

square meters, and underweight is defined as a BMI lower than 18.5, normal weight as 18.5–24.9, overweight as 25.0–29.9, and obesity as a BMI of 30.0 kg/m(2) or greater (4). Cases with an overnight FPG level of 126 mg/dl (7.0 mmol/l) or greater on two occasions or already receiving antidiabetic medications were defined as diabetics (4). An oral glucose tolerance test with 75-gram glucose was performed in cases with an FPG level between 110 and 126 mg/dl (6.0–7.0 mmol/l), and diagnosis of cases with a 2-hour plasma glucose level 200 mg/dl (11.0 mmol/l) or higher is DM (4). Additionally patients with dyslipidemia were detected, and we used the National Cholesterol Education Program Expert Panel's recommendations for defining dyslipidemic subgroups (4). Dyslipidemia is diagnosed when LDL-C is 160 (4.1 mmol/l) or higher and/or TG is 200 (2.2 mmol/l) or higher and/or HDL-C is lower than 40 mg/dl (1.0 mmol/l). Office blood pressure was checked after a 5-minute of rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2-hour. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked HT after a 10-minute education about proper BP measurement techniques (5). The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5-minute in the seated position before measurement. An additional 24-hour ambulatory blood pressure monitoring was not required due to the equal efficacy of the method with HBP measurement to diagnose HT (6). Eventually, HT is defined as a BP of 135/85 mmHg or greater on HBP measurements (5). Eventually, all cases with urolithiasis were collected in one, and age and sex-matched cases without urolithiasis were collected in the other groups. Both groups were compared according to the mean body weight, height, and BMI, prevalences of DM and HT, and mean values of LDL-C, HDL-C, and TG. Independent samples t-test and comparison of proportions were used as the methods of statistical analysis.

Results

Totally 200 cases, 80 with urolithiasis and 120 without urolithiasis, were studied. General properties of the cases with and without urolithiasis are shown in Table 1. Mean age of urolithiasis cases was 49.0 years, and 52.5 % (42 cases) of them were female. When we compared the two groups according to the mean body weight, there was a significant difference between them (*p=0.013*). Mean body weight of the urolithiasis cases was 76.0 kg, whereas it was 80.8 kg in the group without urolithiasis. On the other hand, the prevalence of DM was significantly higher in the urolithiasis group with unknown reasons (17.5 % vs 7.5 %, *p<0.01*). Out of mean body weight and prevalence of DM, there was no significant difference in respect to the mean body height, BMI, prevalence of HT, and mean values of LDL-C, HDL-C, and TG between the urolithiasis cases and cases without urolithiasis (*p>0.05 for all*).

Discussion

Despite the high incidence of urolithiasis in the society, the exact underlying pathology is unkonown. This gap in the knowledge on the underlying etiology of urolithiasis should be filled up.. There are only some reports of systemic illnesses with an increased risk of urolithiasis in the literature. For example, patients with chronic diarrheal illnesses such as ulcerative colitis and Crohn's disease can develop enteric hyperoxaluria, which results in an increased risk of renal stones (7). It is often thought that oxalate is the primary problem in these patients, since excess oxalate is absorbed through the inflamed bowel wall. Similarly, low-grade inflammation induced increased absorption of oxalate may be the development mechanism of the urolithiasis in irritable bowel syndrome (IBS), since it was shown in a previous study by us that there is a significant association between urolithiasis and IBS in general population (2). Although indirectly, increased oxalate absorption induced urolithiasis has also been shown previously (8,9). In the previous study, we additionally compared the IBS and urolithiasis groups according to

hyperuricemia and obesity, but the differences were insignificant (2).

Recent studies have revealed that adipose tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin, which are closely related to the development of complications (10, 11). For example, the cardiovascular field has recently shown great interest in the role of inflammation in the development of atherosclerosis, and numerous recent epidemiological studies have indicated that inflammation plays an important role in the pathogenesis of atherosclerosis and thrombosis (12–14). Obesity is considered as a strong factor for controlling of the circulating CRP concentrations, because adipose tissue is involved in the regulation of cytokines (15). On the other hand, individuals with excess weight will have an increased circulating blood volume as well as an increased volume of cardiac output, thought to be the result of increased oxygen demand of the extra body tissue. The prolonged increase in circulating blood volume can lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of HT. The relationship between the excess weight and HT is also described under the heading of the metabolic syndrome. In addition to the HT, the prevalence of high FPG, high serum total cholesterol, and low HDL-C, and their clustering were all raised with increases in BMI (16). Combination of these cardiovascular risk factors will eventually lead to an increase in left ventricular stroke work with a higher risk of arrhythmias, cardiac failure, or even sudden cardiac death. So the above prospective cohort study showed that the BMI is one of the independent risk factors for stroke and coronary heart disease (CHD) (16). Similarly, the incidences of CHD and stroke, especially ischemic stroke, have increased with an elevated BMI in other studies (17). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increases throughout the range of moderate and severe excess weight both for men and women in all age groups (18). Although the already known several terrible effects of excess weight on physical health, we could not detect any association between urolithiasis and excess weight in the study, even cases with urolithiasis had a significantly lower mean body weight (*p: 0.013*). Although BMI is probably a more valuable parameter to show the weight status of individuals, as shown in a previous study by us body weight alone has also a significant importance (19). Similarly, authors in the Adult Treatment Panel III reported (4) that most of the cases classified as overweight due to their larger muscular mass actually have excess body fat, and both overweight and obesity do not only predispose to CHD, stroke, and numerous other conditions, they also have a high burden of other risk factors for CHD including dyslipidemia, type 2 DM, and HT. Similarly, the differences between the normal weight and overweight groups according to the increasing prevalences of DM, HT, and dyslipidemia were highly significant in the study (*p*<0.05 for all) (19). Additionally, when we compared the underweight, normal weight, and overweight cases with a mean age of 24 years, there was a significantly decreased prevalence of sustained normotension against a significantly increased prevalence of white coat hypertension in another study, despite the very low mean age of them, as a probable indicator of effect of body mass on blood pressure (20). As a similar result to ours, increasing weight showed a significant increase in prevalence of HT in a linear relationship in another study (21). Although the already known association between excess weight and type 2 DM, the highly significant association of urolithiasis with type 2 DM even in the absence of excess weight in the study must be explained.

There may be several mechanisms increasing the incidence of urolithiasis in DM. First of all, chronic hyperglycemia may cause a chronic low-grade inflammation in gastrointestinal epithelium by disturbing the normal balance between intestinal flora and circulatory defence mechanisms. The low-grade inflammation induced increased absorption of oxalate, as seen in chronic diarrheal illnesses, may be the development mechanism of urolithiasis in DM. Autonomic neuropathy induced motility disorders may aggravate this instability, since diarrheal fluid losses induced low urinary pH and citrate levels increase urinary CaOx and uric acid supersaturations, because citrate may inhibit calcium crystallization by binding to it. Even gastrointestinal and urinary tracts' epithelial edema, developed secondary to diabetic nephropathy induced hypoalbuminemia, may aggravate the absorptional and secretory instabilities. Secondly, chronic hyperglycemia may disturb both gastrointestinal and urinary tracts' epithelial functions for absorption and excretions of elements, so facilitating directly a stone or just a nidus formation for stone. Even glycosuria induced electrolyte imbalance in urine may facilitate urolithiasis. Thirdly, immunosuppression secondary to DM and chronic glycosuria induced urinary tract infections may cause urolithiasis, since some types of bacteria can provoke urinary supersaturation and modify the environment, thus leading to formation of crystal deposits that may be a factor promoting urolithiasis. In fact, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme, urease. Lastly, diabetic nephropathy induced glomerular dysfunctions may alter urinary content, facilitating urolithiasis. So there probably are hundreds of mechanisms with variable priorities for urolithiasis in DM, and the result of the study should not be surprising for us.

As a conclusion, despite several terrible effects of excess weight on health, we could not detect any association with urolithiasis, but there is a highly significant association between urolithiasis and type 2 DM, and it may have hundreds of mechanisms with variable priorities, which must be explained with further studies.

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