Estimation of urinary citrate , calcium and PH levels in diabetic patients and the risk of urinary stone formation in correlation with type of disease

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Abstract

Objectives : This study designed to evaluate urinary value of calcium , citrate , and the PH then assess the relation between urinary calcium and citrate with fasting blood sugar and evaluate the risk of renal stones in diabetes patients dependent of their type (type 1 and type 2) .

Patients and methods : Fifty four diabetic patients selected with no history of hypertension, no heart disease , and no other disease or smoking. Fasting blood and 24 hour urine samples were collected to evaluate fasting blood sugar, urine calcium, urine citrate , and urine PH.

Results: 30 male (55.6 %) and 24 women (44.4%) in a total of 54 patients with diabetes mellitus, aged between 20-65 years. The statistic results of DM type are 25(46.3 %) with type 1 and 29 (53.7 %) with type 2. F.B.S increased (11.79 ± 4.66 mmol/l) significantly ($P < 0.01$) as compared to healthy individuals (4.5 ± 0.98 mmol/l). Urine calcium significantly elevated in DM patients (6.184 ± 1.67 mmol/day) . Urine citrate significantly decreased (0.47 ± 0.57 mmol/day) comparing with healthy individual (2.22 ± 0.55 mmol/day). Urine PH (4.46 ± 0.50) significantly ($P < 0.05$) lower than control (6.16 ± 0.38). There are a positive correlation between F.B.S and urine calcium for all patients but there are adverse correlation with urinary citrate . There are no significant differences ($P > 0.05$) in FBS and urine calcium between DM types except in urine citrate ($P < 0.01$), and urine PH ($P < 0.05$) significantly decreased in type 2.

Conclusion: Findings from this study suggest that poor control of diabetes result in increased the risk of urinary stone by causing hypercalciuria, hypocitruturia, and urine acidity . Urine citrate concentration and PH level are more sensitive to the metabolic changes

in diabetic patients and correlated with type of disease, their levels in type 2 diabetic patients are significantly lower than type 1, so both types of diabetes have relative risk of prevalent stone disease but type 2 diabetic patients predisposes to calcium Urolithiasis more than type 1.

تقدير مستوى الستريت والكالسيوم والدالة الحامضية في إدرار مرضى السكري ومدى علاقة خطورة تكون حصى الكلى بنوع مرض السكري

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الخلاصة

الاهداف :صممت الدراسة الحالية لقياس تركيز كلا من الكالسيوم والستريت ودالة الحامضية في ادرار مرضى السكري وكذلك تقدير مدى العلاقة بين مستوى الكالسيوم والستريت في الادرار مع مستوى سكر الدم لمعرفة اي النوعين (النوع الاول والنوع الثاني) لمرضى السكري اكثر عرضة لتكويتن حصى الكلى.

طريقة العمل :جمع حوالي 54مريض مصاب بداء السكري لايعاني من امراض ارتفاع ضغط الدم اوامراض قلب او اي امراض اخرى وكذلك غير مدخنين. جمعت نماذج الدم والإدرار بعد الصيام ثم تم قياس مستوى سكر الدم وتركيز الكالسيوم والستريت و دالة الحامضية في الادرار.

النتائج :30 رجل (55,6 %) و 24 امراءة (44,4%) من مجموع 54 مريض تتراوح أعمارهم بين 20 -65 سنة . نتائج التحليل الاحصائي لنوع مرض السكري كانت 25 (46.3%) مصاب بداء السكري النوع الاول و29(53.7%) مصاب بالنوع الثاني . الزيادة في تركيز سكر الدم الصيامي (66 . 11.79±4 ملي مول / لتر) كانت ملحوظة($P < 0.01$)مقارنة بالأشخاص الأصحاء (8 9 . ±0 4.5) . كالسيوم الادرار(1.67 ± 6.184 ملي مول / اليوم) ارتفع ايضا بشكل ملحوظ مقارنتا بالأشخاص الأصحاء($P < 0.01$) بينما لوحظ انخفاض في مستوى ستريت الادرار (0.57 ± 0.47 ملي مول / اليوم) ($P < 0.01$) . الدالة الحامضية انخفضت(0.50 ± 4.46) بشكل ملحوظ ($P < 0.05$) مقارنة بالأشخاص الأصحاء (0.38 ± 6.16). توجد علاقة اطردية بين فرط السكر ومستوى كالسيوم الإدرار ($P < 0.01$) بينما العلاقة عكسية بين فرط السكر وستريت الادرار($P < 0.01$) . كما لوحظ عدم وجود فروقات في مستوى سكر الدم الصيامي وكالسيوم الادرار بين النوع الاول والثاني لمرضى السكري($P > 0.05$) ماعدا ستريت الادرار والدالة الحامضية , حيث قدر انخفاظ ملحوظ في مستوى ستريت($P < 0.01$) والدالة الحامضية ($P < 0.05$) في ادرار مرضى السكري من النوع الثاني مقارنة بالنوع الاول

الاستنتاجات :

من النتائج السابقة نستنتج ان فرط السكر الغير مسيطر عليه يزيد من احتمالية تكون الحصى نتيجة لزيادة مستوى كالسيوم وانخفاض مستوى الستريت والدالة الحامضية في الإدرار. ستريت الإدرار والدالة الحامضية اكثر تاثرا بالتغيرات الايضية لمرضى السكري وبنوع مرض السكري حيث انخفضت مستوياتها بشكل ملحوظ لدى مرضى السكري من النوع الثاني , وعليه فان كلا نوعي مرض السكري عرضة لخطورة تكون حصى الكالسيوم لكن النوع الثاني اكثر خطورة .

الكلمة مفتاح : نوع مرض السكري ,حصى الكلى ,كالسيوم الإدرار , ستريت الإدرار, الدالة الحامضية .

Key word : Diabetes mellitus type, Renal stones, Urine calcium, Urine citrate and Urine Ph

Introduction

Diabetes mellitus (DM) is a complex endocrine metabolic disorder associated with hyperglycemia which, commonly leads to alterations in the functions of several organs in the human body such as kidneys, eyes, nerves, gastrointestinal, hepatobiliary organs[1-3] .

Diabetes is due to either the pancreas not producing enough insulin (type 1), or because cells of the body do not respond properly to the insulin that is produced (type 2) [4]

kidney stone formatted as a result of an imbalance between urinary-promoting and inhibiting factors (as in table 1). The substances that can be modified in practice at this time are citrate as an inhibiter , calcium , and PH as an promoters [5,6]. Diabetes has also been associated with endogenous oxalate synthesis, which is a mechanism of stone formation [7,8].

Table 1 : Urinary-promoting and inhibiting factors.

Promoting factors	Inhibiting factors
Calcium	**Inorganic**
Sodium	Citrate
Oxalate	Magnesium
Urate	Pyrophosphate
Cystine	**Organic**
Low urine pH	Tamm-Horsfall protein
Tamm-Horsfall protein	Urinary Prothrombin fragment 1
Low urine flow	Protease inhibitor: inter α inhibitor
	Glycosaminoglycans
	Osteopontin (Uropontin)
	Renal lithostathine
	Other Bikunin, Calgranulin
	High urine flow

Citrate, is a tricarboxylic acid, synthesized in mitochondria from oxaloacetate and acetyl-CoA by the enzyme citrate synthase[5,6]. When citrate present in urine forms soluble complexes with calcium leading to decrease the super saturation of calcium oxalate and calcium phosphate. In many studies involving patients with urinary tract stone disease the excretion of citrate is significantly low [9].

Calcium is a versatile intracellular messenger that is used throughout the life cycle of an organism to control diverse biological processes [10]. It has been suggested that diabetes is linked by a common defect of divalent cation metabolism, including calcium [11].

Calcium is important for insulin mediated intracellular processes in insulin responsive tissues such as adipose tissue and skeletal muscle with a very narrow range necessary for optimal insulin action because it's necessary for insulin receptor phosphorylation and proper signal transduction and thus optimal GLUT-4 transporter activity [12]. Diabetes mellitus is associated with a decrease in bone mineral content and increased urinary excretion of calcium and phosphate [13].

Defects in urinary acidification (excretion of inappropriately alkaline or acidic urines, respectively) contribute to kidney stone disease [14], so urine pH is an important factor in the production of kidney stones such as: uric acid, cystine, and calcium oxalate stones, which are tend to form in acidic urine, whereas struvite (magnesium ammonium phosphate) and calcium phosphate stones form in alkaline urine [15]

Several studies have evaluated urinary citrate levels in patients with urolithiasis and in normal individuals. The results have been conflicting; some have shown low urinary citrate output in stone formers as compared to controls [16-18], while other studies have shown no difference [19-21].

Also there is little data available on the relationship between fasting blood glucose , urine calcium and urine citrate in diabetes mellitus , on other hands a few studies were fond that type 1, related with the presence of renal stone more than type 2. This finding was in contrast with other findings which suggested that insulin resistance was a risk factor of renal stone [22,23].

So this study are design to estimate urinary value of calcium , citrate , and the PH then assess their relation with fasting blood sugar (F.B.S) level and type of diabetes mellitus disease to evaluate the most probability of calcium stones formation in diabetes patients dependent of their type (type 1 and type 2) .

Patients and methods

Fifty four diabetic patients selected with no history of hypertension, no heart disease , and no other disease or smoking. Fasting blood and 24 hour urine samples were collected to evaluate fasting blood sugar, urine calcium, urine citrate , and urine PH. The parameters analyzed dependent to standard methods [24-27] .

Statistical analysis

The data for biochemical analysis was subjected to standard statistical analysis using the Statistical Package for Social Science (SPSS) version 19 , through using independent sample t test for comparing between data base of diabetes patients and the correlation between parameters we used biveriate pearson, finally figures or curves done by using curve estimation options .

Results

Data descriptive of fifty four diabetes mellitus patients are presented in table 2, which show that patients consists of 30 male (55.6 %) and 24 women (44.4%) in a total of 54 patients with diabetes mellitus, aged between 20-65 years . The statistic results of DM type are 25(46.3 %) with type 1 and 29 (53.7 %) with type 2.

Table 2: Data descriptive of fifty four diabetes mellitus patients.

Characteristic of patients	Number (%)
Gender *Male *Female	 30(55.6 %) 24(44.4 %)
Age ,yr	20-65 yr
DM type *Type 1 *Type 2	 25 (46.3 %) 39 (53.7%)

In table 3, we can show values of F.B.S, urine calcium, urine citrate and urine PH for fifty healthy subjects and fifty four diabetic patients. F.B.S concentration (11.79 ± 4.66 mmol/l) increased significantly ($P < 0.01$) as compared to healthy individuals (4.5 ± 0.98 mmol/l).

Also urine calcium significantly elevated ($P< 0.01$) in diabetic patients (6.184 ± 1.67) the results were in the upper limit of normal range (2.5 - 6.2 mmol / day) [25].

Urine citrate significantly ($P< 0.01$) decreased (0.47 ± 0.57) comparing with healthy individuals (2.22 ± 0.55), The mean urinary citrate excretion is (3.34 mmol/l) 640 mg/d in

healthy individuals [28]. Finally urine PH (4.46 ± 0.50) is significantly ($P < 0.05$) lower than control (6.16 ± 0.38).

Table 3: The values of F.B.S, Urine Calcium, Urine Citrate, and urine PH for healthy subjects and diabetic patients .

Urine Parameters	Healthy individual (n=50)	Diabetic patients (n=54)
Fasting Blood Sugar (mmol/L)	4.5 ± 0.98 [a]	11.79 ± 4.66 [b*]
Urine Calcium (mmol/ day)	4.11 ± 0.88 [a]	6.18 ± 1.67 [b*]
Urine Citrate (mmol/ day)	2.22 ± 0.55 [a]	0.47 ± 0.57 [b*]
Urine PH	6.16 ± 0.38 [a]	4.46 ± 0.50 [b**]

***Each value represents mean ± SD values with non identical superscript (a , b or c …etc.) were considered significantly different ($P \leq 0.01$), ** significantly different ($P \leq 0.05$).**

The correlation between F.B.S and urinary calcium can be shown in figure 1, there are a positive correlation between F.B.S and urine calcium for all patients. but figure 2 shows adverse correlation between F.B.S. and urine citrate.

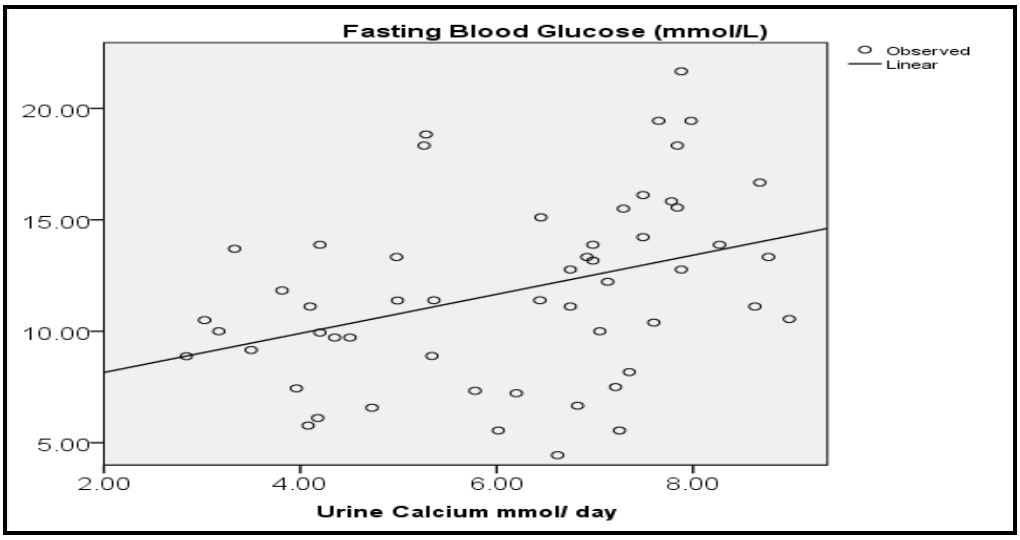

Figure 1 : The correlation between F.B.S and urine calcium.

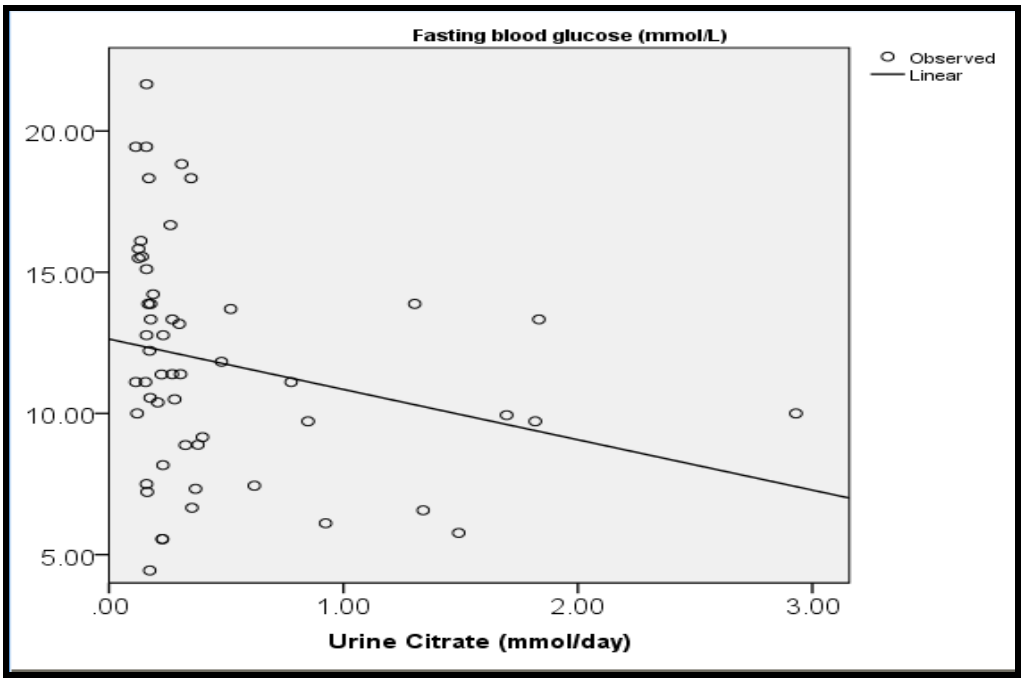

Figure 2: The correlation between F.B.S. and urine citrate.

The comparing results for all parameters between both diabetes patients type are presented in table 4. There are no significant differences ($P > 0.05$) in FBS and urine calcium except in urine citrate ($P < 0.01$), and urine PH ($P < 0.05$) significantly decreased in type 2.

Table 4: The relation between diabetic type and the value of F.B.S, urine calcium, urine citrate and PH for diabetic patients.

Parameters	DM type 1 (n=25)	DM type 2 (n= 29)
F.B.S	11.185 ± 3.76[a]	12.31 ± 4.3 [a]
Urine calcium	5.99 ± 1.83 [a]	6.27 ± 1.64 [a]
Urine citrate	0.61 ± 0.72 [a]	0.35 ± 0.36 [b*]
Urine PH	5.0 ± 0.71 [a]	4.12 ± 0.44 [b**]

***Each value represents mean ± SD values with non identical superscript (a , b or c …etc.) were considered significantly different (P <0.01) , ** significantly different (P < 0.05).**

Discussion

Both types of diabetic patients have increasing with no significant differences in urine calcium concentration and its concentration increased with the increasing of fasting blood glucose level. But its level in the upper limit of normal range (2.5 - 6.2 mmol / day). In this state patients will be under risk of hypercalciuria and the precise cause of this, that uncontrolled blood glucose may be stimulate parathyroid hormone, leading to reduce the tubular reabsorption of calcium , increase urinary losses of calcium and finally the negative calcium balance in body [29-31].

The positive relation between blood glucose and urine calcium (figure 1) provide a direct evidence of a rise in cytosolic free calcium concentration depends on glucose metabolism and is a primary signal for insulin secretion[32-35] , so the severity of stone formation increased with hyperglycemia degree and to the low blood glucose control, which might contribute in addition of stone also to the development of osteopenia [36].

In fifty four diabetic mellitus patients urine citrate significantly decreased ($P< 0.01$) but adversely related with fasting blood glucose level, and on other hand, its concentration in patients with type 2 is significantly lower than type 1($P<0.01$) .

Hypocitraturia, defined as urinary citrate excretion less than 1.67 mmol (320 mg) per day for adults, is a common metabolic abnormality in stone formers, occurring in 20% to 60%.[37]

Modulation of citrate excretion in the kidney is influenced by multiple factors; however, pH (systemic, tubular, and intracellular) has the strongest impact [38]. Although the majority of patients have idiopathic hypocitraturia, there are a number of causes for this abnormality, including distal renal tubular acidosis, hypokalemia, bowel dysfunction, a high-protein, and low-alkali diet. Other factors associated with altered citrate excretion include genetic factors , certain drugs, renal insufficiency, hyperaldosteronism, type I glycogen storage disease, and exercise [39].

Management of hypocitruturia by high fluid and citrus fruit intake, normal calcium consumption, and restriction of sodium, oxalate, animal protein, and fructose intake. The administration of citrate preparations or other alkali has been demonstrated to benefit hypocitraturic stone formers. Although many forms of citrate have been used for these patients (potassium citrate, sodium citrate, potassium-magnesium-citrate), potassium citrate has emerged as the most beneficial [40].

Patients who either cannot tolerate or cannot afford potassium citrate may benefit from consuming citrus juices, which contain significant amounts of citrate [39,41]. Most of the orally ingested citrate gets converted to bicarbonate conferring alkali load which may result in increased urine-pH depending concomitant acid load. Despite being richer in citrate, lime,

lemon or lemonade generally do not increase urinary pH (0.1 point increase) presumably due to acidic nature, whereas orange juice does by 0.6-0.8 points, similar to potassium-citrate (K-cit)][42,43]

Another finding of this study was that , the urine acidity increased significantly ($P<0.05$) in diabetes patients, and especially in patients with type 2 . Insulin therapy may modify urine pH independent of glycemic control [44], but Insulin resistance may reduce ammonium excretion by the proximal tubule, where high luminal calcium concentrations stimulate urinary acidification and reduce urinary concentration via a calcium-sensing receptor, resulting in the excretion of acidic and diluted urine [14].

Finally we can concluded that, poorly controlled of hyperglycemia increased the risk of urinary stone by increasing hypercalciuria, hypocitruturia, and urine acidity . Urine citrate concentration and PH level are more sensitive to the metabolic changes in diabetes patients and correlated with type of disease, their levels in type 2 are significantly lower than type 1, so both diabetes patients have relative risk of prevalent stone disease but type 2 diabetic patients predisposes to calcium Urolithiasis more than type 1. These findings may be helpful in further elucidating the etiology of urolithiasis. and assessment provide information about stone-forming factors that can guide prevention in diabetes mellitus patients..

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