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Association Between Adiponectin and Insulin Resistance in Diabetic Urolithiasis

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ABSTRACT

Objectives: The prevalence of urolithiasis is increasing worldwide. Diabetes mellitus (DM) is characterized by insulin resistance, which increases the risk of kidney stone formation. Adiponectin is an insulin-sensitizing and anti-inflammatory cytokine, which is known to improve glucose tolerance and insulin resistance in humans. The association of insulin and adiponectin with kidney stones is not clear. Hence, the present study aim to assess the serum levels of adiponectin and insulin resistance in DM patients with urolithiasis in comparison to those without. ***Methods***: This study involved two groups, group A consisted of 30 patients with DM and urolithiasis, and group B consisted of 30 patients with DM but without urolithiasis (control group). Biochemical parameters studied were serum adiponectin, insulin, glucose, urea, creatinine, and 24 hours urinary calcium and phosphate. ***Results:*** The serum adiponectin level was significantly increased in the diabetic urolithiasis cases (group A) compared to the control group (group B). The levels of 24 hours urine calcium and phosphorus were also significantly increased in group A. There was no significant difference in serum insulin and homeostasis model assessment of insulin resistance between the two groups. A negative correlation was seen between serum adiponectin and insulin among the cases ($r = -0.368$ and $p = 0.045$). ***Conclusions:*** We found that serum adiponectin levels are increased in patients with DM and urolithiasis.

The worldwide prevalence of urolithiasis is increasing since the last quarter of the 20th century.[1] Several reasons have been attributed to this increased prevalence, the predominant being metabolic disturbances such as diabetes mellitus (DM). DM is characterized by insulin resistance, which may increase the risk of kidney stone formation.[2] Several mechanisms by which DM can predispose to stone formation were studied by previous investigators including the DM induced oxidative stress.[3,4]

Insulin resistance causes a defect in ammonia production and acid excretion. A defect in renal acid excretion results in hypocitraturia, an important risk factor for calcium nephrolithiasis. It also leads to low urine pH, which favors the production of uric acid stones.[5,6]

Diabetes induced oxidative stress is being investigated as other causative agent for development of urolithiasis. Hyperinsulinemia caused by insulin resistance may lead to the formation of calcium stones by increasing the urinary excretion of calcium.[3]

Adiponectin, a protein secreted from adipose tissue, is an insulin-sensitizing, anti-inflammatory, and vasculoprotective cytokine which has been shown to improve glucose tolerance and insulin resistance in humans.[7] It was demonstrated by previous reports that adiponectin protects against the development of kidney stones.[3,8] Obesity was shown to have associated with lower adiponectin in earlier studies along with high rate of urolithiasis, due to changes in the composition of urine favouring stone formation.[9–12] Even though the prevalence of kidney stones is increasing in DM, the mechanisms that link the two morbidities were not fully explored till now. Hence, the present study was designed to assess the serum levels of adiponectin and insulin resistance in DM patients with urolithiasis in comparison to those without.

METHODS

This case control study was conducted in the Department of Biochemistry, Jawaharlal Institute

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of Postgraduate Medical Education and Research (JIPMER), Puducherry, in collaboration with the Department of Urology, JIPMER, during 2013–2014. Ethical approval was obtained from the Institute Ethics Committee (no. IEC/SC/2012/4/103). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and written informed consent was obtained from all the study subjects.

Sample size was calculated with an expected difference in mean adiponectin levels between the cases and control, 3 µg/mL with standard deviation (SD) of 3.5 µg/mL at 5% level of significance and 80% power.[10] The minimum sample size required for the study was estimated as 30 patients in each group, using the Power and Sample Size Calculator version 3.0.

The subjects recruited for the study were categorized into two groups. Group A (n = 30) included all cases of urolithiasis diagnosed on the basis of ultrasonography/computed tomography/X-ray who presented with diabetes. Group B (n = 30), the control group, included DM patients without urolithiasis who were matched for age and gender with the first group. The patients were on treatment with oral hypoglycemic drugs for a period of five to 10 years. Patients with obstructive uropathy, ureteric colic, renal failure, inflammatory and infectious diseases, malignancy, and ischemic heart disease were excluded from the study. Diabetic patients taking insulin were also excluded.

After obtaining written informed consent, clinical and anthropometric parameters of the study subjects were recorded. A 5 mL of blood was drawn from the antecubital vein after 12 hours fasting and was processed for biochemical analysis.

Routine parameters like fasting blood glucose level, urea, and creatinine were estimated immediately. Serum was separated and stored at -80 ^{0}C for further analysis of other biochemical parameters. Insulin and adiponectin levels were estimated using commercially available enzyme-linked immunosorbent assay kits. A 24-hour urine sample was also obtained from the subjects after proper instructions. Twenty-four hour urinary levels of calcium and phosphate were also estimated in an autoanalyzer using reagent kits.

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula:

$$\text{HOMA-IR} = \frac{\text{Fasting insulin (µIU/mL)} \times \text{Fasting glucose (mg/dL)}}{405}$$

Statistical analysis was performed using SPSS Statistics (SPSS Statistics Inc., Chicago, US) version 16. The results were expressed as mean ± SD and/or as median and range. The comparison of biochemical parameters between the study groups was carried out using independent Student t-test and Mann-Whitney U test for normal and non-normal distributed data, respectively. The correlation between insulin and adiponectin was tested by Pearson's correlation. A *p*-value of < 0.050 was considered statistically significant.

RESULTS

The study included 60 patients and the patients were divided into two groups. Group A consisted of DM patients with urolithiasis (n = 30), and group B as the control group with DM patients without urolithiasis (n = 30).

The serum adiponectin levels in group A were significantly increased compared to the control

Table 1: Comparison of BMI and various serum parameters between groups A and B.

Parameters	Group A (n = 30)	Group B (n = 30)	*p*-value
Age, mean (SD), years	55.3 (8.9)	55.0 (9.1)	0.890
Gender			0.730
Male	18	19	
Female	12	11	
BMI, median (IQR), kg/m²	25.2 (23.4-28.5)	25.0 (22.7-26.0)	0.060
Glucose, mean (SD), mg/dL	130.2 (67.5)	122.2 (49.3)	0.602
Urea, mean (SD), mg/dL	25.0 (15.0-111.0)	25.5 (14.0-91.0)	0.767
Creatinine, mean (SD), mg/dL	1.1 (0.7-4.8)	1.1 (0.8-5.4)	0.519
Adiponectin, mean (SD), µg/mL	11.3 (4.0)	8.2 (3.8)	0.003*
Insulin, mean (SD), µIU/mL	25.5 (15.3)	19.8 (10.4)	0.093
HOMA-IR, mean (SD)	9.0 (8.9)	5.6 (3.3)	0.062

**Denotes statistically significant*
BMI: body mass index; SD: standard deviation; IQR: interquartile range; HOMA-IR: homeostasis model assessment of insulin resistance.

Table 2: Comparison of 24-hour urine parameters between groups A and B.

Parameters	Group A (n = 30)	Group B (n = 30)	*p*-value
Urine volume, mean (SD), mL	1480.0 (454.0)	1531.0 (415.8)	0.652
Calcium, mean (SD), mg/24h	247.8 (142.5)	182.2 (48.2)	0.022*
Phosphorus, mean (SD), mmol/24h	310.1 (305.0)	44.4 (20.8)	<0.001**

**Denotes p <0.050. **Denotes p < 0.001.*
SD: standard deviation.

group. However, no significant difference was seen in serum insulin, HOMA-IR, blood glucose, urea, and creatinine between the groups [Table 1].

Group A cases showed a significant ($p < 0.050$) increase in the levels of 24-hours urine sample calcium and phosphorous compared to the control group [Table 2].

In the present study, we obtained a negative correlation between adiponectin and insulin among the cases (r = -0.368, $p = 0.045$) [Figure 1]. The correlation between adiponectin and HOMA-IR was not statistically significant ($p = 0.077$).

DISCUSSION

The worldwide prevalence of metabolic syndrome is rising, and its presence has been linked with an increased risk of urolithiasis. Previous studies have shown that high body mass index (BMI) and HOMA-IR were associated with increased risk of symptomatic urolithiasis and recurrent stone formation.[2,13,14] In our study, we obtained a non-significant increase in BMI and HOMA-IR values in group A as compared to group B. The urinary levels of calcium and phosphorus were also significantly higher among the cases in our study. These findings are supported by previous studies and this has been attributed to increased excretion of stone promoters.[12,15]

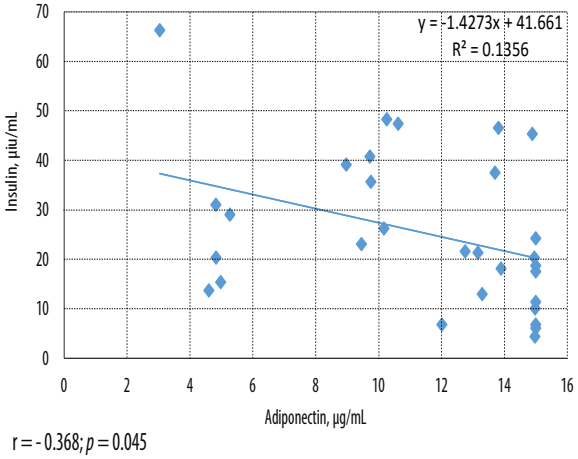

Figure 1: Scatter plot showing correlation of adiponectin with insulin in diabetes mellitus patients with urolithiasis.

Adiponectin has renoprotective, anti-atherosclerotic, anti-inflammatory, and antioxidative function.[16–19] In our study, patients in group A have a significantly higher serum adiponectin levels. The mechanism for the increased levels of adiponectin in group A patients compared to group B is unclear. A previous study shows that adiponectin has a renoprotective role by inhibiting inflammation and apoptosis.[8] Thus, the increase in adiponectin may be a compensatory mechanism for preventing further progression of urolithiasis and onset of its complications by improving insulin sensitivity. This might be the reason for trivial significant difference in the levels of insulin and HOMA-IR between the two groups in our study.

CONCLUSION

The serum adiponectin levels was increased in group A patients. However, future studies involving larger number of subjects are needed to confirm the protective role of high adiponectin against the disease progression.

Disclosure
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