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Original Article

Correlation of blood uric acid with urinary albumin creatinine ratio in hypertension and diabetic nephropathy

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ARTICLE INFO

Article history:
Received 9 July 2015
Accepted 22 July 2015
Available online 8 September 2015

Keywords:
Microvascular complication
Diabetic nephropathy
Renin angiotensin aldosterone system
Uric acid
Albumin creatinine ratio

ABSTRACT

Background: Diabetic nephropathy (DN) is a microvascular complication of Type 2 diabetes mellitus. Uric acid (UA) is the end product of purine nucleotide metabolism and its primary mode of clearance is by renal excretion. Modifiable factors such as blood pressure, albuminuria, glycemic control, etc., play an important role in the progression of DN and none of them are curative. Hence, there is a pressing interest to identify other potentially modifiable factors such as UA in the progression of DN.

Methods: The present case–control study included 180 subjects, categorized into three groups: Group I, Group II, and Group III. Anthropometric and biochemical parameters were analyzed by standard methods.

Results: The mean fasting blood sugar, HbA1c, serum creatinine, spot urine albumin, albumin creatinine ratio, and triglycerides were significantly higher in Group III than in Group I and Group II. In Group I, eGFR, spot urine creatinine, total cholesterol, HDL cholesterol, and LDL cholesterol were statistically significantly higher than in Group II and Group III. Pearson's correlation coefficient of UA with systolic, diastolic blood pressure, and albumin creatinine ratio in Group II and Group III showed positive correlation, and no significant difference was found.

Conclusion: UA induces endothelial dysfunction, leading to renal injury in DN. In our study, UA, blood pressure, and ACR did not show significant correlation. Future studies with huge sample size are necessary to evaluate UA and ACR as the genuine markers, which help clinicians to assess the kidney failure in diabetes with these routine biochemical markers.

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Abbreviations: SD, standard deviation; BMI, body mass index; OBI, obesity index; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; FI, fasting insulin; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; T2DM, type 2 diabetes mellitus; UA, uric acid; DN, diabetic nephropathy; RAAS, renin angiotensin aldosterone system; ESRD, end stage renal disease; MDRD, modification of diet in renal disease; VEGF, vascular endothelial growth factor; AGE, advanced glycation end products; TGF-β, transforming growth factor-β; NOS, nitrous oxide system.

http://dx.doi.org/10.1016/j.apme.2015.07.011

1. Introduction

Diabetes mellitus (DM), a group of chronic diseases, is characterized by hyperglycemia. Chronic hyperglycemia injures the human body in many ways. One of the chief injuries arising from hyperglycemia is injury to vasculature, which may be either a small vascular injury (microvascular disease) or injury to the large blood vessel of the body (macrovascular disease).[1] A large number of patients diagnosed each year with microvascular and macrovascular complications are attributed to type 2 diabetes mellitus (T2DM).[1] Nephropathy related to type 2 diabetes mellitus is one of the leading causes of end-stage renal disease (ESRD) and is associated with an increased risk of cardiovascular morbidity and mortality. Modifiable risk factors, such as arterial blood pressure, albuminuria, glycemic control, lipid control, and various inhibitors of the renin angiotensin aldosterone system (RAAS) play an important role in the progression of diabetic nephropathy (DN) and it is believed that none of them are curative.[2] Hence, there is a pressing interest to identify other potentially modifiable factors in the progression of DN.

Uric acid (UA), the final product of endogenous and dietary purine nucleotide metabolism, is formed by conversion of xanthine into hypoxanthine, which is catalyzed by enzyme xanthine oxidase. UA is a weak acid with a pK_a of 5.75. In the extracellular compartment at physiological pH of 7.4, 98% of UA is in the ionized form as urate. In the collecting tubules of the kidneys, where the pH can fall to 5.0, UA formation is favored. Renal excretion of UA involves mainly 4 pathways: filtration, reabsorption, secretion, and post-secretory reabsorption. Urate is freely filtered at the glomerulus. An active anion-exchange process in the early proximal convoluted tubule reabsorbs most of it. Most urinary UA appears to be derived from tubular secretion, possibly from the S2 segment of the proximal tubule. Overall, 98–100% of filtered urate is reabsorbed; 6–10% is secreted, ultimately appearing in the final urine. Studies conducted by Tseng et al., reported that increased serum UA levels induces endothelial dysfunction, glomerular hypertension, renal hypertrophy, and decrease renal perfusion leading to kidney injury.[3–5] Studies done by Fukui et al. and Khosla et al. on diabetic patients reported that hyperuricemia is associated with kidney damage, independent of hypertension.[6,7] On the other hand, higher levels of serum insulin may decrease UA clearance by the kidneys.[8] Therefore, diabetic patients are more prone to UA injury. This encouraged us to take up the study to find the association of serum UA levels with blood pressure and albumin creatinine ratio (ACR) in diabetes as well as DN subjects.

2. Objectives

1. Comparison of anthropometric and biochemical indices between clinically proven healthy controls (Group I), type 2 diabetes without nephropathy (Group II) and type 2 diabetes with nephropathy (Group III).
2. Correlation of serum UA levels with blood pressure and ACR in diabetes without nephropathy (Group II) and diabetes with nephropathy (Group III) subjects.

3. Materials and methods

A total of 180 subjects from the outpatient clinics of Medicine Department at Sri Devaraj Urs Medical College attached to Sri R.L. Jalappa Hospital, Kolar were included in this study. Informed consent was obtained from all the enrolled patients and Institutional ethical clearance was obtained to start the study. These subjects were grouped into three categories

Group I Fifty-nine clinically proven healthy controls.
Group II Sixty-three T2DM subjects without nephropathy.
Group III Fifty-eight DN subjects.

Type 2 diabetes Mellitus was diagnosed based on the World Health Organization criteria.[9] None of the patients had diabetic ketoacidosis at the onset of disease. All of them were being treated by anti-diabetic oral agents or insulin at the time of the study. For those receiving insulin treatment, insulin therapy had not been started in the first year of diagnosis of DM. Patients on treatment with UA lowering agents, or diuretics and patients with acute illness, fever, urinary tract infection, a glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 were excluded. Patients enrolled in the study were recommended not to have heavy exercise 24 hours before examination. Anthropometric measurements such as body height, weight, hip circumference (HC), waist circumference (WC), obesity index (OBI), and waist hip ratio (WHR) were measured and calculated respectively using standard methods. Body mass index (BMI) was calculated by Quetlet index formula.[10] Right arm's blood pressure was measured in sitting position using mercury sphygmomanometer. After 10 hours of overnight fasting, blood samples were collected and the parameters were estimated by the following methods: fasting blood sugar (FBS) by glucose-oxidase method,[11] serum UA, total cholesterol, high-density lipoproteins, triglycerides, and urine creatinine were measured by an enzymatic methods,[12,13] these variables were analyzed using Johnson & Johnson Vitros-250 dry chemistry Autoanalyzer which works on the principle reflectance Photometry. Fasting Insulin was done by chemiluminiscence[12] and HbA_1c by HPLC methods.[12] The low-density lipoproteins cholesterol (LDLC) and eGFR were calculated using Friedewald formula and modification of diet in renal disease (MDRD) formula, respectively.[14,15] Previous studies conducted and published from our institution did not find any significant difference in the estimated or calculated LDLC.[16] Thus, we calculated the LDLC after considering the limitations of the Friedewald formula. Albumin was measured by early morning urine sample by dipstick method and those with high values or detectable and suspected to be at risk, the microalbumin was estimated by using commercially available kit method and autoanalyser. Urinary albumin–creatinine ratio (ACR) was calculated by dividing the urinary albumin concentration in microgram by the urinary creatinine concentration in milligram. An ACR of 30.0 μg/mg or lower was considered as ''normal,'' an ACR between 30 μg/mg and 299 μg/mg was considered as ''microalbuminuria.'' Very high ratios (ACR ≥ 300 μg/mg) were defined as ''overt albuminuria''.[17]

The differences between the three groups were assessed using analysis of variance (ANOVA). The correlation between