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SHORT COMMUNICATION article

Uric acid and glucose metabolism in uncomplicated Libyan diabetic patients

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Abstract: Uric acid has increasingly been associated with insulin resistance, hyperinsulinemia, and type 2 diabetes mellitus. Diabetic patients who are hyperuricemic have a risk of developing diabetic complications. Pathogenesis of uric acid may decrease nitric oxide bioavailability in vascular smooth muscle, endothelial cells and direct scavenging of nitric oxide by uric acid. A decrease in endothelial nitric oxide production by uric acid has also been associated with endothelial dysfunction and insulin resistance. This study aims to determine the relationship between uric acid and glucose levels in patients with type 2 diabetes mellitus. The study included 161 Libyan patients (67 males and 94 females) diagnosed with type 2 diabetes mellitus. Both levels of serum uric acid and hemoglobin A1c (HbA1c) were determined. The patients were divided into two groups. The controllable diabetic group with HbA1c of less than 06.0% and the uncontrollable diabetic group with HbA1c of more than 06.0%. Patients who are suffering from type 2 diabetes mellitus without complications were included whereas patients with smoking, alcoholism, nephrotic disease, malignancy, hepatitis, and renal failure or kidney disease were excluded. The mean and standard deviation of uric acid, HbA1c and Pearson correlation coefficient test were considered. In the controllable diabetic group, serum uric acid mean was found to be 4.807±1.39 and HbA1c was found to be 5.032±1.39. In the uncontrollable diabetic group, serum uric acid was 4.897±1.66 and HbA1c was 8.396±1.65. Uric acid level has significantly been correlated with $HBA1_C$ in controlled and uncontrolled diabetic patients ($p<0.05$). In addition, the uric acid level was found to be higher in the uncontrolled diabetic group than that in the controlled group ($p<0.05$). A possible relationship between serum uric acid and the incidence of type 2 diabetes mellitus was noted. Thus, uric acid can be used as a potential biomarker to indicate impaired glucose metabolism.

Introduction

Diabetes mellitus refers specifically to a disease in which the ability to metabolize glucose is defective due either to the failure of the pancreas to produce insulin or to tissue resistance to insulin [1]. Type 2 diabetes mellitus (T2DM) the cause is a combination of resistance to insulin and inadequate compensatory insulin secretory response type 2, also called noninsulin-dependent diabetes mellitus (NIDDM), typically develops in

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adults over 40 years old. However, the demographic of this disease is changing, and it is becoming increasingly common in children and young adults [2]. It is far more common than IDDM, and its occurrence in the population is correlated with obesity [1, 3]. T2DM is a more complex metabolic disorder characterized by obesity, impaired β-cell function, increased endogenous hepatic glucose output, and insulin resistance in target tissues [3]. Insulin resistance leads to impaired suppression of hepatic glucose production and reduced peripheral uptake of glucose. Resistance to the ability of insulin to suppress very low-density lipoprotein cholesterol production leads to increased serum triacylglycerol, while resistance in adipose tissue impairs the ability of insulin to inhibit lipolysis, and results in increased circulating free fatty acids [4, 5]. Uric acid (UA) is the final oxidation product of purine degradation. UA is mainly derived from endogenous production and food intake with 70.0% being excreted by the kidney and the remainder being primarily eliminated by the intestine [6]. Serum urate is frequently elevated in patients with metabolic syndrome and increases with several components of this condition. Metabolic syndrome is characterized by the presence of hyperinsulinemia and an insulin-resistant state. Hyperinsulinemia is conjoint in subjects with asymptomatic hyperuricemia and individuals with diabetes or hypertension. One potential explanation is that hyperinsulinemia may cause hyperuricemia. Insulin acts on the proximal tubule to stimulate urate reabsorption coupled with sodium [7]. Fasting insulin levels inversely correlate with urinary UA clearance and are positively associated with serum uric acid (SUA) in healthy subjects [4]. High normal SUA was also associated with the future development of T2DM among lean healthy and normoglycemic women [5]. Increased hepatic glucose production is a distinguished feature of insulin resistance and T2DM. Intracellular UA stimulates adenosine monophosphate dehydrogenase and inhibits adenosine monophosphate protein kinase enzyme activity. Adenosine monophosphate dehydrogenase stimulates hepatic gluconeogenesis [8]. Thus, this study is aimed to determine the relationship between SUA levels and T2DM in Libyan patients.

Materials and methods

The target individuals who have T2DM for different periods. The diagnosis of diabetes was based on the previous history of diabetes based on the American Diabetes Association criteria 2006 ($HBA1_C$ ≥6.5%, or FPG level ≥126 mg/dl, or 2-hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test). This study included 161 Libyan diabetic patients (67 males and 94 females). The parameters analyzed were serum levels of UA and HbA1c. The individuals were divided into two groups. The controllable diabetic group was HbA1c at less than 6.0% and the uncontrollable diabetic group was HbA1c at more than 6.0%. Patients with smoking, alcoholism, nephrotic disease, malignancy, hepatitis, and renal failure or kidney disease were excluded from the study. Full automated COBAS INTEGRA 400 plus (ROCH, Germany) was used for estimating HbA1c and UA levels determined by Photometer 4040v5+. Guidelines of ethical approval and consent to participate in this study were followed. The study protocol was approved by the Libyan International Medical University ethics committee, in Benghazi, Libya. Data was analyzed for relationship by using the Pearson correlation coefficient test and $p<0.05$ was considered significant.

Results and discussion

The sample size of the study consists of 161 participants, 67 were males and 94 were females. The subjects were divided into two groups. The diabetic group controlled $HbA1_C$ whose $HbA1_C$ <06.5% were 16 patients among them 11 were females and five were males. The diabetic group with uncontrolled $HbA1_C$ whose $HbA1_C$ ≥6.0, 145 of 83 were females and 62 were males. **Table 1** shows the mean±standard deviation, correlation coefficient values, and probability value of $HBA1_C$ ≥6.0 and SUA levels. A significance of $p=0.031$ was found with a correlation of 0.59 between the two levels. In the present case-control study of 161 diabetic patients, UA levels have significantly been correlated with $HBA1_C$ in controlled and the uncontrolled diabetic patients

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(**Tables 1 and 2**). Moreover, considering the comparison between SUA in the controlled and the uncontrolled groups, the level of SUA was significantly higher in the uncontrolled diabetic group than its level in the controlled diabetic group (**Table 1)**. This finding is in line with the previously reported data in which hyperuricemia has been associated with T2DM [4, 9, 10]. Persons diagnosed with T2DM have shown a high UA level in their blood compared to people suffering from gout. This indicates that the condition of diabetes may have effects on the oxidation of purine nucleotides. However, the actual relationship between the two is not fully understood due to the complications of metabolic syndrome [10]. Hyperuricemia is usually the result of under-excretion of urate [6], and the renal clearance of urate was shown to be inversely related to the degree of insulin resistance [9]. Moreover, hyperinsulinemia may decrease UA clearance by the kidney [6, 8]. Indeed, Reaven [11] has attributed the presence of hyperuricemia in metabolic syndrome to a secondary response to hyperinsulinemia. The association has been attributed to the effects of insulin on proximal tubular urate reabsorption [4]. Insulin can also enhance renal tubular sodium reabsorption which in turn can reduce renal excretion of UA [5, 6]. Hidayat and others [12] have reported a fairly significant negative correlation between SUA, FBS, and HbA1c. T2DM is associated with oxidative stress where hyperglycemia can induce oxidative stress via glucose auto-oxidation and the subsequent formation of advanced glycation end products. Oxidative stress causes a reduction in the antioxidant status of the body. This may explain the reduction of SUA in that study as UA is regarded as one of the total antioxidant substances present in the body. Choi and Ford [13] in their study of Haemoglobin A1c, fasting glucose, serum C-peptide, and insulin resistance about SUA levels, observed that SUA levels and the frequency of hyperuricemia increased with moderately increasing levels of HbA1c and FPG and then decreased with further increasing levels of HbA1c (bell-shaped relation). A biological mechanism underlying the bell-shaped relation [12]. Between blood glucose level and SUA level is thought to be due to the uricosuric effect of glycosuria, which occurs when the blood glucose level is greater than 180 mg/dl. Higher insulin levels are known to reduce the renal excretion of urate [13]. Insulin may enhance renal urate reabsorption via stimulation of the urate-anion exchanger URAT1 and/or the sodium-dependent anion co-transporter in brush border membranes of the renal proximal tubule [6]. Previous studies showed UA as a pro-oxidant and a risk factor for diseases associated with oxidative stress as cardiovascular disease, hypertension, renal impairment, and T2DM and its complications [13]. Measurement of UA is easy in terms of analytics, can be performed with simple methods in routine laboratories, and is inexpensive. Thus, a preventive, cost-effective approach is available with potential implications for public health [14]. People with diabetes, men and women, are at an increased risk of developing complications of diabetes such as kidney disease, gout, and cardiovascular disease. However, due to the small sample size recruited in this study and the selection of the participants from Benghazi Diabetic Center which make it is hard to generalizability of the findings across Libya.

Table 1: Correlations of HBA1$_C$ ≥6 and uric acid

n=145	Mean±SD	R	P
HbA1c	8.396±1.65	0.59	0.031
Uric acid	4.897±1.66		

Table 2: Correlation of HBA1$_C$ <6 and uric acid

n=145	Mean±SD	R	P value
HbA1c	5.032±1.39	0.67	0.04
Uric acid	4.807±1.39		

Table 3: Uric acid in controlled and uncontrolled diabetic groups

Serum uric acid	n=161	Mean±SD	P value
SUA in controlled group (n=16)	16	4.807±1.39	0.033
SUA in uncontrolled group (n=145)	145	4.897±1.66	

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Conclusion: This finding concludes that uric acid plays a significant role in the etiopathogeneses of type 2 diabetes mellitus and it is a potential biomarker of glucose metabolism.

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Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

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