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Correlation Between Serum Uric Acid, Insulin and Hba1c In Type 2 Diabetes Mellitus

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Abstract

Objective: The study aims to determine the relation of serum uric acid levels, glycated haemoglobin A1c (HbA1c) and insulin levels in Type II Diabetes Mellitus as well as their role as potential disease predictors

Method: This cross-sectional study was conducted in the Department of General Medicine, Fauji Foundation Hospital, Rawalpindi (Jan-Jul 2020). A total of 160 adults with diagnosed type II diabetes mellitus were included. Blood reports of patients were analyzed for serum uric acid, HbA1c levels and insulin levels. The data was stratified into the following types of patient groups: a low & high HbA1c level group (<6.5% and >6.5% respectively), and a low & high insulin level group (with 25 mIU/L being the cut-off value) in male and female gender groups. Post-stratification relation was calculated. A p-value <0.05 was considered statistically significant.

Results: Among 160 patients, the mean age was 50.52+13.35 years; there were 59 (36.9%) males and 101(63.1 %) females. There was no significant correlation observed between serum uric acid levels and HbA1c levels concerning gender stratification, as well as, between serum uric acid and HbA1c levels at low & high insulin levels in type II diabetes mellitus.

Conclusion: The study concluded no positive relation between serum uric acid levels, glycated haemoglobin A1c as well as serum insulin levels in type II diabetes mellitus patients.

Keywords: Type II Diabetes Mellitus (DM-II). Glycated haemoglobin A1c, HbA1c, uric acid, Insulin.

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1. Introduction

Diabetes mellitus is the result of multiple chronic metabolic diseases among the population.[1] Hyperuricemia ranks as one of the highest risk factors for developing diabetes mellitus in the normal population.[2] Hyperinsulinemia is associated with hyperuricemia and hypouricosuria.[3] Type II diabetes mellitus is the result of a myriad of chronic metabolic disorders with multiple risk factors mentioned in increasing order of their incidence; hypertension, hypertriglyceridemia, hyperuremia, fatty liver, polycystic ovarian syndrome and abdominal obesity. Evidence indicates that hyperuricemia is an independent risk factor in patients with type II diabetes mellitus as it causes impairment of fasting glucose (IFG) level. Many authors have proposed serum uric acid levels as an indicator of glucometabolic diseases, especially diabetes.[4] The CARDIA study 2007 is a landmark trial that elucidated the impact of serum uric acid levels on multiple metabolic syndrome components over 10 years,[5] and its utility as an indicator of glucometabolic disease markers, especially diabetes. However, the literature on the relationship between serum uric acid level and glycated haemoglobin A1c in type II diabetes mellitus remains inconsistent, i.e. some studies suggest a positive relation whereas others suggest a negative relation. Hyperinsulinemia in itself is also interlinked with increased serum uric acid levels, whereas, glucose metabolism also causes hyperuricemia and hypouricosuria.[6,7]

Nevertheless, conflicting data exists on these relationships i.e. some studies suggest a linear relationship between serum uric acid & HbA1c levels whereas others suggest a bell-shaped curve such that in the pre-diabetic population an increase in blood glucose level is associated with a corresponding increase in serum uric acid levels whereas, in known type II diabetics the serum uric acid levels decrease with increasing blood glucose levels i.e. serum uric acid levels tend to fall after their initial rise.[8,9] However, an agreement exists on the fact that serum uric acid levels are directly related to serum insulin levels whereas, serum HbA1c levels are negatively associated with serum insulin levels in both males and females as evidenced by the 2016 study.[8] Given these contradictory findings over the years, this study was aimed at further investigating and reaching a liaison on potential significant relationships between serum levels of uric acid, HbA1c & insulin, in type II diabetes mellitus patients, within 1 year of diagnosis

and determining if these variables are useful as potential disease indicators.

2. Materials & Methods

This cross-sectional study was conducted in the Department of General Medicine, Fauji Foundation Hospital Rawalpindi from 16th Jan to 16th Jul 2020. Patients were selected by consecutive non-probability sampling. The sample size was calculated by the WHO calculator; with a confidence level of 95%, Pearson Correlation Coefficient of 0.368[5], and significance level of 5%. The *inclusion criteria* were patients with newly diagnosed (within the last 1 year) type II diabetes mellitus as per ADA criteria, 30 to 70 years of age, of both genders. The *exclusion criteria* were patients using uricosuric drugs or insulin therapy, those with impaired liver or kidney functions, type 1 diabetes mellitus, steroid-induced diabetes, endocrine disorders, gout, haematological malignancy and gestational diabetes. All 160 patients in this study were examined in detail by the researchers. Patients' blood reports were analyzed for serum uric acid, HbA1c and fasting insulin levels. Findings were recorded on a pre-designed proforma.

The data was entered and analyzed using SPSS version 23, a Computer software program. Qualitative variables like gender were measured in the form of percentages and frequencies. Means and Standard deviations were calculated for quantitative data like age, duration of type II diabetes mellitus, weight, serum uric acid levels, HbA1c levels and serum insulin levels. Pearson correlation tests were used to assess the relationship between serum uric acid & HbA1c, and serum uric acid & insulin levels. The data was stratified according to the following types of patient groups: a low and high HbA1c group (<6.5% and >6.5% respectively), a low and high insulin level group (with 25 mIU/L being the cut-off value) in male and female gender groups. Post stratification relation was calculated. A p-value less than 0.05 was considered statistically significant.

3. Results

A total of 160 patients were included. The mean age (years) in the study was 50.52±13.35 (30-70) years. There were 59 (36.9%) male and 101 (63.1%) female patients. The mean duration of type II diabetes mellitus patients was 6.56±1.63 (4-12) months. The mean serum uric acid was 7.11±0.74 (6.1-8.6) mg/dl. The mean hbA1c was

6.08±1.24 (range 4-8)%. The average serum insulin level among patients was 24.99±3.21 (20-30) mIU/L. As per our reference study, there was an inverse correlation (r=0.196, p-value 0.013) of serum uric acid & HbA1c levels in newly diagnosed type II diabetes mellitus patients based on their status of elevated blood insulin levels, whereas, no relation was noted at low insulin levels. [8] This result was not in line with our findings.

In our study, the effect modifier like gender stratification was compared with a correlation of serum uric acid and HbA1c levels in type II diabetes mellitus patients. Among male patients, there was a weak positive correlation (r=0.243, p-value 0.064) between serum uric acid levels and HbA1c levels, though the p-value being greater than 0.05 shows that this is not statistically significant. Also, an almost negligible relation (r=0.039, p-value 0.770) of serum uric acid levels and insulin levels was observed in males and the p-value indicates that this correlation is statistically insignificant also. Among female patients, the relation (r=0.173, p-value 0.084) of serum uric acid & HbA1c levels as well as serum uric acid & fasting insulin levels in type II diabetes mellitus (r=0.127, p-value 0.205) was noted, which was proven statistically insignificant. Hence concluding that serum uric acid levels are not strongly associated with either HbA1c or serum insulin levels for either gender. Effect modifiers like HbA1c (low/high) stratification were also compared with the relation of serum uric acid and HbA1c levels in type II diabetes mellitus patients. Among patients with low HbA1c, there was a weak positive yet statistically insignificant relation (r=0.125, p-value 0.217) of serum uric acid and HbA1c levels in type II diabetes mellitus as well as of serum uric acid and insulin (r=0.079, p-value 0.432). Among patients with high HbA1c, there was a very weak positive yet statistically insignificant relation (r=0.105, p-value 0.426) between serum uric acid and HbA1c levels as well as, between serum uric acid and fasting insulin levels (r=0.111, p-value 0.399). Effect modifier like insulin (low/high) stratification was compared concerning the relation of serum uric acid and HbA1c levels in type II diabetes mellitus patients. Among patients with low insulin levels, there was a weak positive yet statistically insignificant relation (r=0.184, p-value 0.073) of serum uric acid and HbA1c levels as well as of serum uric acid and insulin levels in type II diabetes mellitus patients (r=0.120, p-value 0.245). Among patients with high insulin levels, there was a very weak positive yet statistically insignificant relation (r=0.204, p-value 0.106) between serum uric acid and HbA1c levels, and also a very weak negative yet statistically insignificant correlation between serum uric acid and insulin levels (r=0.112, p-value 0.380) in type II diabetes mellitus patients.

Table 1: The demographic variables and laboratory values of HbA1c, uric acid and Fasting insulin levels in Type 2 DM cases (n=160)

Variable	Mean ± SD	Range
Age (years)	50.52±13.35	30-70
Duration of DM (months)	6.56±1.63	04-12
HbA1c (%)	6.08±1.24	04-08
Uric acid (mg/dl)	7.11±0.74	6.1-8.6
Fasting insulin level (mIU/L)	24.99±3.21	20-30

Table 2: Effect modifier Gender stratification with Correlation of Serum Uric Acid with HbA1c & Serum Fasting Insulin in Type-2 diabetes mellitus (n=160)

		Serum Uric Acid levels (mg/dL)	P-value
Male	HbA1c	r=0.243	0.064
	Serum Insulin level (mIU/L)	r=0.039	0.770
female	HbA1c	r=0.173	0.084
	Serum Insulin level (mIU/L)	r=0.127	0.205

Table 3: Effect modifier like HbA1c (low/high) stratification with Correlation between Serum Uric Acid & Serum Fasting Insulin in Type-2 DM (n=160)

		Serum Uric Acid levels (mg/dL)	P-value
low HbA1c	HbA1c	r=0.125	0.217
	Serum Insulin level (mIU/L)	r=0.079	0.432
high HbA1c	HbA1c	r=0.105	0.426
	Serum Insulin level (mIU/L)	r=0.111	0.399

Table 4: Effect modifier Insulin (low/high) stratification with Correlation of Serum Uric Acid with HbA1c & Serum Fasting Insulin in Type-2 diabetes mellitus (n=160)

		Serum Uric Acid levels (mg/dL)	P-value
low Insulin	HbA1c	r=0.184	0.073
	Serum Insulin level (mIU/L)	r=0.120	0.245
high Insulin	HbA1c	r=0.204	0.106
	Serum Insulin level (mIU/L)	r=-0.112	0.380

4. Discussion

A deeper look into the delicate interplay between the serum uric acid, glycated haemoglobin A1c (HbA1c) and insulin levels in type II diabetes mellitus patients brings to light the multifaceted nature of this metabolic disorder. Our study investigates the underlying relationships between serum uric acid, HbA1c & serum insulin levels and contributes to the growing body of research on this matter.

To begin with, our study results do not corroborate the previous research conducted on this conflicting topic. Previously, both positive and negative relationships were seen between serum uric acid levels and HbA1c in type 2 diabetes mellitus patients i.e. our reference study mentions an inverse correlation of HbA1c and uric acid in high insulin groups,[8] whereas, another study established a significant correlation of the two along with emphasizing that an increased serum uric acid levels can raise the chance of glucometabolic diseases and metabolic syndromes.[10] This relationship also accentuates the potential utility of serum uric acid levels as biomarkers of glucometabolic dysregulation.[11]

Given the conflicting literature on serum uric acid level and glycated hemoglobin A1c in type II diabetes mellitus a liaison was needed on the fact that whether serum uric acid levels were correlated with serum insulin levels or HbA1c levels in any way or not.

Our study delved into this enigma along with gender-specific variations. Our study population included patients with mean age (years) of 50.52+13.35 with the male and female distribution of 36.9% and 63.1% respectively with serum uric acid level of 7.11+0.74 (mg/dl), serum HbA1c level of 6.08+1.24 (%) and serum insulin levels of 24.99+3.21 (mIU/L). The effect of serum insulin on uric acid metabolism and glycosylated hemoglobin A1c levels at cellular levels has been explained individually such that in the state of hyperinsulinemia, the hexose phosphate shunt system is stimulated, which in turn promotes the conversion of purines; hence increasing the uricogenesis.[12,13] Interestingly, as per the findings of our study, no significant correlation was noted between either serum uric acid and insulin levels or HbA1c levels respectively. Furthermore, when data was interpreted at low and high HbA1c levels about serum insulin level and serum uric acid levels respectively, still it was non-significant. Probing deeper into our findings, when the relationship between serum uric acid and glycosylated haemoglobin A1c levels was examined by stratified analysis about low and high serum insulin levels, no significant relationship was seen. The closest correlation, to being statistically significant, was seen between serum uric acid and HbA1c levels in males and individuals with low insulin levels but neither of these met the 0.05 threshold and, hence were statistically insignificant. Simultaneously, increased insulin levels increase the renal reabsorption of uric acid by activating the anion

urate transporter in the proximal tubule membrane,[14] resulting in a rise in serum uric acid levels. Normally, high fasting insulin lowers blood glucose levels.[15] Hence, it explains the very weak negative correlation of serum uric acid and glycosylated haemoglobin A1c levels, once serum fasting insulin levels are high, given the potential insulin resistance associated with type II diabetes mellitus.[15,16] In conclusion, our study has been unable to establish any such relations directly which may elucidate these parameters as potential disease predictors, hence limiting their utility to being disease biomarkers only. Importantly, our study results were bounded due to the limited number of testing kits available, further limiting our study population too, but this highlights the need to further probe into the underlying physiological and biochemical mechanisms driving these relationships. Comprehensive longitudinal and mechanistic investigations applied on a larger sample size are also needed to provide insights into causative interlinking pathways of these variables, which may ultimately prove if any potential disease prediction could also be made based on these.

5. Conclusion

The study concluded no significant correlations between serum uric acid, insulin and HbA1c levels in type II diabetes mellitus patients. Therefore, these variables cannot be used as potential disease predictors but can only serve as disease biomarkers.

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