Original Article

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Biochemistry Section

Study on Association of Serum Uric Acid and Calcium with Insulin and its Resistance in Newly Diagnosed Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is a multifactorial pathological condition associated with insulin resistance and insulin deficiency. Uric acid and calcium have shown inconsistent association with occurrence of diabetes.

Aim: To evaluate the role of uric acid and calcium in development of T2DM.

Materials and Methods: This was a case-control study conducted in Department of Biochemistry from March to November 2019 in Sriram Chandra Bhanja, Medical College and Hospital, Cuttack, Odisha, India. A 180 subjects undertaken with the objective of finding any association of serum uric acid and calcium with insulin and its resistance in newly diagnosed T2DM cases. Newly diagnosed T2DM patients were taken as cases. Age and sex matched healthy individuals were taken as controls. Fasting Plasma Glucose (FPG), serum insulin, serum uric acid and ionised calcium were measured in autoanalyser and insulin resistance was calculated using Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Other confounding risk factors for T2DM like Body Mass Index (BMI), family history was taken into account.

Results: A significant positive correlation of serum uric acid with serum insulin (p=0.029) and its resistance (p=0.032) in cases. Serum calcium was negatively associated with insulin and its resistance in both cases and controls. Regression models showed serum uric acid as a strong independent risk factor for levels of insulin and its resistance.

Conclusion: The findings of the study showed that regular evaluation of serum uric acid and calcium should be done in those who are at risk of developing T2DM. Larger prospective studies will be required for definite assessment.

Keywords: Homeostasis model assessment for insulin resistance, Insulin deficiency, Obesity

INTRODUCTION

The colossal thrust of T2DM has raised concern worldwide and efforts to tackle it at its earliest have now become a crucial approach. T2DM is multifactorial and there has been considerable interest in identifying new factors that may lead to the disease. According to International Diabetes Federation (IDF), 463 million people in the world were suffering from DM in 2019 and about 77 million of those cases belonged to India. It is expected to increase 153 million by 2045 in South East Asia [1]. Uric acid, the primary end product of purine metabolism has been shown in studies to be elevated in T2DM, Hypertension and Metabolic Syndrome [2,3]. There is hypothesis suggestive of stimulatory effect of uric acid on pro-inflammatory markers like Interleukin-6 (IL-6), Tumour Necrosis Factor-α (TNF-α), Nuclear Factor Kappa β (NFK β) which results in defective insulin signalling. Elevated serum uric acid levels decrease Nitric Oxide (NO) production resulting in endothelial dysfunction and poor glucose uptake in peripheral tissues like skeletal muscle and adipocytes. There have also been studies showing apoptotic action of uric acid on beta cells of pancreas [4,5].

In contrast some cohort studies have not found any significant association between serum uric acid and insulin resistance [6,7]. The role of serum uric acid in development of frank T2DM is still not very clear.

Calcium is another mineral whose exact role in development of insulin resistance and T2DM has garnered attention in recent years. There are findings suggestive of impaired calcium homeostasis interfering with carbohydrate metabolism and insulin secretion [8]. Voltage-gated calcium channels in pancreatic beta cells under normal physiological conditions cause insulin exocytosis, but some studies have found that their downregulation is associated with T2DM and its over-regulation with death of beta cells [8].

The occurrence of diabetes is multifactorial. There are unknown factors in various geographic regions which may be driving this metabolic disease and these factors need to be explored. Studies on role of serum uric acid and ionised calcium with insulin resistance and development of T2DM are limited in Odisha, an eastern state of India. It is a state where carbohydrate rich diet remains the staple food. Studies done outside India have not proven anything conclusively. This study was undertaken to evaluate the association of serum uric acid and calcium levels with fasting serum insulin and its resistance in the newly diagnosed T2DM and compare it with apparently health controls.

MATERIALS AND METHODS

This was a case-control study conducted in Department of Biochemistry from March to November 2019 in collaboration with Departments of General Medicine and Community Medicine of Sriram Chandra Bhanja, Medical College and Hospital, Cuttack, Odisha, India. The study protocol was approved by the Institutional Ethics Committee (IEC) vide reference no 709/28.9.18. All study subjects gave their consent to get enrolled in this study.

Inclusion and Exclusion criteria: A 90 newly diagnosed patients of T2DM with no history of use of any oral hypoglycaemic agent or insulin in past were taken as cases. This was a time bound study and authors could only enroll a fixed number of participants which would make data collection and analysis feasible within the time period of study. Age and sex matched healthy volunteers who were not first degree relative of cases were taken as controls. Subjects with known history of any chronic disease and endocrine disorders,

autoimmune disease, cancer, gout, rheumatoid arthritis, drug abuse, smokers, active hepatitis were excluded from the study.

T2DM was diagnosed according to American Diabetes Association (ADA) criteria (Fasting blood glucose level ≥126 mg/dL (7.0 mmol/L), or two hours postprandial blood glucose level ≥200 mg/dL (11.1 mmol/L), or Oral Glucose Tolerance Test (OGTT) after a dose of 75 gm of glucose, or HbA1c ≥6.5%) [9]. A detailed history of all subjects was taken.

Study Procedure

A 5 mL of fasting venous blood was collected for estimating plasma glucose, serum insulin, uric acid and ionised calcium. Plasma glucose was estimated by glucose oxidase-peroxidase method, serum uric acid by uricase method and serum insulin by chemiluminescence assay adapted to autoanalyser (TBA-120 FR and Cobas E- 411 using Agappe kits) in Department of Biochemistry, SCBMCH, Cuttack, Odisha, India. Serum calcium (freely ionised) was analysed in ion selective electrode based on potentiometric principle. Serum freely ionised calcium is a better measurement of biologically active calcium ions than total serum calcium which includes protein bound calcium ions [10]. Insulin resistance was estimated by the Homeostasis Model Assessment- Insulin resistance (HOMA-IR) which was calculated as:

Fasting insulin (lU/mL)* fasting glucose (mg/dL)/405 [11].

BMI was measured by weight in kilogram/height in (metre)^2.

STATISTICAL ANALYSIS

Data was entered in MS Excel and analysed using Statistical Package for Social Science (SPSS) version 22.0 (IBM, Armonk, NY: IBM Corp.). Baseline comparison of cases and controls were done, mean±standard deviation (SD), while categorical variables were expressed in percentages. Pearson's correlation and linear regression were used to determine if the studied parameters were related to change in other studied parameters in the same group. A p-value of ≤0.05 was considered to be significant.

RESULTS

Serum Uric Acid and Insulin, HOMA-IR

The [Table/Fig-1] shows baseline comparison of the study participants. FPG, serum insulin and HOMA-IR were significantly higher among newly diagnosed cases compared to controls. Serum uric acid was found to be significantly lower among cases than controls. BMI and persons having positive family history was significantly higher in cases. The [Table/Fig-2] shows correlation matrix and correlation coefficient (r) of serum uric acid with serum insulin and HOMA-IR among cases, control and overall subjects. A significant weak positive correlation of serum uric acid with insulin (r=0.231) and HOMA-IR (r=0.226) was present among the cases. Overall, we found a mild positive significant correlation between serum uric acid and insulin level (r=0.159).

Variables	Cases	Controls	p-value
Age (years)	42.24±14.13	38.76±12.72	0.421
Sex, n (%)			
Male	50 (55.6)	53 (58.9)	0.584
Female	40 (44.4)	37 (41.1)	
Family history (1st degree relative)			
Positive	64 (71.1)	51 (56.7)	0.044*
Negative	26 (28.9)	39 (43.3)	
BMI (kg/m^2)	26.13±5.03	27.31±5.12	0.161
FBS (mg/dL)	166±67.86	97±9.86	<0.001*
Serum insulin (μIU/mL)	15.12±8.76	12.32±4.87	0.003*
HOMA-IR (lU/mL)	6.13±3.13	2.76±1.37	<0.001*
Serum uric acid (mg/dL)	4.87±1.51	5.33±1.63	0.050*
Serum calcium (mmol/L)	1.11±1.12	0.97±0.12	0.303

[Table/Fig-1]: Baseline comparison between cases and control.
*p-value ≤0.05: significant; Quantitative variables between two groups were compared using independent sample t-test while qualitative variable using Pearson Chi-square test

Variables	Serum insulin (μIU/mL)					
	Case		Control		Overall	
	r	p-value	r	p-value	r	p-value
Serum uric acid (mg/dL)	0.231	0.029*	0.162	0.128	0.159	0.033*
Serum calcium (mmol/L)	-0.092	0.389	-0.155	0.146	-0.068	0.367
	HOMA-IR					
	Cases		Control		Overall	
Variables	r	p-value	r	p-value	r	p-value
Serum uric acid (mg/dL)	0.226	0.032*	0.149	0.160	0.092	0.217
Serum calcium (mmol/L)	-0.034	0.748	-0.168	0.114	-0.004	0.962

[Table/Fig-2]: Correlation of serum uric acid and serum calcium with serum insulin and insulin resistance' (HOMA-IR).
*p-value ≤0.05: significant; Pearson correlation test was used to calculate correlation coefficient

To determine the factors independently affecting serum insulin level we entered FPG, HOMA-IR, family history of diabetes, BMI, gender, serum uric acid, serum calcium into our regression models and regression coefficients (β) were calculated [Table/Fig-3]. Insulin levels increased with increase in serum uric acid among cases (β=0.055; p=0.597), controls (β=0.225; p=0.021) and overall (β=0.154; p=0.033) subjects. BMI had a significant role in affecting insulin levels (p<0.001) among cases. Female gender and positive family history significantly decreased insulin level among the controls.

Variables	Cases		Controls		Overall	
	β	p-value	β	p-value	β	p-value
FBS (mg/dL)	-0.150	0.149	0.271	0.005*	0.038	0.614
Serum uric acid (mg/dL)	0.055	0.597	0.225	0.021*	0.154	0.033*
Serum calcium (mmol/L)	0.050	0.609	-0.549	0.292	0.007	0.925
Family history of Type 2 diabetes mellitus	0.046	0.631	-0.205	0.034*	-0.078	0.280
BMI (kg/m^2)	0.468	<0.001*	0.020	0.172	0.365	<0.001*
Gender (male as reference)	-0.134	0.195	-0.200	0.047*	-0.070	0.315

[Table/Fig-3]: Independent predictors of serum insulin.
*p-value ≤0.05: significant; Multiple linear regression analysis was done to calculate unstandardised coefficient (β)

The [Table/Fig-4] shows independent factors influencing the insulin resistance. Insulin resistance increased with increase in BMI of cases (β=0.049; p<0.001), controls (β=0.156; p=0.096) and overall subjects (β=0.355; p<0.001). Serum uric acid did not have any significant impact on insulin resistance among the cases (β=0.130; p=0.229) but

Variables	Cases		Controls		Overall	
	β	p-value	β	p-value	β	p-value
Serum uric acid (mg/dL)	0.130	0.229	0.198	0.031*	0.162	0.022*
Serum calcium (mmol/L)	0.089	0.381	-0.094	0.304	0.032	0.650
Family history	0.032	0.747	-0.208	0.021*	-0.068	0.334
BMI (kg/m^2)	0.494	<0.001*	0.156	0.096	0.355	<0.001*
Gender	-0.079	0.460	-0.145	0.119	-0.006	0.932

[Table/Fig-4]: Independent predictors of insulin resistance.
*p-value ≤0.05: significant; Multiple linear regression analysis was done to calculate unstandardised coefficient (β)

did have a significant influence among controls (β=0.198; p=0.031) and overall subjects (β=0.162; p=0.022). Insulin resistance was lower among females in cases, controls and overall subjects. Insulin resistance was significantly lower in controls with negative family history (β=-0.208; p=0.021) but no significant results were obtained in cases (β=0.032; p=0.747) and overall subjects (β=-0.068; p=0.334).

Multivariate regression analysis showed chances of T2DM decreased with increase in serum uric level (odd's ratio=0.715) when adjusted for BMI, gender, family history, serum calcium and insulin resistance.

Serum Calcium and Insulin, HOMA-IR

The mean serum calcium level was more in cases than controls but the difference was not significant [Table/Fig-1]. Serum calcium showed a non significant weak negative correlation between both serum insulin and HOMA-IR among both cases and controls [Table/Fig-2]. Overall subjects (β=0.007) and case (β=0.050) showed very mild increase in insulin level with increase in serum calcium, while in controls decrease in insulin was seen with increase in calcium (β=-0.549). None of this relationship was significant [Table/Fig-3]. Serum calcium did not influence the insulin resistance level significantly [Table/Fig-4]. It increased with increase in insulin resistance among cases (β=0.089) and overall subjects (β=0.032), but decreased with increase in insulin resistance among controls (β=-0.094).

A multivariate logistic regression was done to find out the independent predictors of development of T2DM. Those with positive family history had almost double the odds of developing T2DM. The development of diabetes did not have significant relationship with serum calcium status. Higher BMI had a higher risk of developing diabetes [Table/Fig-5].

Factors	Adjusted odds ratio	95% Confidence interval	p-value
Sex			
Male	1		0.656
Female	1.188	0.557-2.535	
Family history			
Negative	1		
Positive	1.922	0.877-4.210	0.102
BMI	1.103	0.768-0.930	0.001*
Serum uric acid	0.715	0.553-0.924	0.010*
Serum calcium	0.948	0.515-1.745	0.864
HOMA-IR	2.057	1.604-2.638	<0.001*

[Table/Fig-5]: Multivariate logistic regression to show the predictors of development of Type 2 DM.
*p-value ≤0.05: significant

DISCUSSION

T2DM results from an intricate linkage of genetic and environmental factors [12]. It is marked by compromised insulin secretion, enhanced glucose production and insulin resistance. The present study showed lower uric acid levels in newly diagnosed cases of DM compared to controls. Study done by Haque T et al., had found lower serum uric acid in prediabetic and diabetic individuals compared to healthy non diabetics [13]. A prospective cohort study by Taniguchi Y et al., did not find any association of uric acid with development of T2DM [14]. In contrast, studies by Causevic A et al., and Grover A et al., found higher serum uric acid in prediabetic and diabetic than healthy controls [15,16]. It has been hypothesised hyperuricaemia leads to insulin resistance by increase in inflammation (TNF @, NFK β, IL6, CRP), oxidative stress, endothelial dysfunction and decrease in insulin signalling [17]. Lower uric acid in diabetics and prediabetics may be due to hyperglycaemia which leads to defective uric acid reabsorption as both glucose and urate are reabsorbed from proximal tubules in kidney.

Serum insulin and insulin resistance showed a positive correlation with serum uric acid levels in cases, controls and overall (case+control) subjects. In cases, a significant positive correlation was found of insulin and insulin resistance with serum uric acid. Studies by Hu Y et al., Gill A et al., Bandaru P and Shankar A, had shown positive correlation of serum uric acid with serum insulin among cases of DM [17-19]. Cross-sectional study by Wu Y et al., and prospective studies by Wu WC et al., and Zhang Q et al., has shown positive correlation of serum uric acid and insulin resistance [20-22]. Li L et al., did not find any correlation of serum uric acid with insulin resistance among obese and overweight T2DM patients [23]. Higher levels of insulin lead to increase in Hexose Monophosphate (HMP) pathway leading to an uricogenic state. Hyperinsulinaemia is also found to be associated with increased urate reabsorption from proximal tubule of kidneys [3,24]. In the present study, insulin resistance (HOMA-IR) positively correlated with serum uric acid in all the three groups. Studies by Han T et al., and Krishnan E et al., found a positive corelation between serum uric acid and insulin resistance [25,26].

In the present study, linear regression was done to find out the independent predictors of serum insulin and insulin resistance. Serum uric acid was found to be a significant independent predictor of insulin among controls and also when cases and controls were taken together. No such significant results were seen in newly diagnosed cases. But in all the three categories serum insulin increased with increase in serum uric acid. Among both cases and controls insulin resistance increased significantly with increase in uric acid level. This finding is supported various studies done by many other investigators [25-30]. de Miranda JA et al., have found serum uric acid to be an independent predictor of insulin resistance in obese non diabetic children and adolescents, while Chen J et al., have found similar results in non diabetic adults [31,32].

Serum insulin and insulin resistance also increased significantly with increase in BMI. The insulin resistance atherosclerosis study has also found increased BMI to be a significant independent predictor of both insulin and its resistance [33]. There are also some studies suggesting that obesity may act as a confounding factor for hyperuricaemia and T2DM [2,34].

Serum calcium was found to be elevated in newly diagnosed T2DM than healthy volunteers in present study. Prospective study on Spanish population by Becerra-Tomás N et al., have found increased serum calcium levels in newly developed T2DM [35]. Systemic review and meta-analysis by Zhu J et al., and cross-sectional study Sun G et al., have also found similar results [36,37].

In the present study, a negative correlation of insulin and insulin resistance was seen with calcium in cases, controls and overall subjects. Similar findings have been found in various other studies [35,36]. It is hypothesised that in T2DM the glucose threshold for insulin secretion is raised and the physiological biphasic pulsatile insulin secretion is switched to monophasic due to impairment of voltage gated calcium channels [35]. This may account for negative correlation of serum calcium with insulin. (cases-r=-0.092; control-r=-0.155)

Studies done by Sun G et al., and Wu X et al., reveal decrease in serum calcium levels may lead to increase in insulin resistance in peripheral tissues by defective insulin signalling and decreased GLUT 4 receptors [37,38]. This finding is in support of present negative correlation of serum calcium with HOMA-IR. In contrast, the Furukawa Nutrition and Health Study, a cross-sectional study on Japanese population and another Indian study have found positive correlation of calcium with HOMA-IR [39,40]. Factors like BMI, muscle mass, ethnicity have shown to affect the relationship [40].

Few studies have explored the role of calcium being an independent predictor of insulin and its resistance [38,40]. In the present study, both serum insulin and insulin resistance showed miniature increase with increase in serum calcium in cases but none of them were significant. In controls serum insulin decreased with increase in serum calcium level but even they were not significant.

Prospective study by Wu X et al., have found high calcium levels precede peripheral insulin resistance [38]. Cross-sectional study

done on Indian population by Shridhar K et al., have found serum calcium to be positively associated with insulin resistance [40]. Insulin stimulates glucose mediated insulin secretion from pancreas by causing efflux of calcium from endoplasmic reticulum [41].

A multivariate regression analysis was done to find how the level of uric acid and calcium influence the occurrence of DM when adjusting for sex, family history, BMI and HOMA-IR. The odds of developing DM decreased with increase in serum uric acid level and serum calcium level. The relationship between uric acid and development of T2DM was significant (p-0.010).

Prospective study by Krishnan E et al., and Juraschek SP et al., have found hyperuricaemia leading to development of T2DM while Taniguchi Y et al., have found no link of uric acid in development of T2DM [14,26,30]. A cohort study by Hagstorm E et al., showed increased endogenous calcium may have a role in development of T2DM [42].

Limitation(s)

There may be confounders with other biological parameters like dyslipidaemia which the present study has not accounted for. A sample size calculation was not done for this study and this remains a major limitation. The causality of the observed associations between study parameters should be more comprehensively studied in prospective cohort studies with a large sample size to obtain a clarified view of role of serum uric acid and calcium and its role in influencing levels of insulin and HOMA-IR in development and progression to T2DM.

CONCLUSION(S)

In the current study, it was observed that, increased uric acid leads to increase in insulin resistance but the levels of uric acid were lower in person newly diagnosed with T2DM. The exact biochemical mechanism responsible for this observation is not clear and a conclusive relationship of serum calcium with insulin and its resistance could not be established. To find true associations between total serum calcium in T2DM, it is vital to exclude possible confounding factors like muscle mass, physical activity, diet and other hormonal interactions.

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