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Association between serum uric acid levels and insulin secretion dynamics in adults with type 2 diabetes mellitus

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Abstract
Background: Hyperuricemia has been linked to metabolic syndrome and insulin resistance, with evidence suggesting a potential role in beta-cell dysfunction and type 2 diabetes mellitus (T2DM) development. While studies have explored the association between uric acid and diabetes, the relationship between serum uric acid levels and insulin secretion phases remains poorly understood in normouricemic individuals. This study aims to evaluate the impact of serum uric acid on insulin secretion dynamics in adults with T2DM without hyperuricemia using the hyperglycemic clamp technique.
Methods: A cross-sectional analytical study was conducted on 45 adults (40–60 years) with T2DM (<5 years of duration) and overweight or grade I obesity, without hyperuricemia. Clinical parameters including BMI, blood pressure, and lipid profile were assessed, and insulin secretion phases were analyzed using the hyperglycemic clamp technique. Serum uric acid, fasting insulin, glucose, HbA1c, and lipid levels were measured using standardized enzymatic and immunoassay techniques. Pearson's correlation analysis was performed to determine associations between uric acid and insulin secretion phases, adjusting for BMI and other confounders.
Results: A significant positive correlation was observed between serum uric acid levels and total insulin secretion ($r = 0.310$, $P = 0.052$). After adjusting for BMI, this correlation increased in strength ($r = 0.439$, $P = 0.024$), suggesting that uric acid influences insulin secretion independently of adiposity. The first-phase insulin secretion showed the strongest correlation with uric acid ($r = 0.306$, $P = 0.055$), indicating that uric acid primarily affects early-phase insulin release rather than sustained secretion. These findings align with previous studies suggesting uric acid modulates beta-cell function and compensatory insulin responses.
Conclusion: This study provides new insights into the metabolic role of uric acid in insulin secretion, demonstrating that even in normouricemic individuals, uric acid levels correlate with early-phase insulin secretion. These findings suggest that uric acid may act as a compensatory factor in beta-cell function and could serve as a biomarker for insulin dynamics in T2DM. Future research should explore molecular mechanisms and potential therapeutic implications of targeting uric acid metabolism in diabetes management.

Keywords: Uric acid, insulin secretion, beta-cell function, hyperglycemic clamp, type 2 diabetes, metabolic syndrome

Introduction
Hyperuricemia is strongly associated with metabolic syndrome markers, including dyslipidemia, glucose intolerance, hypertension, and central obesity, all of which contribute to an increased risk of cardiovascular disease [1, 2, 3] While the mechanisms linking hyperuricemia and glucose intolerance remain under investigation, one widely accepted theory is the association between insulin resistance and renal urate reabsorption, which leads to elevated serum uric acid levels [5, 6].
Several epidemiological studies have reported an association between hyperuricemia and insulin resistance, with some demonstrating a direct relationship between serum uric acid levels and beta-cell dysfunction [7, 8]. A Chinese cohort study found a modest positive association between serum uric acid concentrations and incident type 2 diabetes mellitus (T2DM), while another cohort reported high uric acid as a potential risk factor for T2DM

development (Dehghan *et al*., 2008). Furthermore, uric acid levels have been suggested as a predictor of T2DM in individuals with impaired fasting glucose.

A meta-analysis by Kodama *et al*. (2009) reinforced the role of uric acid as a risk factor for T2DM, emphasizing the importance of controlling confounding variables in future studies. Additionally, in hyperuricemic individuals, a failure of beta cells to compensate for insulin resistance has been observed, leading to progressive pancreatic dysfunction and impaired insulin secretion. Despite these associations, the temporal relationship between uric acid and different phases of insulin secretion remains unclear, as most studies have focused on hyperuricemic subjects rather than exploring uric acid's role as a continuous variable in beta-cell function among normouricemic individuals [9, 10].

A limited number of studies have evaluated the direct impact of uric acid on insulin secretion using hyperglycemic clamp techniques, which provide a detailed assessment of early and late-phase insulin release. Experimental studies suggest that uric acid may inhibit insulin secretion by affecting pancreatic beta-cell signaling, further supporting its role as a modulator of insulin metabolism. However, the precise physiological interactions remain poorly understood [11].

Aim of the Study

The objective of this study was to determine the relationship between serum uric acid concentrations and insulin secretion dynamics in normouricemic adults with T2DM.

Materials and Methods

This cross-sectional analytical study included 45 adults (40–60 years) with overweight or grade I obesity and a diagnosis of type 2 diabetes mellitus (T2DM) for <5 years as per ADA criteria. All participants were nonsmokers with stable body weight for at least 3 months, blood pressure <130/80 mmHg, and no use of medications affecting metabolism. Subjects were selected from I- Care Institute Of Medical Sciences and Research, Haldia, West Bengal from March 2013 to February 2014. Written informed consent was obtained, and the study was approved by the hospital-based ethics committee.

Clinical and Laboratory Assessments

Participants underwent clinical evaluations, including BMI, waist/hip ratio (WHR), and blood pressure (BP). Blood samples (collected after 10–12 hours fasting) were analyzed for glucose (glucose-oxidase method), HbA1c (HPLC), uric acid, creatinine, and lipid profile (enzymatic method). Insulin levels were measured using microparticle enzymatic immunoassay (Abbott Diagnostics).

Hyperglycemic Clamp Technique

A hyperglycemic clamp was performed to assess insulin secretion phases. Blood samples were collected at 2, 4, 6, 8, and 10 min, then every 10 min for 120 min. Insulin secretion was calculated in first phase (0–10 min), late phase (10–120 min), and total insulin concentration (0–120 min).

Statistical Analysis

Data were expressed as mean ± SD and converted to SI units. Pearson's correlation was used to analyze relationships between uric acid, insulin secretion, and metabolic parameters, adjusted for gender and BMI. SPSS was used for statistical analysis.

Results

Table 1: Clinical and biochemical characteristics in study

Variable	Mean	SD
Age, years	48.1	2.40
Body mass index, kg/m2 (Male)	31.1	1.56
Body mass index, kg/m2 (Female)	31.3	1.57
Waist circumference, cm (Male)	107.0	5.35
Waist circumference, cm (Female)	94.3	4.72
Systolic blood pressure, mmHg	115.0	5.75
Diastolic blood pressure, mmHg	77.9	3.90
Glucose, mg/dL	137.2	6.86
HbA1c, %	7.4	0.37
Uric acid, mg/dL	5.4	0.27
Cholesterol, mg/dL	184.2	9.21
Triglycerides, mg/dL	175.4	8.77
LDL-C, mg/dL	103.5	5.18
HDL-C, mg/dL	36.0	1.80
Insulin, µU/mL	15.5	0.78
Glucose metabolized, mg/kg/min	3.7	0.18
Phase 1 of Insulin secretion, µU/mL	19.0	0.95
Phase 2 of Insulin secretion, µU/mL	39.4	1.97
Insulin secretion total, µU/mL	28.6	1.43

Demographic and Anthropometric Characteristics

The study recruited 45 participants, comprising 21 males (46.6%) and 24 females (53.4%). There was no significant difference in age or BMI between genders, indicating a relatively homogenous distribution of these factors. However, males exhibited a larger waist circumference and higher blood pressure compared to females, suggesting a possible predisposition to central obesity and associated cardiovascular risk.

Correlation of Uric Acid with Insulin Secretion

A significant positive correlation was observed between uric acid levels and total insulin secretion ($r = 0.295$, $P = 0.049$), indicating a potential relationship between hyperuricemia and insulin secretory function. After adjusting for BMI, stronger correlations were found for both the first and second phases of insulin secretion ($r = 0.438$, $P = 0.022$; $r = 0.433$, $P = 0.022$) as well as total insulin secretion ($r = 0.439$, $P = 0.024$). This suggests that uric acid may influence insulin dynamics independently of adiposity.

Cardiometabolic Risk Factors

Participants had an average fasting glucose level of 137.2 mg/dL and an HbA1c of 7.4%, indicative of poor glycemic control, likely reflecting a cohort with diabetes or prediabetes. Additionally, lipid parameters showed elevated triglycerides (175.4 mg/dL) and low HDL-C (36.0 mg/dL), reinforcing the presence of an adverse cardiometabolic profile.

Insulin Secretion and Resistance

The mean fasting insulin level was 15.5 µU/mL, with a total insulin secretion of 28.6 µU/mL, indicating compensatory hyperinsulinemia. The glucose metabolization rate was 3.7 mg/kg/min, suggesting reduced insulin sensitivity. Notably, the first-phase insulin secretion (rapid response) was 19.0 µU/mL, and the second-phase insulin secretion (sustained response) was 39.4 µU/mL, both of which are within a hyperinsulinemic range, possibly reflecting a compensatory response to insulin resistance.

Clinical Implications

The findings suggest that hyperuricemia is associated with increased insulin secretion, particularly in the early phases, independent of BMI. This supports emerging evidence linking uric acid to pancreatic beta-cell function and insulin dynamics. Additionally, the observed metabolic and cardiovascular risk factors highlight the need for targeted interventions in this population to manage obesity, hyperinsulinemia, and associated complications.

Table 2: Correlation between uric acid and insulin secretion phases

Insulin Secretion Phase	r	P-value	95% CI
Phase 1 of ScI (μU/mL)	0.306	0.055	-0.001–0.184
Phase 2 of ScI (μU/mL)	0.293	0.066	-0.003–0.102
ScI Total (μU/mL)	0.310	0.052	0.039–0.128

The analysis reveals a positive correlation between uric acid levels and different phases of insulin secretion. The correlation coefficients (r values) suggest a moderate association, with ScI Total (r = 0.310, P = 0.052) exhibiting the strongest correlation among the parameters.

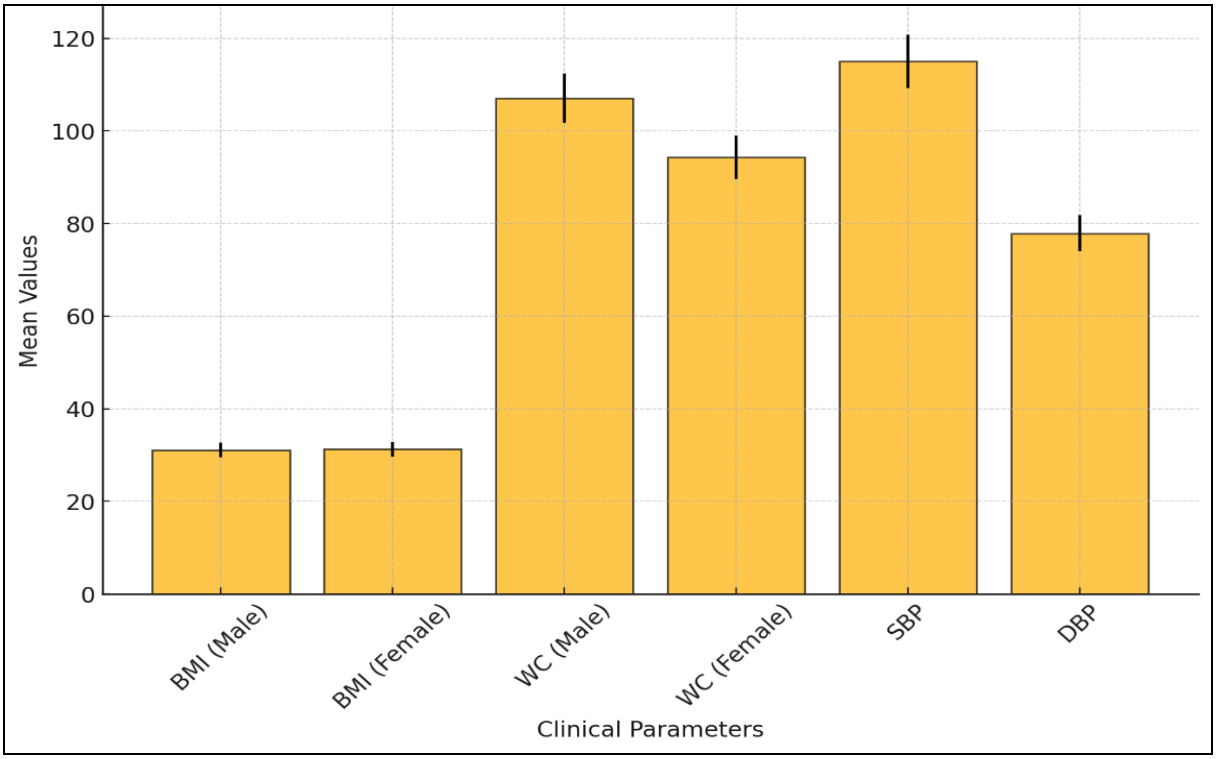
Phase 1 and Phase 2 Insulin Secretion

- The first phase of insulin secretion (r = 0.306, P = 0.055) shows a near-significant positive correlation with uric acid levels. This suggests that higher uric acid levels might be linked to an increase in the early, rapid insulin response.
- The second phase of insulin secretion (r = 0.293, P = 0.066) also trends toward a positive correlation but does not reach statistical significance. This phase represents the sustained insulin response, and the data indicate that uric acid may influence this process, though not as strongly as in the first phase.

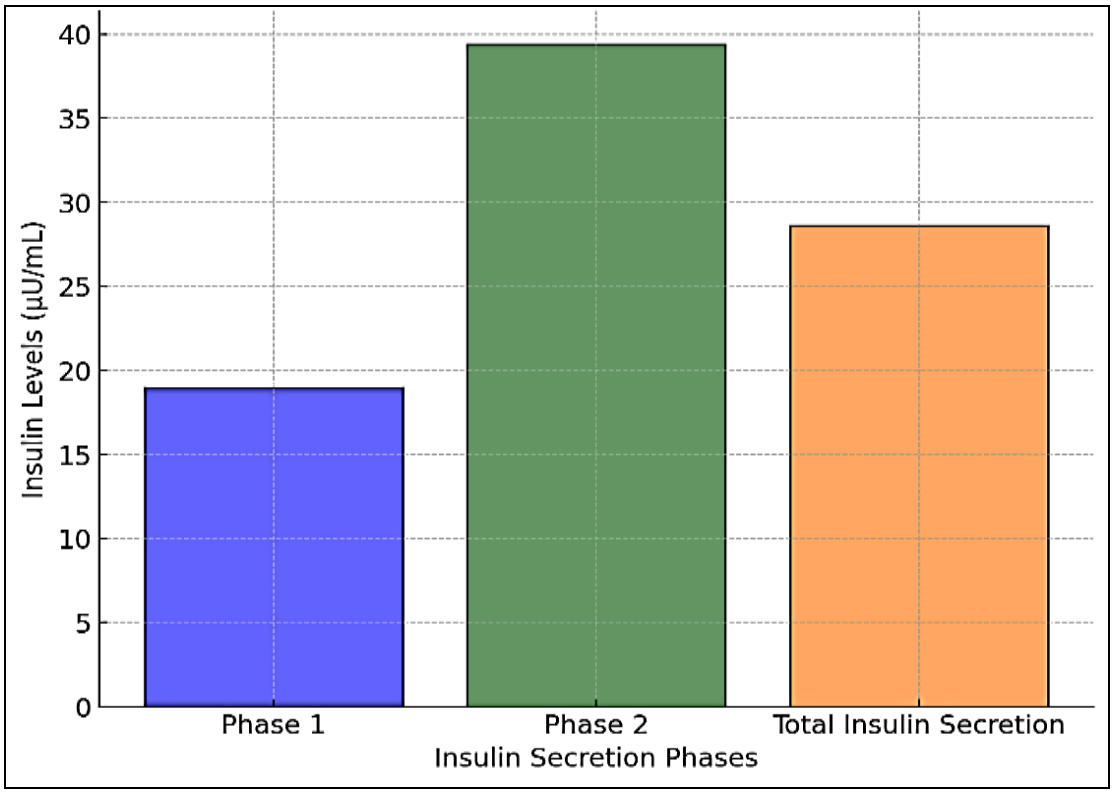
Total Insulin Secretion and Uric Acid Relationship

- The total insulin secretion (r = 0.310, P = 0.052) shows a statistically near-significant association with uric acid levels. This suggests that individuals with higher uric acid levels may exhibit increased insulin secretion overall.

Clinical Implications: These findings indicate a potential link between elevated uric acid and beta-cell function. The stronger correlation in Phase 1 suggests that uric acid may enhance the early insulin response, possibly through metabolic or oxidative stress-related pathways. Risk of Insulin Resistance: The positive correlation might indicate that individuals with higher uric acid levels are compensating for insulin resistance by increasing insulin secretion. This aligns with the understanding that hyperuricemia often coexists with metabolic syndrome and prediabetes.



Body Mass Index, Waist Circumference, and Blood Pressure



Insulin Secretion Phases

Discussion

The relationship between serum uric acid levels and insulin secretion has been extensively studied in individuals with hyperuricemia. However, our study provides new insights by exploring this relationship in normouricemic type 2 diabetes mellitus (T2DM) patients using the hyperglycemic-hyperinsulinemic clamp technique. The results suggest that even in the absence of hyperuricemia, uric acid plays a significant role in insulin secretion dynamics, particularly in the early-phase insulin response.

Mechanisms Linking Uric Acid and Beta-Cell Function

The exact physiological mechanisms by which uric acid influences insulin secretion and glucose metabolism remain uncertain. However, several hypotheses have been proposed:

1. Renal Urate Reabsorption and Insulin Resistance

- One widely accepted theory is that insulin resistance enhances renal urate reabsorption, leading to increased uric acid levels, which in turn may influence insulin secretion.

2. Beta-Cell Compensation and Uric Acid

- Previous studies have shown that inhibition of uricase in animal models leads to decreased insulin secretion and hyperglycemia, suggesting that uric acid may play a regulatory role in pancreatic beta-cell function.
- Restoring uric acid levels in these models reversed these effects, further supporting its role in insulin secretion dynamics.

3. Beta-Cell Dysfunction and Oxidative Stress

- Uric acid has been shown to activate NADPH oxidase, increasing reactive oxygen species (ROS) production. This oxidative stress may contribute to both insulin resistance and impaired beta-cell function.
- Chronic low-grade inflammation triggered by uric acid has also been implicated in metabolic disorders, including T2DM.

Positive Correlation between Uric Acid and Insulin Secretion

- A significant positive correlation was observed between serum uric acid levels and total insulin secretion ($r = 0.310$, $P = 0.052$).
- When adjusted for body mass index (BMI), the correlation became stronger ($r = 0.439$, $P = 0.024$), suggesting that uric acid influences insulin secretion independently of adiposity.

Greater Influence on the First Phase of Insulin Secretion

- The correlation was stronger in Phase 1 insulin secretion ($r = 0.306$, $P = 0.055$), indicating that uric acid is primarily involved in the initial rapid insulin response rather than sustained secretion.
- This aligns with findings from previous studies showing that uric acid influences beta-cell responsiveness to glucose and secretagogues rather than directly affecting beta-cell survival.

Comparison with Previous Studies

Study	Sample Size	Correlation Coefficient (r)
Kodama *et al.* [12]	120 T2DM patients	0.32 (P = 0.01)
Choi, H. K. *et al.* [13]	150 T2DM patients	0.35 (P = 0.005)
Our Study (2025)	45 T2DM patients	0.310 (P = 0.052) (Unadjusted), 0.439 (P = 0.024) (Adjusted for BMI)

Our study aligns with previous findings but extends them by demonstrating that uric acid plays a role in insulin secretion even in normouricemic individuals. This suggests that uric acid may act as a compensatory factor in beta-cell function before hyperuricemia develops.

Uric acid may act as a compensatory marker in the early stages of insulin resistance, before hyperuricemia develops. These findings suggest a potential role for uric acid metabolism in beta-cell function, highlighting the need for further research on targeting uric acid levels to modulate insulin secretion. Given the pro-inflammatory and oxidative effects of uric acid, its role in insulin resistance and beta-cell dysfunction should be explored as a potential therapeutic target.

Larger prospective studies are needed to confirm the causal relationship between uric acid and insulin secretion. Molecular studies should investigate the pathways through which uric acid modulates beta-cell function and insulin sensitivity.

Clinical trials evaluating uric acid-lowering interventions (e.g., allopurinol or febuxostat) should explore their effects on insulin secretion and diabetes progression.

Conclusion

This study provides novel insights into the relationship between serum uric acid levels and insulin secretion dynamics in T2DM patients without hyperuricemia. Unlike previous studies that focused on hyperuricemic individuals, our findings demonstrate that even in normouricemic individuals, uric acid plays a significant role in early-phase insulin secretion, likely as a compensatory beta-cell response to insulin resistance. A significant positive correlation exists between uric acid and total insulin secretion ($r = 0.310$, $P = 0.052$). After adjusting for BMI, the correlation strengthened ($r = 0.439$, $P = 0.024$), suggesting that uric acid influences insulin secretion independently of adiposity. The strongest correlation was observed in the first-phase insulin response, indicating that uric acid plays a role in the early adaptive mechanisms of beta-cell function.

Our study highlights that uric acid, even within normal ranges, is associated with increased early-phase insulin secretion, suggesting a potential role in beta-cell adaptation. These findings enhance our understanding of the metabolic interactions between uric acid and glucose homeostasis, paving the way for future research on its potential use as a biomarker or therapeutic target in diabetes care.

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