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Original Research Article

Serum C1q/Tumor Necrosis Factor-Related Protein 3 (CTRP3) Levels in Individuals with Type 2 Diabetes Mellitus and Healthy Controls: A Comparative Cross-Sectional Study

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, progressive pancreatic ß-cell dysfunction, and persistent hyperglycemia. C1q/Tumor Necrosis Factor-Related Protein 3 (CTRP3) is an adipokine with anti-inflammatory and insulin-sensitizing properties that has been implicated in glucose and lipid metabolism. However, its association with dyslipidemia in T2DM remains incompletely understood.

Objective: To compare serum CTRP3 concentrations between patients with T2DM and healthy controls and to evaluate the association of CTRP3 with glycaemic and lipid profile parameters.

Methods: A hospital-based comparative cross-sectional study was conducted among 60 participants, including 30 patients with established T2DM and 30 age- and sex-matched healthy controls recruited from Government Medical College Hospital, Thiruvananthapuram. Serum CTRP3 concentrations were measured using a sandwich enzyme-linked immunosorbent assay. Fasting blood glucose (FBS), glycated hemoglobin (HbA1c), and lipid profile parameters were analyzed using standard automated biochemical methods. Statistical analysis was performed using SPSS version 24.0, and Pearson's correlation coefficient was used to assess associations between CTRP3 and biochemical variables.

Results: Serum CTRP3 concentrations were significantly lower in patients with T2DM than in healthy controls (405 ± 82.5 vs. 559 ± 124 ng/mL; $P < 0.001$). Serum CTRP3 showed a significant inverse correlation with FBS ($r = -0.434$, $P = 0.017$) and triglycerides ($r = -0.423$, $P = 0.020$). Negative correlations were observed with HbA1c, total cholesterol, and LDL cholesterol, while HDL cholesterol showed a positive correlation; however, these associations were not statistically significant.

Conclusions: Serum CTRP3 concentrations were significantly reduced in patients with T2DM and were inversely associated with fasting blood glucose and triglyceride concentrations. These findings suggest that CTRP3 may serve as a potential biomarker of metabolic dysfunction in T2DM. Larger prospective studies are required to determine its role in predicting disease progression and diabetes-related complications.

Keywords: Type 2 Diabetes Mellitus, CTRP3, Adipokines, Insulin Resistance, Lipid Profile, Biomarker.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents the most common form of diabetes, accounting for nearly 90–95% of diabetes cases globally. It is a multifactorial metabolic disease characterized by impaired insulin action, gradual deterioration of pancreatic β-cell function, and sustained hyperglycemia. Over time, these metabolic

abnormalities lead to both microvascular and macrovascular complications, making T2DM a leading contributor to morbidity and mortality worldwide.[1–5]

The burden of T2DM has increased rapidly across the globe, largely driven by urbanization, aging populations, rising obesity rates, reduced physical activity, and unhealthy dietary patterns. India has experienced a particularly steep increase in disease prevalence, with T2DM becoming one of the country's major public health concerns.[1,4-8] Although diagnostic and therapeutic strategies have improved considerably, a substantial proportion of individuals remain undiagnosed until irreversible complications become evident. This has intensified the search for reliable biomarkers to identify metabolic disturbances in the early phases of disease development.[9,10-15]

Adipose tissue is no longer viewed merely as an energy storage site but is now recognized as an endocrine organ that plays a critical role in maintaining glucose and lipid balance through the secretion of various adipokines.[16-18] Among these molecules, C1q/TNF-related protein-3 (CTRP3), a member of the C1q/TNF superfamily, has attracted increasing attention because of its insulin-sensitizing, anti-inflammatory, and glucose-regulating effects.[18-21] Experimental studies have shown that CTRP3 reduces hepatic gluconeogenesis, enhances insulin signaling pathways, improves lipid metabolism, and suppresses chronic low-grade inflammation, thereby influencing several pathways implicated in the development of T2DM.[19-22]

Clinical investigations have consistently reported lower circulating CTRP3 levels in individuals with T2DM and obesity.[23-27] However, its association with dyslipidemia remains unclear. Since insulin resistance and abnormal lipid metabolism are closely linked and play a major role in the development of cardiovascular complications in diabetes, evaluating the relationship between CTRP3 and lipid profile parameters may provide additional evidence supporting its utility as a biomarker of metabolic dysfunction.[5,24-30] Therefore, the present study was undertaken to assess serum CTRP3 levels in patients with T2DM, compare them with healthy individuals, and investigate their association with lipid profile parameters.

Mechanistic Background of CTRP3 in Type 2 Diabetes Mellitus

The pathogenesis of T2DM involves the combined effects of insulin resistance in skeletal muscle, liver, and adipose tissue along with progressive impairment of pancreatic β-cell function. These defects reduce peripheral glucose uptake, increase hepatic glucose output, and ultimately lead to persistent hyperglycemia.[3,5,10-15] In addition, chronic low-grade inflammation, oxidative stress, lipotoxicity, and ectopic fat deposition further worsen insulin resistance and promote the onset of vascular complications associated with diabetes.[5,11-15] As a result, adipokines have become an important area of research due to their roles in regulating glucose metabolism, lipid homeostasis, and inflammatory processes.[16-18]

CTRP3 is a secretory adipokine predominantly synthesized by adipose tissue and belongs to the C1q/TNF-related protein family.[17-20] Although it shares structural similarities with adiponectin, CTRP3 exhibits distinct biological functions within the CTRP family.[17-20] Experimental evidence indicates that CTRP3 suppresses hepatic glucose production by activating AKT- and ERK-dependent signaling pathways, downregulating gluconeogenic enzyme expression, promoting lipid oxidation, and decreasing triglyceride synthesis. Collectively, these actions enhance insulin sensitivity independently of circulating insulin levels.[19-22]

Apart from its metabolic effects, CTRP3 also possesses significant anti-inflammatory activity. It inhibits the release of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, reduces macrophage-mediated inflammation within adipose tissue, and improves insulin signaling in peripheral tissues.[21,22,28] Furthermore, CTRP3 expression appears to be modulated by both metabolic and inflammatory stimuli and may contribute to adipose tissue homeostasis through interactions with adiponectin-related signaling pathways.[20,21,28] These combined actions enhance insulin responsiveness while reducing chronic metabolic inflammation, both of which are fundamental mechanisms in T2DM progression.[5,21,22,28]

Recent evidence also suggests that CTRP3 exerts protective effects against diabetes-related complications. Experimental studies have demonstrated improvements in endothelial function, preservation of vascular integrity, reduction of oxidative stress and inflammation, and attenuation of diabetic cardiomyopathy through AMPK- and AKT-mediated signaling mechanisms.[29,30] Clinical studies have similarly shown significantly lower

circulating CTRP3 concentrations in patients with T2DM, obesity, metabolic syndrome, and diabetic nephropathy, indicating its potential value as a biomarker of insulin resistance and metabolic dysfunction.[23-27] Nevertheless, evidence linking CTRP3 with dyslipidemia remains limited, providing the scientific basis for undertaking the present investigation.

MATERIALS & Methods

Study Design

A hospital-based cross-sectional comparative study was conducted to evaluate serum CTRP3 concentrations in patients with type 2 diabetes mellitus and healthy controls.

Study Setting

The study was carried out in the Endocrinology Outpatient Department, Department of Endocrinology, Government Medical College Hospital, Thiruvananthapuram, Kerala, India. Biochemical analyses were performed in the Department of Biochemistry, Government Medical College Hospital, Thiruvananthapuram.

Study Duration

The study was conducted over a period of one year, from July 2021 to July 2022. Ethical approval was obtained from the Human Ethics Committee of Government Medical College, Thiruvananthapuram, before commencement of the study.

Sample Size

The sample size was estimated using the standard formula for comparison of two independent means:

$$n = \frac{(Z1\text{-}\alpha/2 + Z1\text{-}\beta)2\ (\sigma\ 2 + \sigma 22)}{(\mu_1 - \mu_2)^2} \quad 1$$

$$(Z1 - \alpha/2 + Z1 - \beta)2\ value, when\ \beta = 90\%\ is\ 10.49\ \sigma 1 - 80.73\ \sigma 2 - 69.79$$

μ_1 – 328.17, μ_2 – 257.61. The expected mean values were 328.17 and 257.61, with corresponding standard deviations of 80.73 and 69.79 for the two groups.

The estimated minimum sample size was 24 participants. To improve the reliability of the analysis and facilitate a meaningful comparison between groups, the final sample size was increased to 30 participants in each group. Accordingly, the study included 30 patients with type 2 diabetes mellitus (study group) and 30 healthy individuals (comparison group).

Study Population

The study included patients with established type 2 diabetes mellitus (T2DM) attending the Endocrinology Outpatient Department, Government Medical College Hospital, Thiruvananthapuram, and age- and sex-matched healthy controls.

Inclusion Criteria

Study group: Patients aged 20–75 years with established T2DM receiving treatment at the Department of Endocrinology.

Comparison group: Age- and sex-matched healthy volunteers who provided written informed consent.

Exclusion Criteria

Patients with type 1 diabetes mellitus, those receiving GLP-1 receptor agonists or DPP-4 inhibitors, and individuals unwilling to provide informed consent were excluded. Healthy controls who did not provide informed consent were also excluded.

Ethical Approval

Written informed consent was obtained from all participants before enrolment. The study was approved by the Human Ethics Committee, Government Medical College, Thiruvananthapuram (HEC No. 03/13/2021/MCT; approved on 05 March 2021).

Sampling Method

Participants fulfilling the eligibility criteria were recruited consecutively until the required sample size was achieved.

Data Collection

Demographic and clinical data were collected using a structured study proforma after obtaining written informed consent.

Biochemical Measurements

Sample Collection

After a 12-hour overnight fast, 3 mL of venous blood was collected under aseptic precautions. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at −20°C until analysis.

Serum CTRP3 Estimation

Serum CTRP3 concentrations were measured using a commercially available Human Intact CTRP3 sandwich ELISA kit (Bioassay Technology Laboratory). The assay had a detection range of 0.05–30 ng/mL and a

sensitivity of 0.026 ng/mL. Serum samples were diluted 1:20 with phosphate-buffered saline before analysis. Absorbance was recorded at 450 nm, and concentrations were calculated from the standard calibration curve after correction for the dilution factor. The intra-assay and inter-assay coefficients of variation were less than 8% and less than 10%, respectively.

Fasting Blood Glucose and HbA1c

Fasting blood glucose was estimated by the enzymatic hexokinase method using a Beckman Coulter automated chemistry analyzer. HbA1c was measured using the turbidimetric immunoinhibition method on the same analyzer, following the manufacturer's instructions.

Lipid Profile

Serum total cholesterol, triglycerides, and HDL-cholesterol were measured using standard enzymatic methods on the Beckman Coulter automated analyzer. LDL-cholesterol was calculated using the Friedewald equation for samples within the valid triglyceride range, and VLDL-cholesterol was estimated as triglycerides divided by five.

RESULTS

Demographic Characteristics

A total of 60 participants were included in the study, comprising 30 patients with T2DM and 30 age- and sex-matched healthy controls.

The proportion of females was 56.7% (17/30) in the T2DM group and was comparable to that of the control group, with no significant difference in sex distribution between groups (Chi-square test, p = 0.795). The control group counts (16 females, 14 males) are consistent with the reported non-significant sex distribution (p = 0.795).

Characteristic	T2DM (n = 30)	Controls (n = 30)	P value
Male, n (%)	13 (43.3)	14 (46.7)	0.795
Female, n (%)	17 (56.7)	16 (53.3)	
Male:Female ratio	1:1.31	1:1.14	—

Table 1. Baseline demographic characteristics of the study population

*Values are presented as n (%). Sex distribution was comparable between the T2DM and control groups (Chi-square test, P = 0.795).

Clinical Characteristics of Patients with T2DM

Among the 30 patients with T2DM, 17 (56.7%) had dyslipidemia, indicating that lipid abnormalities were common in the diabetic population. The distribution of diabetes duration is shown in Figure 1.

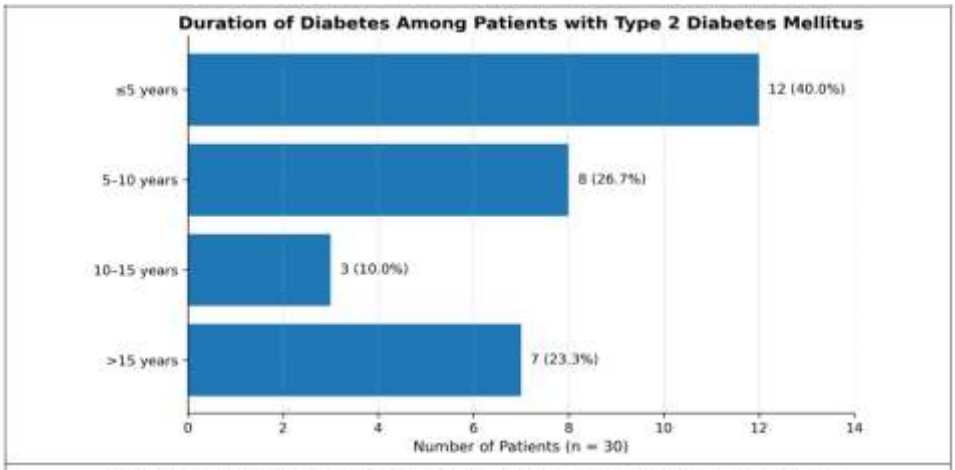

Figure 1: Distribution of diabetes duration among patients with T2DM

Figure 1 Horizontal bar chart showing the distribution of diabetes duration among patients with T2DM. The largest proportion of patients had diabetes for ≤5 years (40.0%), followed by more than 15 years (23.3%), 5–10 years (26.7%), and 10–15 years (10.0%).

Comparison of Biochemical Parameters Between Groups

Serum CTRP3 concentrations were significantly lower in patients with T2DM than in healthy controls. Mean serum CTRP3 concentration was 405 ± 82.5 ng/mL in the T2DM group compared with 559 ± 124.0 ng/mL in controls (P < 0.001). Mean total cholesterol was slightly higher in patients with T2DM (181 ± 59.5 mg/dL) than in controls (177 ± 29.6 mg/dL), but this difference was not statistically significant (P = 0.726).

Parameter	T2DM (n=30) Mean ± SD	Controls (n=30) Mean ± SD	P value
Total cholesterol (mg/dL)	181 ± 59.5	177 ± 29.6	0.726
Serum CTRP3 (ng/mL)	405 ± 82.5	559 ± 124.0	<0.001
Table 2. Comparison of biochemical parameters between patients with T2DM and healthy controls			
Values are expressed as mean ± standard deviation			

Association Between Serum CTRP3 and Glycaemic Parameters

Pearson correlation analysis demonstrated a significant inverse correlation between serum CTRP3 and fasting blood glucose (r = −0.434, P = 0.017). Although CTRP3 also showed a negative correlation with HbA1c (r = −0.314), the association was not statistically significant (P = 0.091). These findings suggest that lower circulating CTRP3 concentrations were associated with poorer fasting glycaemic status but not with long-term glycaemic control in this study population.

Parameter	Pearson's r	P value
Fasting blood glucose	-0.434	0.017
HbA1c	-0.314	0.091
Table 3. Correlation of serum CTRP3 with glycaemic parameters in patients with T2DM		

Association Between Serum CTRP3 and Lipid Profile Parameters

Serum CTRP3 showed a significant inverse correlation with serum triglyceride concentration (r = −0.423, P = 0.020). In contrast, correlations with total cholesterol (r = −0.087, P = 0.646), LDL cholesterol (r = −0.164, P = 0.387), and HDL cholesterol (r = 0.081, P = 0.672) were not statistically significant. The observed inverse relationship between CTRP3 and triglycerides suggests a potential association between lower CTRP3 concentrations and diabetic dyslipidemia.

Lipid parameter	Pearson's r	P value
Total cholesterol	-0.087	0.646
Triglycerides	-0.423	0.020
LDL cholesterol	-0.164	0.387
HDL cholesterol	0.081	0.672
Table 4. Correlation of serum CTRP3 with lipid profile parameters in patients with T2DM		

DISCUSSION

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, progressive β-cell dysfunction, chronic low-grade inflammation, and disturbances in lipid metabolism, all of which contribute to the development of vascular complications.[1-5,10-15] Adipokines have emerged as important regulators of these metabolic pathways, and CTRP3 has attracted increasing attention for its anti-inflammatory, insulin-sensitizing, and glucose-regulating properties.[16-22] The present study evaluated circulating serum CTRP3 concentrations in patients with T2DM and examined their relationship with glycaemic status and lipid profile parameters.

The principal finding of this study was that serum CTRP3 concentrations were significantly lower in patients with T2DM than in healthy controls. In addition, serum CTRP3 showed significant inverse correlations with fasting blood glucose and serum triglyceride concentrations, whereas no significant associations were observed with HbA1c, total cholesterol, LDL cholesterol, or HDL cholesterol. These findings suggest that

reduced circulating CTRP3 levels are associated with impaired metabolic regulation in T2DM.[23-30]

The reduction in serum CTRP3 observed in the present study is consistent with several previous clinical investigations. Ban et al. reported significantly lower CTRP3 concentrations in patients with newly diagnosed T2DM, suggesting that reduced CTRP3 may be an early metabolic abnormality in diabetes.[23] Similar findings have been described in patients with diabetic nephropathy and other insulin-resistant conditions, where decreased CTRP3 concentrations were associated with worsening metabolic dysfunction.[25-27] Experimental studies have also demonstrated reduced CTRP3 expression in obesity and insulin resistance, supporting its role as a protective adipokine that helps maintain glucose homeostasis.[18-22] Collectively, these observations strengthen the evidence that diminished circulating CTRP3 is a characteristic feature of T2DM.

However, not all studies have reported similar findings. Choi et al. observed higher circulating CTRP3 concentrations in individuals with T2DM and metabolic syndrome.[24] Differences between studies may reflect variations in participant characteristics, obesity status, disease duration, antidiabetic therapy, ethnicity, and laboratory methods used for CTRP3 estimation.[20,24] Such heterogeneity highlights the need for standardized methods and larger multicentre studies to better define the clinical behavior of CTRP3 across different populations.

A significant inverse correlation was identified between serum CTRP3 and fasting blood glucose in the present study. This finding is consistent with studies showing reduced CTRP3 concentrations in individuals with obesity, insulin resistance, and impaired glucose metabolism.[25,28] The biological basis for this relationship is supported by experimental evidence showing that CTRP3 suppresses hepatic gluconeogenesis, enhances insulin signaling through AKT- and ERK-mediated pathways, and improves peripheral glucose utilization.[18-22] In addition, CTRP3 has been shown to reduce the production of pro-inflammatory cytokines and improve insulin sensitivity in adipose tissue, mechanisms that may contribute to improved glycaemic regulation.[21,22,28] Although causality cannot be established in a cross-sectional study, the observed association supports the proposed metabolic role of CTRP3 in glucose homeostasis.

Serum CTRP3 showed a negative correlation with HbA1c, although the association was not statistically significant. HbA1c reflects long-term glycaemic control over approximately three months, whereas CTRP3 may be more closely related to current metabolic and inflammatory status than to cumulative glycaemic exposure. The lack of statistical significance may also be attributable to the relatively small sample size and variability in diabetes duration among participants. Similar inconsistent associations between CTRP3 and HbA1c have been reported in previous studies.[23-30]

Among the lipid parameters evaluated, serum triglycerides demonstrated a significant inverse correlation with CTRP3. This observation is clinically relevant because hypertriglyceridemia is a common feature of insulin resistance and contributes substantially to cardiovascular risk in patients with T2DM.[5,11-15] Wolf et al. reported an inverse association between circulating CTRP3 concentrations and triglyceride levels in obese individuals, while Deng et al. demonstrated similar relationships in patients with obesity and hypertension.[25,27] Experimental evidence suggests that CTRP3 promotes lipid oxidation, suppresses triglyceride synthesis, and improves hepatic lipid metabolism, providing a plausible explanation for the observed association.[19-22] These findings indicate that CTRP3 may influence both glucose and triglyceride metabolism through interconnected metabolic pathways.

Although serum CTRP3 showed negative correlations with total and LDL cholesterol and a positive correlation with HDL cholesterol, none of these associations were statistically significant. Previous studies have reported variable relationships between CTRP3 and individual lipid fractions.[23-30] The absence of significant associations in the present study may reflect the limited sample size, differences in lipid-lowering therapy, dietary habits, and the relatively heterogeneous duration of diabetes among participants. Therefore, the present findings do not exclude a possible relationship between CTRP3 and cholesterol metabolism but suggest that this association requires further evaluation.

The findings of the present study have potential clinical implications. Identification of biomarkers that reflect early metabolic dysfunction may improve risk stratification in

patients with T2DM before the development of overt vascular complications.[9,13-15] The observed reduction in serum CTRP3 and its association with fasting blood glucose and triglycerides suggest that CTRP3 may serve as an adjunctive biomarker for insulin resistance and metabolic dysregulation. However, its role as a diagnostic or prognostic biomarker requires validation in larger prospective studies.[20-30]

This study has several strengths. It included age- and sex-matched healthy controls and evaluated CTRP3 alongside glycaemic and lipid parameters in a well-defined, hospital-based population. Standardized biochemical methods were used to estimate CTRP3 and other laboratory parameters. Nevertheless, certain limitations should be acknowledged. The cross-sectional design precludes causal inference; the sample size was relatively small, and measurements were obtained at a single tertiary care center. Information on body mass index, inflammatory biomarkers, insulin levels, and medication effects was not evaluated, which may have influenced circulating CTRP3 concentrations.

In conclusion, the present study demonstrates that serum CTRP3 concentrations are significantly reduced in patients with T2DM and are inversely associated with fasting blood glucose and serum triglyceride concentrations. These findings support emerging evidence that CTRP3 is involved in glucose and lipid metabolism and may serve as a promising biomarker of metabolic dysfunction in T2DM.[23-30] Larger longitudinal studies are required to clarify its predictive value and its potential role in the development of diabetic complications.

Limitations

- The study was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings.
- The cross-sectional design and single-time-point measurement of serum CTRP3 precluded assessment of causal or temporal relationships with T2DM and dyslipidemia.
- Nutritional status, body composition, and dietary intake were not assessed and may have influenced circulating CTRP3 concentrations.

CONCLUSION

Serum CTRP3 concentrations were significantly lower in patients with type 2 diabetes mellitus than in healthy controls. Serum CTRP3 showed significant inverse correlations with fasting blood glucose and triglyceride concentrations. No significant associations were observed between serum CTRP3 and HbA1c, total cholesterol, LDL cholesterol, or HDL cholesterol.

These findings suggest that reduced circulating CTRP3 may serve as a potential biomarker of metabolic dysfunction in type 2 diabetes mellitus. Further prospective studies are needed to validate its role in disease progression and diabetes-related complications.

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