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RESEARCH ARTICLE

Serum Phosphorylated Tau Protein in Type 2 Diabetes Mellitus as a Potential Biomarker for Alzheimer's disease

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) has been associated with an increased risk of neurodegenerative changes, while abnormal tau phosphorylation is a key feature of Alzheimer's disease (AD).

Objective: This observational case-control study evaluated serum phosphorylated tau protein levels in T2DM patients compared with healthy controls and assessed their potential relevance as an early biomarker of AD-related changes.

Methods: Serum samples were collected from 35 individuals, including 25 patients with T2DM and 10 healthy controls. Fasting blood glucose, lipid profile, creatinine, urea, insulin, and phosphorylated tau levels were measured using standard biochemical assays and ELISA.

Results: Phosphorylated tau levels were significantly higher in T2DM patients than controls (142.56 ± 106.82 *vs*. 15.30 ± 34.66 ng/L; $p = 0.001$). LDL cholesterol was also higher in T2DM patients (137.68 ± 72.33 *vs*. 55.30 ± 22.01 mg/dL; $p = 0.001$), as were total cholesterol (249.44 ± 76.40 *vs*. 110.60 ± 23.35 mg/dL; $p < 0.001$) and HDL cholesterol (86.28 ± 56.62 *vs*. 35.90 ± 10.08 mg/dL; $p = 0.009$). No significant differences were observed in creatinine, urea, triglycerides, or insulin levels.

Conclusion: The findings suggest a possible association between T2DM and increased serum phosphorylated tau levels. However, larger studies including cognitive assessment, body mass index, dietary evaluation, and AD-specific phosphorylated tau isoforms are required before clinical use can be established.

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- Type 2 diabetes mellitus
- Phosphorylated tau
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- Biomarker
- ELISA
- Insulin resistance

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both. Chronic hyperglycemia contributes to systemic complications, including vascular, renal, neurological, and cardiovascular disorders [1,2]. In addition to

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peripheral complications, growing evidence suggests that T2DM may affect the central nervous system and may increase vulnerability to cognitive impairment and dementia [3,4].

Alzheimer's Disease (AD) is characterized by amyloid-β deposition and neurofibrillary tangles, the latter being strongly associated with abnormal phosphorylation of tau protein [5]. Phosphorylated tau biomarkers, particularly p-tau181, p-tau217, and p-tau231, have gained increasing attention as indicators of AD pathology and disease progression [6].

The biological connection between T2DM and tau pathology may involve insulin resistance, impaired glucose metabolism, oxidative stress, inflammation, and changes in kinase signaling pathways that regulate tau phosphorylation. A recent meta-analysis reported that impaired glucose metabolism and diabetes status were associated with higher tau biomarkers, although the relationship with amyloid-β biomarkers was less consistent [7]. Other recent work in individuals with T2DM and overweight or obesity showed that not all blood-based AD biomarkers are equally associated with cognitive outcomes, supporting the need for cautious interpretation of peripheral biomarker findings [8].

The present study aimed to compare serum phosphorylated tau levels between patients with T2DM and healthy controls and to explore whether phosphorylated tau may serve as a potential peripheral biomarker related to AD risk in the context of metabolic dysfunction.

Materials and Methods

Study design and participants

This was an observational case-control study involving 35 individuals divided into two groups: 25 patients with clinically diagnosed T2DM and 10 apparently healthy control subjects. Serum samples from T2DM patients were collected from the Institute of Diabetes and Endocrine System under clinical supervision. Control samples were obtained from individuals with no known diagnosis of diabetes. Participants were included when serum samples were available and suitable for biochemical and ELISA analysis. Samples with insufficient volume, visible hemolysis, or incomplete measurements were excluded from analysis.

Ethical considerations

The study was conducted as an academic research project under faculty and clinical supervision. Serum samples were handled confidentially and analyzed without participant-identifying information. No formal ethics approval number was available in the archived study record.

Biochemical analysis

Fasting Blood Glucose (FBG), total cholesterol, triglycerides, High-Density Lipoprotein (HDL), creatinine, and urea were measured using commercially available Biodiagnostic enzymatic colorimetric kits according to the manufacturer's protocols. Low-Density Lipoprotein (LDL) cholesterol was calculated using the Friedewald equation: LDL cholesterol (mg/dL) = total cholesterol - HDL cholesterol - (triglycerides/5).

Insulin and phosphorylated Tau measurement

Serum insulin levels were measured using an Immunospec Insulin ELISA kit. Serum phosphorylated tau levels were measured using a Bioassay Technology Laboratory Human Phospho Tau ELISA kit. For phosphorylated tau measurement, standards and samples were processed according to the kit protocol, and optical density was read at 450 nm using a microplate reader. Sample concentrations were calculated from the standard curve.

Statistical analysis

Data were expressed as mean ± standard

Table 1: Comparison of biochemical and biomarker parameters between T2DM patients and control subjects.

Parameter	T2DM patients (*n* = 25)	Controls (*n* = 10)	*p*-value
Creatinine (mg/dL)	1.27 ± 0.38	1.07 ± 0.24	0.136
Urea (mg/dL)	29.36 ± 7.37	32.60 ± 6.60	0.236
Total cholesterol (mg/dL)	249.44 ± 76.40	110.60 ± 23.35	<0.001
Triglycerides (mg/dL)	150.44 ± 69.29	116.50 ± 66.43	0.195
HDL cholesterol (mg/dL)	86.28 ± 56.62	35.90 ± 10.08	0.009
LDL cholesterol (mg/dL)	137.68 ± 72.33	55.30 ± 22.01	0.001
Phosphorylated tau (ng/L)	142.56 ± 106.82	15.30 ± 34.66	0.001
Insulin (µIU/mL)	91.68 ± 59.50	88.89 ± 69.28	0.905

deviation (SD). Distribution normality was assessed using skewness and kurtosis tests before group comparison. Mean values between T2DM patients and controls were compared using Student's t-test. Pearson's correlation coefficient was used to assess associations between variables where appropriate. Statistical analysis was performed using SPSS version 13.1 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

Results

Demographic characteristics

The T2DM group included 25 participants, with a female predominance (20 females and 5 males; median age 48 years, range 18–67 years). The control group included 10 participants, with 7 males and 3 females (median age 37 years, range 28–70 years).

Biochemical parameters

The comparison of laboratory parameters between T2DM patients and controls is summarized in table 1. Creatinine, urea, triglycerides, and insulin levels were not significantly different between groups. Total cholesterol, HDL cholesterol, LDL cholesterol, and phosphorylated tau levels were significantly higher in the T2DM group.

Phosphorylated Tau and lipid findings

Phosphorylated tau levels were markedly higher in T2DM patients than in controls (142.56 ± 106.82 *vs.* 15.30 ± 34.66 ng/L; p = 0.001; figure 8). LDL cholesterol was also significantly higher in T2DM patients (137.68 ± 72.33 *vs.* 55.30 ± 22.01 mg/dL; p = 0.001; figure 4). Total cholesterol and HDL cholesterol were significantly elevated in the T2DM group (p < 0.001 and p = 0.009, respectively; figures 3 and 6). Urea, triglycerides, and insulin levels showed overlapping distributions between groups (Figures 1,2,5,7).

Discussion

This study found significantly higher serum phosphorylated tau levels in patients with T2DM compared with healthy controls. This observation supports a possible relationship between metabolic dysfunction and tau phosphorylation, although the cross-sectional design and small sample size prevent causal interpretation.

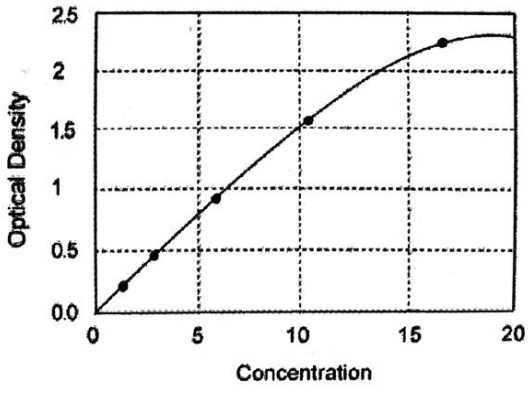

Figure 1 Standard curve for phosphorylated tau ELISA showing the relationship between optical density and standard concentration.

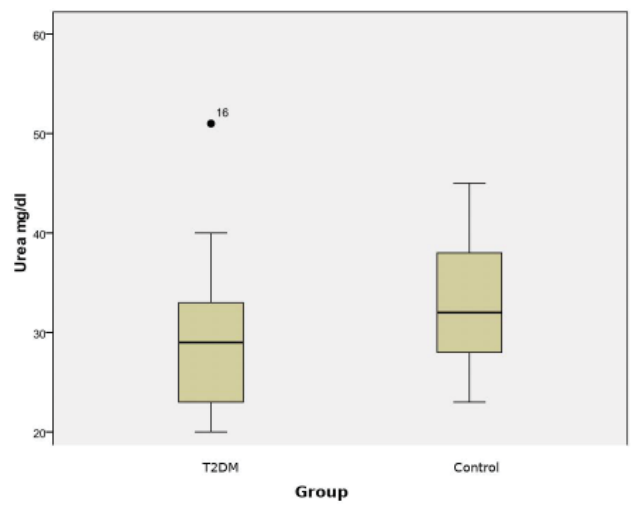

Figure 2 Serum urea levels in T2DM patients and control subjects.

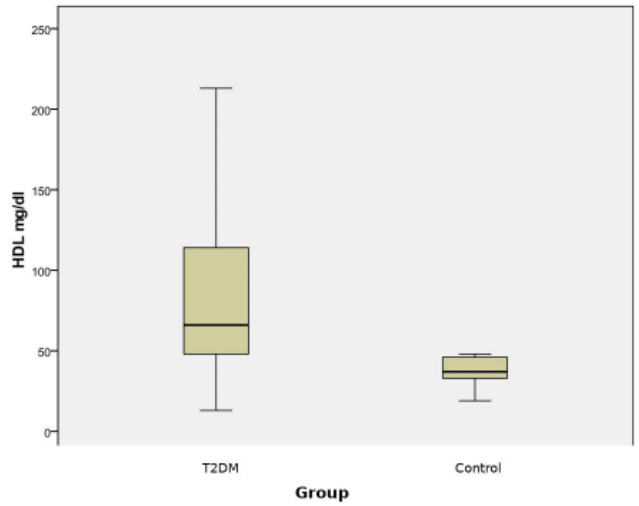

Figure 3 Serum HDL cholesterol levels in T2DM patients and control subjects.

Several mechanisms may explain a link between T2DM and tau phosphorylation. Insulin resistance may alter intracellular signaling pathways such as PI3K/Akt and GSK-3β, which are involved in tau phosphorylation regulation. Hyperglycemia may also contribute through oxidative stress, advanced glycation end-products, inflammation, and impaired neuronal glucose metabolism [4,9,10]. In addition, peripheral relevance of tau has been suggested by reports of beta amyloid and hyperphosphorylated tau deposits in pancreatic tissue in T2DM [11], although serum phosphorylated tau remains an exploratory marker.

The present findings are consistent with the broader hypothesis that diabetes-related metabolic dysfunction may be associated with tau-related biomarkers. A 2024 systematic review and meta-analysis reported that impaired glucose metabolism and diabetes status were associated with higher tau biomarkers, while amyloid-β associations were less consistent [7]. However, recent longitudinal evidence in individuals with T2DM and overweight or

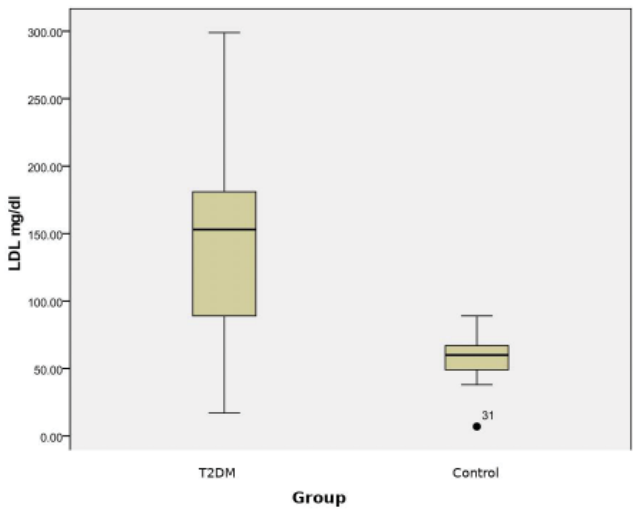

Figure 4 Serum LDL cholesterol levels in T2DM patients and control subjects.

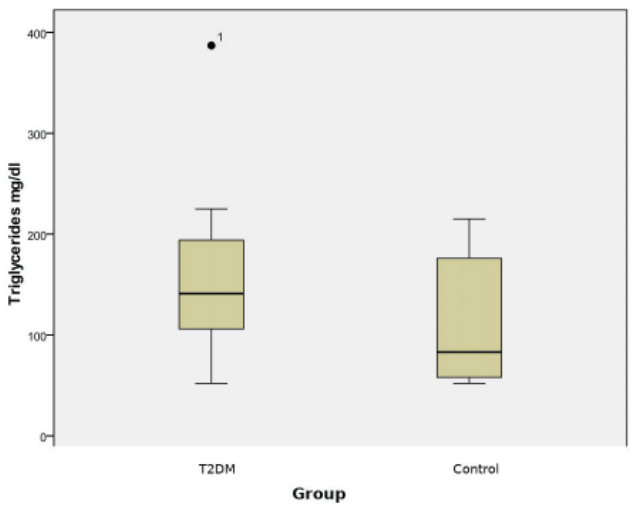

Figure 5 Serum triglyceride levels in T2DM patients and control subjects.

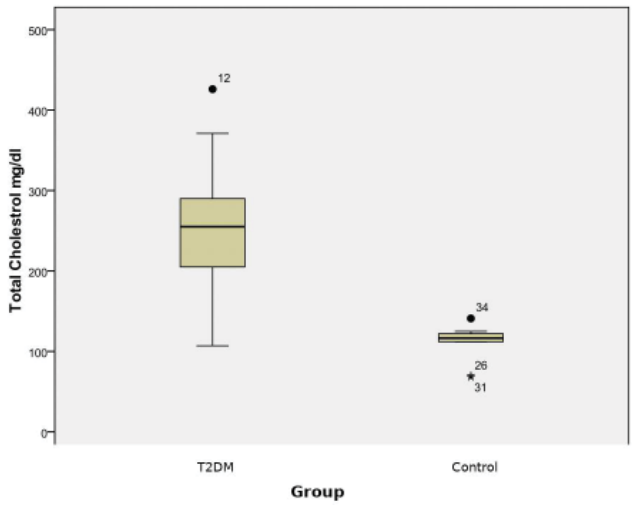

Figure 6 Serum total cholesterol levels in T2DM patients and control subjects.

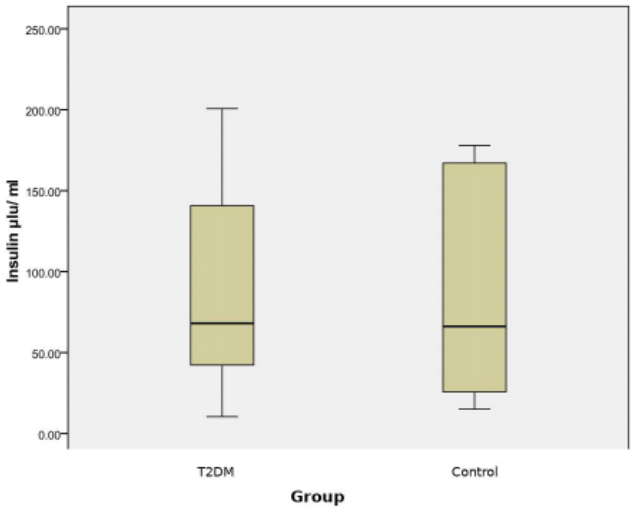

Figure 7 Serum insulin levels in T2DM patients and control subjects.

obesity found that plasma pTau-181 was not clearly associated with cognitive outcomes, whereas other biomarkers such as NfL and GFAP were more strongly related to cognitive decline [8]. These findings highlight that peripheral tau measurements should be interpreted cautiously and within the context of assay type, tau phosphorylation site, disease stage, and comorbidities.

The lipid profile results showed significantly higher LDL and total cholesterol levels in the T2DM group. Dyslipidemia is common in T2DM and may contribute to vascular dysfunction, inflammation, and increased risk of cognitive decline. The unexpectedly high HDL levels in the T2DM group may reflect sample variability and outlier effects, particularly given the small sample size. Insulin levels were not significantly different between groups. This may reflect heterogeneity in T2DM duration, medication use, pancreatic β-cell function, and insulin resistance severity. Therefore, insulin findings should not be interpreted as evidence against insulin resistance, but rather as a limitation of using a single peripheral insulin measurement without additional indices such as HOMA-IR.

Study Limitations

This study has several limitations. First, the sample size was small and the groups were unequal in number, age distribution, and sex distribution. Second, cognitive assessment, AD diagnosis, neuroimaging, and cerebrospinal fluid biomarkers were not included. Third, BMI, dietary intake, diabetes duration, glycemic control history, medication use, and insulin resistance indices were not available for all participants. Fourth, the phosphorylated tau ELISA kit measured serum phosphorylated tau but did not specify clinically established

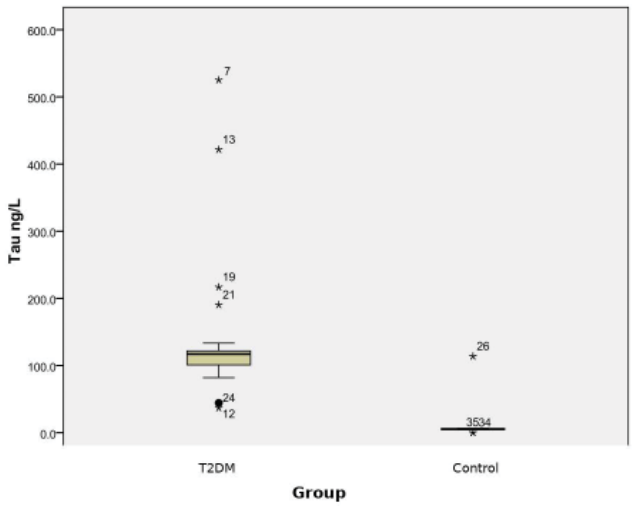

Figure 8 Serum phosphorylated tau protein levels in T2DM patients and control subjects.

AD phosphorylation sites such as p-tau181, p-tau217, or p-tau231. Finally, the cross-sectional design does not allow determination of causality or prediction of future AD development.

Conclusion

Serum phosphorylated tau levels were significantly higher in patients with T2DM compared with healthy controls in this small case-control study. These findings suggest a possible association between T2DM and tau phosphorylation; however, phosphorylated tau should be considered a potential exploratory biomarker rather than a confirmed diagnostic marker for Alzheimer's disease in this population. Larger longitudinal studies using standardized AD-specific tau biomarkers and cognitive assessment are required to confirm clinical relevance.

Author Contributions

Mohamed A. Elmasry contributed to the study design, performed the experimental work, collected and analyzed the data, and drafted the manuscript. A. Abd El Razik contributed to data interpretation, critical review, and manuscript revision. Ingy Badawy supervised the study, contributed to the conceptualization of the research, and provided final review and approval of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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