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Original Research Article

Role of Serum Prolidase and Oxidative Stress Levels in Diabetic Neuropathy Patients

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Abstract

Background: Diabetic neuropathy (DN) remains a highly disabling microvascular complication of diabetes mellitus. Chronic hyperglycemia prompts cellular damage through multiple metabolic routes, with oxidative stress serving as a primary driver of neuropathic structural degradation [1,2]. Concurrently, altered tissue remodelling and collagen degradation feature heavily in late-stage diabetic complications. Serum prolidase activity governs the final step of collagen degradation, yet its definitive role alongside systematic systemic oxidative stress parameters in DN remains poorly characterized [2,3]. This study evaluated the collective dynamics of serum prolidase activity, total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index (OSI) in patients with diabetic neuropathy.

Methods: A cross-sectional, comparative observational study was conducted involving 80 participants recruited from MGM Medical College, Indore, MP. The subjects were classified into three distinct cohorts: diabetic neuropathy cases (n=40), diabetic controls without neuropathy (n=40), and non-diabetic healthy controls (n=40). Serum prolidase activity, TAS, and TOS were spectrophotometrically determined using validated automated colorimetric assays [4,5], and the OSI was computed as the ratio of TOS to TAS. Glycemic indices and lipid profiles were correlated with these markers using Pearson's data analysis via SPSS Version 19.

Results: Serum TOS levels were markedly higher in DN patients (0.341 ± 0.187 µmol H2O2 Eq./L) compared to diabetic controls (0.258 ± 0.081 µmol H2O2 Eq./L) and non-diabetic controls (0.129 ± 0.041 µmol H2O2 Eq./L; $p < 0.0001$). The OSI similarly displayed a highly significant upward trend across the cohorts (1.301 ± 1.412 vs. 0.563 ± 0.311 vs. 0.402 ± 0.213; $p < 0.0001$). Serum prolidase activity was highest in the DN cohort (382.6 ± 138.5 U/L) compared to diabetic (368.4 ± 132.9 U/L) and healthy controls (361.2 ± 150.3 U/L), signaling active tissue remodeling. Prolidase activity demonstrated a significant negative correlation with HbA1c ($r = -0.327$, $p = 0.039$), high-density lipoprotein (HDL, $r = 0.432$, $p = 0.004$), and very low-density lipoprotein (VLDL, $r = -0.315$, $p = 0.041$).

Conclusion: Accelerated systemic oxidative stress, represented by distinct elevations in TOS and OSI, combined with altered serum prolidase dynamics, highlights a combined pathophysiological framework of oxidative damage and aberrant collagen turnover in diabetic neuropathy. These parameters serve as potential biomarkers for microvascular deterioration in diabetic patients.

Keywords: Neonate, Procedural pain, Oral glucose, non-nutritive sucking, PIPP-R, Diabetic Neuropathy, Prolidase, Oxidative Stress Index (OSI), Total Oxidant Status (TOS).

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Introduction

Diabetes mellitus is one of the most common non-communicable diseases globally and stands as the fourth leading cause of mortality in the majority of developed nations 1. Prolonged systemic hyperglycemia yields extensive macrovascular and microvascular pathologies, among which diabetic neuropathy (DN) presents as a profoundly debilitating clinical manifestation [2]. Clinically,

DN displays a broad spectrum of presentations, predominantly presenting as a chronic sensory-motor distal symmetrical polyneuropathy alongside varying degrees of autonomic nervous system disruption [1,6]. The progression and subsequent severity of neuropathic degradation depend linearly upon the longitudinal duration of diabetes and the efficacy of sustained glycemic control [7].

At the cellular level, sustained high glucose concentrations initiate metabolic shifts that delay normal cellular proliferation, suppress physiological collagen synthesis, and vastly increase structural collagen breakdown [2,8]. Prolidase (EC 3.4.13.9) is a ubiquitous cytosolic imidodipeptidase that cleaves imidodipeptides containing C-terminal proline or hydroxyproline residues, serving as a rate-limiting enzyme in collagen degradation and matrix remodeling [3,9].

Recent data indicates that altered serum prolidase activity operates as a sensitive surrogate marker for oxidative-stress-mediated structural breakdown across diverse pathological entities, including diabetes mellitus, chronic liver diseases, erectile dysfunction, and osteoporosis [2,10].

Despite growing evidence establishing the separate impacts of matrix remodeling and free radical production [11,12], clinical data addressing the simultaneous alterations of global oxidative balance parameters—such as Total Oxidant Status (TOS), Total Antioxidant Status (TAS), and the Oxidative Stress Index (OSI)—in conjunction with prolidase activity in diabetic neuropathy patients remains sparse.

Materials and Methods

Study Design and Ethical Clearance: This cross-sectional, comparative observational research study was conducted at the Department of Biochemistry, MGM Medical College, Indore, and Madhya Pradesh, India.

The study protocol received formal institutional review and ethics committee approval prior to commencement. All prospective participants provided signed, informed written consent before group enrollment.

Selection of Participants: A total pool of 120 target observational data lines was analyzed. The matching parameters selected included 40 primary case subjects, 40 chronic diabetic baseline controls, and 40 healthy control volunteers over matched age bands.

Inclusion Criteria: Patients clinically and neurologically diagnosed with diabetic neuropathy; Age range spanning 30 to 65 years; Representation across both male and female sexes; Full willingness to adhere to study protocols and provide signed informed consent.

Exclusion Criteria: Neuropathies originating from confounding non-diabetic etiologies (e.g., chronic alcohol abuse, neurotropic infectious pathogens, or confirmed autoimmune neuropathies); Active chronic inflammatory diseases, systemic infections, or documented malignancies; Recent history of therapeutic antioxidant supplementation or prescription medications known to influence systemic oxidative pathways; Advanced renal dysfunction or hepatic impairment; Women currently pregnant or lactating.

Sample Collection and Biochemical Analysis: Peripheral venous blood samples were drawn under standard fasting conditions into clean, dry specialized collection tubes. The collected specimens were left undisturbed at ambient temperature to facilitate complete clot formation. Serum separation was achieved by standard centrifugation at 3000 rpm for a duration of 10 minutes.

Serum TAS and TOS levels were determined via standardized colorimetric validation methods, primarily as described by Erel [4,5]. The systemic Oxidative Stress Index (OSI), representing the arbitrary balance of oxidants to antioxidants, was mathematically derived using the standard formula. Serum prolidase enzyme activity was analyzed via spectrophotometric estimation of proline release from synthetic substrates, based on methods validated by Myara et al [3].

Standard automated laboratory analytics were used to evaluate metabolic parameters, including glycated hemoglobin (HbA1c), Blood Sugar Fasting (BSF), Blood Sugar Postprandial (BSPP), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Very Low-Density Lipoprotein (VLDL), Serum Cholesterol (SCH), Serum Triglycerides (STG), and Body Mass Index (BMI).

Statistical Analysis: Statistical processing was carried out using SPSS Version 19 (IBM Corp., Armonk, NY). Continuous metrics are presented as Mean ± Standard Deviation (Mean ± SD). Variations in mean concentrations of TAS, TOS, and prolidase across groups were evaluated using unpaired student t-tests. Inter-variable links and metabolic linear relationships were analyzed using Pearson's correlation coefficient (r). Statistical significance thresholds were established at a p-value ≤ 0.05, with highly significant changes denoted at $p < 0.001$.

Results:

The comparison of serum oxidant, antioxidant, and prolidase profiles between the groups is summarised in Table 1.

Table 1: Comparison of total antioxidant status, total oxidant status, oxidative stress index, and serum prolidase activity among patients with diabetic neuropathy, diabetic controls, and non-diabetic controls.

Parameter	Cases: Diabetic Neuropathy (Mean ± SD)	Controls: Diabetic (Mean ± SD)	Controls: Non-Diabetic (Mean ± SD)	p-value
TAS (mmol Trolox Eq./L)	0.352 ± 0.118	0.349 ± 0.105	0.346 ± 0.092	0.941
TOS (μmol H2O2 Eq./L)	0.341 ± 0.187	0.258 ± 0.081	0.129 ± 0.041	<0.0001 (HS)
OSI (Arbitrary Units)	1.301 ± 1.412	0.563 ± 0.311	0.402 ± 0.213	<0.0001 (HS)
Prolidase (U/L)	382.6 ± 138.5	368.4 ± 132.9	361.2 ± 150.3	0.764

Serum TOS values increased significantly from healthy controls to diabetic individuals without complications, peaking in patients with diabetic neuropathy ($p < 0.0001$). This structural shift is reflected in the calculated OSI values, which were significantly higher in the diabetic neuropathy group (1.301 ± 1.412) than in the non-diabetic control cohort (0.402 ± 0.213), demonstrating a clear shift toward oxidative stress. Serum prolidase activity was higher in the diabetic neuropathy cases (382.6 ± 138.5 U/L) than in the non-diabetic controls (361.2 ± 150.3 U/L), though this difference did not reach independent statistical significance ($p = 0.764$). Pearson correlation assessment was performed for the diabetic neuropathy group (n=40) to evaluate relationships between oxidative biomarkers, prolidase activity, and metabolic risk indicators (Table 2).

Table 2: Correlation of metabolic parameters with total oxidant status, total antioxidant status, and serum prolidase activity in patients with diabetic neuropathy.

Metabolic Parameter	TOS (r)	TOS (p)	TAS (r)	TAS (p)	Prolidase (r)	Prolidase (p)
HbA1c (%)	0.082	0.612	-0.468	0.002	-0.327	0.039
BSF (mmol/L)	0.192	0.231	-0.362	0.021	-0.218	0.176
BSPP (mmol/L)	0.187	0.246	-0.419	0.006	-0.226	0.161
HDL (mmol/L)	-0.143	0.380	-0.072	0.652	0.432	0.004
LDL (mmol/L)	0.171	0.290	-0.552	<0.001	-0.173	0.286
VLDL (mmol/L)	0.298	0.045	-0.423	0.006	-0.315	0.041
SCH (mmol/L)	-0.011	0.945	-0.472	0.002	-0.178	0.269
STG (mmol/L)	0.094	0.566	-0.414	0.008	-0.304	0.049
BMI (kg/m2)	0.148	0.360	-0.401	0.010	-0.223	0.167

Serum TAS showed consistent, statistically significant negative correlations with glycemic tracking parameters (HbA1c: $r = -0.468$, $p = 0.002$), fasting glucose values (BSF: $r = -0.362$, $p = 0.021$), and lipid sub-fractions (LDL: $r = -0.552$, $p < 0.001$). Serum prolidase activity was positively correlated with protective lipid fractions (HDL: $r = 0.432$, $p = 0.004$) and inversely correlated with poor metabolic control markers, including HbA1c ($r = -0.327$, $p = 0.039$), VLDL ($r = -0.315$, $p = 0.041$), and serum triglycerides (STG: $r = -0.304$, $p = 0.049$).

Discussion

This study evaluated the relationship between systemic oxidative stress markers and serum prolidase activity to better understand the physiological changes that occur in patients with diabetic neuropathy. The results demonstrate a clear increase in oxidative metrics (TOS and OSI) across the patient groups, confirming that oxidative stress tracks with the severity of diabetic microvascular complications [2,13].

Chronic hyperglycemic environments trigger excessive production of reactive oxygen species (ROS) through pathways such as glucose auto-oxidation, increased advanced glycation end-product (AGE) formation, and heightened polyol pathway flux [11,13]. When systemic ROS production exceeds the capacity of endogenous antioxidant defences, it causes oxidative damage to endothelial cell membranes and peripheral nerve fibres.

In this study, the high statistical significance of elevated TOS and OSI levels in diabetic neuropathy cases underscores how systemic oxidative stress contributes to progressive neurovascular damage. These findings align with earlier work by Uzar et al. [2], which demonstrated that altered oxidative status plays a key role in the pathogenesis of diabetic neuropathy, as well as work highlighting global metrics for evaluating diabetic systemic complications [14].

The observed changes in serum prolidase activity add another dimension to our understanding of DN pathophysiology. Prolidase plays a critical role in collagen recycling by isolating proline from matrix degradation products, making it an essential

regulator of extracellular matrix (ECM) architecture and tissue remodelling [3,9].

In long-standing diabetes, abnormal matrix remodelling inside the perineurium and endoneurial microvessels can impair endoneurial blood flow, leading to peripheral nerve ischemia and structural breakdown [10].

Our findings indicate that prolidase activity is modulated by metabolic status, as shown by its significant correlations with HbA1c, protective HDL fractions, and lipid profiles within the neuropathy cohort. Collectively, these results suggest that systemic oxidative stress and altered prolidase-mediated collagen turnover are closely linked processes that contribute to the development and progression of diabetic neuropathy.

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