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Original Article

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Role of biochemical parameters in prediction of diabetic peripheral neuropathy

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Abstract

***Background & Aims*:** Type 2 diabetes mellitus is the most prevalent form of diabetes seen worldwide. Neuropathy is one of the most common micro-vascular complications of type 2 diabetes mellitus. DPN is considered a main risk factor for diabetic foot leading to amputation, and hence a significant cause of morbidity in diabetes mellitus. Increasing age, longer duration of diabetes and poor glycemic control are well recognized risk factors for DPN. Influence of oxidative stress and corresponding inflammatory changes in tissues in chronic diabetes can be evaluated by certain biochemical parameters. The aim of the present study was to evaluate these biochemical parameters in predicting risk for neuropathy.

Materials & Methods: This is a randomized case control study. This study was done in a tertiary care hospital in Andhra Pradesh. The study was conducted for a period of 4 months from the month of June to October 2022. All the subjects were the patents attending medical OPD and demographic characters were noted. The patients were asked for an overnight fast for collecting blood samples for analyzing parameters like fasting plasma glucose, glycosylated hemoglobin, renal and lipid profile. Institutional ethical committee clearance was taken before starting the study. The study includes a total of 200 subjects with 100 cases of diabetic patients with neuropathies compared with 100 controls of diabetic patients without neuropathy for various biochemical parameters. Statistical analysis was done using graph pad prism software for unpaired t- test and p-value.

***Results*:** There was a significant increase in the levels of fasting plasma glucose ($p< 0.0002$) glycosylated hemoglobin ($p <0.0006$), Total Cholesterol ($p<0.0017$), triglycerides ($p <0.0232$), creatinine ($p<0.0001$) and Low-density Lipoprotein cholesterol (LDL-C) ($p< 0.0080$) in patients with diabetic neuropathy when compared to diabetic patients without neuropathy. And there is significant correlation with duration of diabetes ($p<0.0320$) and other associated risk factors like hypertension systolic blood pressure (SBP) ($p< 0.003$) diastolic blood pressure (DBP) ($p<0.0001$) and Body Mass Index BMI ($p<0.002$).

***Conclusion*:** From this study it can be seen that regular screening of diabetic patients using biochemical parameters like glycosylated hemoglobin, lipid profile and creatinine and considering the duration of diabetes and other associated risk factors helps in the prediction and prevention of development of neuropathy at an early stage.

***Keywords*:** Diabetic Neuropathy, Duration of Diabetes, Inflammatory Status, Lipid Profile, Oxidative Stress

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Introduction

Diabetes mellitus (DM) is an important global health problem. Around 425 million people are suffering from diabetes as of now, and this number may rise to 628 million people by 2045 (1). Diabetic peripheral neuropathy (DPN) is the most prevalent complication of diabetes mellitus (2). The prevalence of DPN in type 2 DM ranges from 21.3 to 34.5% and between 7 to 34.2% in type 1 DM. [3,4). DPN is a leading cause of disability, and it affects the quality of life due to chronic pain, high risk of falls, foot ulceration, and limb amputation (5, 6). Furthermore, DPN symptoms often lead to sleep disorders, anxiety, and depression (7, 8). The poor glycemic control and the resulting micro angiopathy are considered the underlying pathophysiology. However, some other additional factors are also involved in the neuropathy progression, such as modifiable cardiovascular risk factors, including dyslipidemia, smoking, and hypertension. Despite the importance of DPN, there are no effective screening methods, which results in delayed diagnosis of DPN. Hence regular monitoring of diabetic patients using biochemical investigations help in early detection of peripheral neuropathy thus helping in prevention and progression of disease (9).

Diabetic peripheral neuropathy is a microvascular complication of diabetes mellitus and in type 2 diabetes, not only hyperglycemia but also other metabolic alterations like renal impairment and persistent inflammatory status due to adiposity play a major role in axon injury (10). The aim of the present study is to find out a better biochemical marker for early detection of diabetic neuropathy in diabetics apart from the existing markers. Hyperglycemia causes endothelial injury leading to vascular damage through generation of free radicals. Oxidative stress plays an important role in the development of diabetes and indirectly by imbalance of ROS production due to inflammation resulting in Cardio Vascular Diseases (CVD). It was observed that the lipid peroxidation in patients with diabetes is directly related with the development of atherosclerosis together with establishment of pro-inflammatory state (11). Also, diabetes as such can be regarded as a pro-oxidant state caused by increased lipid oxidation (12). C-reactive protein, a major cytokine mediator of the acute-phase response, which stimulates acute-phase protein production in the liver and has diabetogenic actions are seen markedly elevated in diabetic population with complications (13). The highest levels of acute-phase markers were found in those patients with most features of the insulin resistance syndrome. Though there are established biomarkers for prediction of DPN, still there is increased prevalence of DPN. The aim of this study is to find out if these alternative biochemical markers such as inflammatory markers like CRP may be helpful in early detection of oxidative stress in chronic diabetics leading to diabetic peripheral neuropathy.

Materials & Methods

This study was a randomized case control study conducted in the Department of Biochemistry, tertiary care hospital, Andhra Pradesh for a period of 4 months from June to October 2022. Type 2 diabetic patients who visited the out-patient and in-patient departments were included in the study. A total of 200 subjects were selected. Sample size was calculated using Cochrane formula. Among these 100 patients were diagnosed with peripheral neuropathy based on clinical findings and the remaining 100 were diabetic patients without neuropathy. Institutional ethical committee clearance was taken before starting the study. All the patients, including the controls, were fully informed about the purpose, the procedures and the hazards of the study. After taking voluntary informed consent, all the subjects were screened for the inclusion criteria and the exclusion criteria. Diabetic patients attending medical OPD for a routine checkup without symptoms and signs of neuropathy were included in the control group. And chronic diabetic patients with symptoms and signs of neuropathy were included in cases. Patients with secondary hyperglycemic states like hypothyroidism, conditions like congestive cardiac failure, renal failure and proven renal diseases, eye disorders before the onset of diabetes mellitus and pregnancy were excluded from the study. Five milliliters of fasting venous blood was collected from all the above-mentioned groups. The

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samples were centrifuged, separated and stored at 4°C until analysis. The blood samples were analyzed for fasting blood sugar, serum creatinine, blood urea, CRP uric acid, and calcium and lipid profile. For glycosylated hemoglobin estimation and C - reactive protein (CRP), EDTA blood samples were used. Fasting blood sugar was investigated by the glucose oxidase method (GOD-POD), serum creatinine by Jaffe's method, cholesterol by the cholesterol oxidase peroxidase (CHOD-POD method, triglycerides by the glycerol -3 – phosphate oxidase peroxidase method (GPO-POD) enzymatic method, high-density lipoprotein cholesterol (HDL-C)by phosphor tungstate precipitation and CHOD–POD, glycosylated hemoglobin (HbA1c) by the cation-exchange resin method, uric acid by enzymatic method and calcium by Arsenazo method. Peripheral neuropathy was tested by using the Joint and Position Sense Method. Blood pressure was measured using manual BP apparatus on the right hand in sitting position.

Statistical Analysis: The statistical analysis proceeded in all groups of study, descriptive statistics were performed using mean and standard deviations (SDs) with least significant difference (LSD) test for (p *value* $\leq$ *0.05*) was considered to be significant. All analyses were performed with the GraphPad QuickCalcs software.

Results

The following findings were observed in this study.

Table 1: Demographic characters of all the subjects

Parameters	Diabetic patients without nephropathy Mean ± SD	Diabetic patients with nephropathy Mean ± SD	P value
Age	49.10 ± 10.74	49.71 ± 10.49	0.6850
Male	51	62	
Female	49	38	
Duration of Diabetes	7.817 ± 5.055	9.17 ± 3.701	0.0320
Systolic BP	125.8 ± 16.95	135.12 ± 18.39	0.0003
Diastolic BP	78.95 ± 10.5	87.22 ± 7.87	0.0001

Results of continuous variables as Mean and Standard Deviation and categorical variables as proportions. Value of p obtained by comparing two groups. BP-Blood pressure.

Table 2*:* Biochemical parameters comparing the groups

Parameters	Diabetic patients without neuropathy Mean ± SD	Diabetic patients with neuropathy Mean ± SD	p- value
Fasting plasma glucose	135.29 ± 44.26	158.98 ± 43.11	0.0002
Glycated Hemoglobin	7.812 ± 1.604	8.551 ± 1.393	0.0006
Total cholesterol	166.57 ± 42.23	184.76 ± 38.32	0.0017
Triacylglycerol	174.32 ± 83.95	199.05 ± 68.13	0.0232
LDL Cholesterol	93.57 ± 36.97	108.09 ± 39.66	0.0080
HDL Cholesterol	38.68 ± 5.4	37.89 ± 5.62	0.3118
Sodium	140.43 ± 4.58	140.88 ± 4.68	0.4929

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Parameters	Diabetic patients without neuropathy Mean ± SD	Diabetic patients with neuropathy Mean ± SD	p- value
Potassium	4.070 ± 0.443	4.235 ± 0.514	0.0159
CRP	7.078 ± 8.626	7.817 ± 6.268	0.4891
Calcium	9.138 ± 0.733	9.036 ± 0.960	0.3995
Uric acid	5.940 ± 1.634	6.308 ± 2.120	0.1708
Urea	32.22 ± 7.33	33.83 ± 8.09	0.1418
Creatinine	1.050 ± 0.253	1.268 ± 0.290	0.0001

Results of continuous variables as Mean and Standard Deviation and categorical variables as proportions. Value of p obtained by comparing two groups. LDL = Low-Density Lipoprotein, HDL = High-Density Lipoprotein, CRP = C-Reactive Protein.

Table-1 shows the demographic characteristics of all the study participants. There is no significant age group difference in diabetic group with neuropathy and without neuropathy. But comparatively duration of diabetes is significantly more in group with neuropathy than without neuropathy. Similarly, there is a significant increase in systolic and diastolic BP in neuropathy cases than without. There is no significant gender difference of incidence on comparison of two groups.

Table-2 shows the comparison of the biochemical parameters between the controls and cases. There was a significant increase in fasting plasma glucose (*p<0.0002*), Glycosylated hemoglobin (*p<0.0006*), Total Cholesterol (*p<0.001*), Triacylglycerol (*p<0.0232*), LDL cholesterol (*p<0.0080level*), creatinine (*p<0.0001*) and potassium (*p<0.0159*) values in cases of diabetes with neuropathy as compared to those of the controls that are diabetics without neuropathy. But there was no significant difference in parameters like HDL Cholesterol, Sodium, CRP, Calcium, Urea and Uric acid between the two groups.

Discussion

Diabetes mellitus (DM) has emerged as the leading cause of morbidity worldwide. Previously, diabetes was confined to developed countries. However, recent studies suggest that the prevalence has increased worldwide, particularly in developing countries like South Asian region with an estimated increase in the prevalence of diabetes of over 151% between 2000 and 2030 (14). Neuropathy is one of the most common micro-vascular complications of diabetes mellitus (15). Neuropathic disorders in diabetes can affect all types of nerves including central, peripheral and/or autonomic nervous systems. This is called as distal peripheral neuropathy (DPN) or diabetic polyneuropathy affecting the peripheral nervous system and it is the most common type of neuropathy seen in DM (16). The resultant impaired peripheral nerve functioning leads to loss of protective sensations and impairs patient's perception of incipient injuries leading to ulcerations in the feet. DPN and its complication diabetic foot is considered the main reason for amputation, and causes a significant morbidity in DM (17). Although, DPN is a common and important complication of diabetes, and it has not been extensively studied as other micro-vascular complications like cataract, retinopathy and nephropathy (18). In this study, the role of biochemical markers such as glycosylated hemoglobin, creatinine, fasting blood sugar, total cholesterol, triglycerides and Low density lipoprotein were found to be remarkably useful in the prediction of the micro vascular complications in diabetic patients.

The severity of neuropathy was related basically to the longer duration of diabetes and the levels of glycosylated hemoglobin. The incidence of neuropathy was significantly increased with the duration of the diabetes mellitus as seen from table 1 (p< 0.032) and it

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was associated with a poor glycemic control as seen from HbA1C levels (*p<0.0006*) in table 2. Similar results were reported by Garede et al (1999) and Klein et al (1996) (19, 20). It was observed that the longer duration of diabetes was one of the predictors of the diabetic microvascular complications in the present study. Przegl Lek et al (2002), observed that the most important predictor for all forms of neuropathy was the duration of diabetes (21). In a study which was carried out by Porta et al (2001) of the EURODLAB Prospective Study Group, the metabolic control of blood glucose levels over a period of time as shown by HbA1C levels and the duration of diabetes were found to be strong indicators of the progression to neuropathy (22). Similar results were observed by Mogensen and Christensen (1984) who observed that the progression of nephropathy was associated with the duration of diabetes and a poor glycemic control (23).

In this study it was observed that creatinine levels (*p<0.0001*) significantly increased in cases with neuropathy than diabetics without neuropathy which indicates that screening for renal impairment at an early stage of diabetes using renal parameters like urine micro albumin levels may help in predicting and preventing neuropathy because renal impairment is one of the major causes of diabetic peripheral neuropathy. But from this study, it was observed that already renal impairment has set in cases with neuropathy as seen from the significantly elevated creatinine levels and potassium levels (*p<0.0159*) as compared to diabetics without neuropathy. If the study included urine microalbumin levels, it might be useful for prediction in the control group. In a study by Viberti et al (1982),it was shown that an increased microalbumin levels indicating the impairment of renal function in patients with diabetes may predict the neuropathy in diabetes mellitus (24). Similar findings were observed by Varghese et al (2001), who reported that the duration of diabetes was the major risk factors for increased creatinine levels, urine albumin levels and that HbA1c was also associated with nephropathy, which was consistent with the findings of the present study (25). There are many studies showing relationship between renal impairment and diabetic peripheral neuropathy (DPN) but the reason remains inconclusive. In a study conducted on Taiwanese people with T2DM, particularly under the age of 65, it was shown that low estimated GFR and high serum creatinine levels are considered predictors of future DPN. Increased duration of DM, advanced age, male gender of all ages, high BMI and elevated HbA1c are other predictors for DPN. Our study confirms there is an association between renal impairment and DPN. It is also a commonly available assessment tool to predict the future DPN. But it is well known that serum creatinine cannot represent the true renal function as it has its own limitations with age being one among them (26). Many recent research studies reported that serum creatinine cannot be considered an effective screening test for renal impairment (27). Because kidney functioning will almost be compromised by the time serum creatinine concentrations raise above the upper reference limit of normal (28).

Fasting Plasma Glucose Concentration from table (1) shows a significant increase in the concentration of (FPG) (*p<0.0002*) in the neuropathy cases as compared to the diabetic cases without neuropathy. Similar findings were observed in a study by Raid M.H. Al-Salih and Zeena M. Ali. The study shows that the concentration of FPG was significantly increased in the group with diabetic foot and diabetic neuropathy cases when compared to diabetics without complications ($P \leq 0.05$). This result is consistent with the results of our study. The fasting plasma glucose level, which is measured after a fast of 8 hours, is the most commonly used indication of overall glucose homeostasis, largely because of disturbing events. A persistent elevation in blood glucose leads to glucose toxicity, which contributes to the cell dysfunction and the organs thereby which together are called as complications of diabetes (29). Long-term hyperglycemia causes many macro vascular and microvascular complications including heart disease, cancer, eye, kidney, and nerve damage (30). Self-management such as controlling the fasting plasma sugar levels of diabetes is an essential element to prevent or mitigate complications of diabetes, as it was stated that FPG levels increased in

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diabetic neuropathy patients as compared to diabetic patients, leading to diabetic foot syndrome, as revealed in this study (31).

In the present study, elevated levels of total cholesterol ($p<0.01$), triglycerides ($p<0.0017$) and LDL levels ($p<0.0080$) were observed in the cases with neuropathy. This was also observed in the studies which were carried out by Tuttle et al (1999) and David et al (1998) (32). The main risk factors for neuropathy in type 2 diabetes mellitus are plasma cholesterol levels. Hyper triglyceridaemia can be considered as a contributor for the development and progression of diabetic neuropathy from the elevated fasting triglycerides in this study (33). Elevated triglycerides may cause insulin resistance, which in turn is a component of the metabolic syndrome along with triglycerides. The atherogenic potential of hypertriglyceridemia contributes to the progression of DPN. The abnormality in Schwann cell lipid metabolism has also been found associated with DPN. The pathological changes in the myelin structure of nerve correlates with elevated triglyceride levels hence considered as a marker for DPN (34, 35). Thus, correction of elevated triglycerides with dietary control or drug treatment may ameliorate the development and progression of DPN.

CRP is an acute phase reactant, and the serum concentration increases during inflammation, infection, and trauma. Elevated CRP levels are due to increased gene transcription in hepatocytes mediated by the inflammatory cytokines. Inflammation is a well-known risk factor for the development of macro-vascular disease (36). Studies have shown that the vascular reactivity of the microcirculation which includes both endothelium-dependent and endothelium-independent vasodilation is impaired in patients with type 2 diabetes. This impaired vascular reactivity is associated with inflammatory cytokines (37, 38). But the present study could not establish an association between CRP $P<0.4891$ and the development of peripheral diabetic neuropathy. As far as diabetes in humans is concerned, there are no previous studies in human diabetes that demonstrated an association between diabetic neuropathy and systemic inflammation in diabetes.

This study shows that DPN is associated with hypertension and raised SBP ($p<0.003$) and DBP ($p<0.001$) in T2DM. It also shows that hypertension has varying effects on small and large fibers, providing an explanation as to why previous studies of BP lowering therapy have shown an improvement in some but not other measures of diabetic neuropathy. We show that hypertension worsens vibration perception in subjects with T2DM, indicating an abnormality of large nerve fibers, but is also associated with loss of corneal nerve fibers using corneal confocal microscopy. This is clinically relevant as small nerve fibers are the earliest to be damaged and underlie the pathogenesis of foot ulceration and painful DPN (39).

Conclusion:

Thus, this study concluded that poor glycemic control, a longer duration of diabetes, dyslipidemia, inflammation, systemic hypertension and the progression of nephropathy can predict the neuropathy complications in patients with Type 2 diabetes mellitus. The drawback for this study is that the study does not include micro albuminuria, which is one of the best screening methods for early detection. Role of oxidative stress and inflammation can be better demonstrated in future studies by evaluating using better markers which may be useful in early and affective prediction of neuropathy.

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Ethical statement:

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Data availability:

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Author contributions:

first author contributions – study design, sample collection, review of literature

Second author contributions: data compilation, statistics, content writing

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Conflict of interest

The authors declare no competing interests in relation to this study.

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