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Impact Of Glutathione Peroxidase On Michigan Neuropathy Scale And Nottingham Health Profile In Type 2 Diabetes Mellitus Patients With Neuropathy: A Cross-Sectional Study

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Abstract
Background: Diabetic peripheral Neuropathy (DPN) is the most common complication of Type-2 Diabetes Mellitus (T2DM) , affecting almost 50% of all the T2DM patients. DPN has been associated with increase in Disability adjusted life years and decreased Quality of life.
Methods: A cross sectional study was conducted at Hayatabad Medical complex Peshawar, in n=88 T2DM patients from January to August 2023 with ethical approval letter DIR/KMU-ASB&RB/AR/001998. Patients were assessed with Michigan neuropathy scale (history and physical) and Nottingham health profile questionnaire. Glutathione peroxidase (GPX), Malondialdehyde (MDA) levels, Superoxide dismutase (SOD, HbA1c, serum creatinine, and Vitamin B12 levels were recorded from the laboratory records of the patients.
Results: Results reported Significant association of GPX with MDA (P=0.041), and Michigan neuropathy score (P=0.036). Regression model reported significant impact of GPX on Pain (P=0.035, CI 88.11-94.84) and Sleep (P=0.002, CI 0.760-12.698) in patients with T2DM. the combined effect of GPX and SOD and GPX and Vitamin B12 was not significant. MAD concentration in the studied sample was 6.92µM, IQR: 2.745, SOD 94.45 U/mL, IQR: 39.95 and GPX 51.91 U/gHb reported. MDA was elevated in 93%, decreased SOD in 80.6% and decreased GPX was reported in 72.7% of the patients.
Conclusion: the concertation of Antioxidants GPX and SOD was decreased and MDA was elevated in T2DM patients. T2DM patients with lower GPX may report higher score on Michigan neuropathy assessment. Concertation of GPX in Diabetic patients can be found associated with pain and disturbed sleep patterns.

Keywords: Diabetes mellitus. Glutathione peroxidase, Malondialdehyde, diabetic neuropathy, Michigan neuropathy assessment, Nottingham health profile.

Introduction

Diabetic Peripheral Neuropathy (DPN) is one of the most common and progressively disabling health conditions caused by Diabetes Mellitus (DM) and Type-2 Diabetes Mellitus (T2DM). Prevalence of DM has been growing worldwide exceeding from 200 million cases in 1990 to 830 million in 2022, increasing in lower middle-income and higher-income countries[1]. T2DM is the most common type of diabetes among older adults and makes up 96% of the total diabetes prevalence worldwide[2] DM can lead to several systemic diseases which increase the risks of hospitalization, increase in healthcare costs. In 2019, Disability Adjusted life years (DALYs) associated with T2DM were counted as 66.3 million, with 801.5 DALYS/100,000 population, with 26.7% of increase since 1990[3]. The burden of diabetes is consecutively increasing within developing countries due to increase in sedentary lifestyles, diet modifications, and genetic and hereditary susceptibilities[4]. According to 2021 estimates, Pakistan ranks 3rd in world diabetes prevalence, with 33 million of the population being diabetic, approximately 26.7% of the country living residents[5,6]
Diabetes is associated with multiple complications and comorbidities which progressively impact health and quality of life (QoL) in diabetic patients[7] Although, regular exercise, changes in lifestyle exercise routine and medicinal management have improved QoL in diabetic patients[8]. DPN can be caused by many factors including older age, comorbidities like hypertension, poor glycaemic control, long history of diabetes, peripheral vascular disease and excessive alcohol consumption[9,10]. DPN is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people

with diabetes after the exclusion of other causes"[11]. DPN causes symmetrical paraesthesia, loss of sensation and hyperalgesia and can lead to severe complications of foot ulcerations, gangrene, and amputations in diabetic patients[12]. Prevalence of DPN in Type 1 diabetes has been reported as 29.1%, and 42.2% to 50% in T2DM patients, with DPN-related pain in 20% of diabetic patients[10,13]

The pathophysiology of DPN is considered to be caused by the mixed interplay of hyperglycaemia, dyslipidaemia and insulin resistance, with alterations in mitochondrial functions, inflammation and oxidative stress[14]. The overproduction of reactive oxygen species (ROS) or the deregulation of antioxidant systems leads to oxidative damage in DPN, thus novel therapeutics are focused on targeting oxidative stress in treating DPN [15]. In Oxidative stress, the amount of free radicals in the body exceeds the number of antioxidants that can eliminate them, while impaired glucose metabolism in diabetes, and excess glucose concentrations lead to excessive accumulation of toxic metabolites, leads to mitochondrial injury and excretion of ROS[16,17]. The most common oxidative stress biomarkers in DPN have been reported to be Malondialdehyde, Thiobarbituric acid reactive substances, and 8-hydroxydeoxyguanosine, while superoxide anions, hydrogen peroxide and hydroxyl radicals are common free radicals associated with development of DPN[18,19] Impacts of oxidative stress are mitigated by natural and synthetic antioxidants like glutathione, Vitamin C and E, Phenolic acids, butylated hydroxyanisole and hydroxytoluene[20–23]. Antioxidants repair or remove the damaged biomolecules from the body caused by ROS, before their accumulation leads to altered cellular metabolism and irreversible damage. The biologically found antioxidants are superoxide dismutase (SOD), catalase, Glutathione peroxidase (GPx), Glutathione (GSH) and some types of proteins[24]. Patients with T2DM have been reported to have lower concentrations of GPx and thus were reported with higher concentrations of ROS[25] GPx is a selenium-containing antioxidant enzyme which catalyses the reduction of hydrogen peroxide and organic hydroperoxides using glutathione (GSH) as hydrogen donor. GPx metabolizes hydrogen peroxide by oxidizing the tripeptide GSH into an oxidized form (GSSG)[26].

$2GSH + H_2O_2 > GSSG + 2H_2O$

Aim of the current was to find out the impact of GPX on DPN in patients with T2DM and to evaluate the impact of GPX on Michigan neuropathy assessment scale and Nottingham health profile as an important antioxidant against ROS.

Methods

The current study is part of a randomised controlled trial approved by the Advanced Study and Research Board of Khyber Medical University, approval letter DIR/KMU-ASB&RB/AR/001998. Ethical approval was issued by the Institution Ethical Review Committee approval number KMU/IBMS/IRBE fourth meeting 2023/9821-21. All the study procedures and protocols were carried out in adherence with the institutional regulations and guidelines, Declaration of Helsinki, and Good Clinical Practice guidelines. The trial was registered with clinicaltrial.gov, registration number NCT06131918. The study included n=100 T2DM patients diagnosed according to American diabetic association guidelines and patients were enrolled in the study from the endocrinology department of Hayatabad Medical Complex (HMC) upon patient verbal and written consent of voluntary participation. Patients were assessed for systolic and diastolic blood pressure, and Michigan Neuropathy history and physical assessment scale were utilised for assessing complications related to diabetes, and responses were recorded in to SPSS (Statistical package for social sciences) version 26. Patients' energy level, pain, emotional reaction, sleep, social isolation and physical abilities were assessed through Nottingham scale. Vitamin B12 (Cobalamin), haemoglobin, alkaline transferase, serum creatinine, glycated haemoglobin (HbA1c), GPx level, superoxide dismutase, Malondialdehyde and levels of superoxide anions were included in the labs. Patients upon receiving in the endocrinology department were confirmed for diabetes through routine lab tests. The inclusion criteria included confirmed diagnosis of diabetes, at least a year of diabetic history, minimum eighteen years old and agreed for voluntarily participation in the study. Upon verbal and written consent, Patients was assessed for systolic and diastolic blood pressure, Michigan neuropathy history and physical assessment were performed followed by Nottingham scale parameters. Laboratory reports of the patients were analysed and findings required for the study were recorded in SPSS. Michigan Neuropathy Screening Instrument (MNSI) was used for evaluation of history and physical assessment of neuropathy in study participants. For history score of >4 was considered as eligible for neuropathy and for physical assessment of neuropathy score of >2.5 was considered as cut-off point for neuropathy assessment.

Results

Current study was conducted in n=88 diabetic patients with dominant female sample including 55.7% (49/88) female and 44.3% (39/88) male patients. Mean age of the participants was 52.19±7.6 years and 74% of participants were in the age group of 46-60 years thus comprising mainly the late adult population. Mean BMI was 27.49±3.95 kg/m², 63.6% of patients were having moderate physical activity occupation, 69.3% of patients were diabetic only and 30.7% were diabetic and hypertensive as given in Table I.

Table I: Sociodemographic parameters of Type II Diabetic patients diagnosed with neuropathy.

Variables	Frequency	%	Mean	Significance with GPx
Gender	Male: 39 Female: 49	44.3 55.7		0.756
Age	18-30 years:1 31-45 years:19 46-60 Years:65 61 years & above:3	1.1 21.6 73.9 3.4	52.19±7.6	0.949

BMI	Underweight: 0 Healthy weight 27: Overweight: 36 Obesity class I: 22 Obesity class II: 2 Obesity class III: 1	0 27 36 22 2 1	27.49±3.95	0.193
Occupation	Strenuous physical:17 Moderate physical:56 Sedentary:15	19.3 63.6 17.0		0.798 0.664 0.998
Co-morbidities	Diabetic Only: 61 Diabetic and hypertensive:27	69.3 30.7		0.180
Diabetes history in years	Less than 5 years: 23 6-10 years: 44 11 years and above:21	26.1 50.0 23.9	8.78±4.2	0.937
Malondialdehyde	Low concentration: 2 Normal concentration: 4 High concentration:55 Very high concentration: 27	2.3 4.5 62.5 30.7	Median: 6.92µM, IQR:2.745	0.041
Superoxide dismutase	Low concentration:71 Normal concentration: 7 High concentration:10	80.6 8.0 11.4	94.45 U/mL, IQR:39.95	0.083
Glutathione peroxidase(GPX)	Low concentration:64 Normal concentration: 16 High concentration:8	72.7 18.2 9.1	51.91 U/gHb	
HbA1c (%)	Pre-Diabetes 4 Diabetes 84	4.5 95.5	10.20±2.56	0.354
Serum creatinine	Low: 24 Normal: 57 High: 7	27.3 64.8 8.0	0.928mg/dL±0.20	0.231
Haemoglobin	Low: 32 Optimal: 56	36.4 63.6	13.60±1.57	0.377
Vitamin B12	Borderline:46 Normal:42	52.3 47.7	291.7±70.15 pg/ml	0.248
Michigan neuropathy History			10.557±0.980	0.571
Michigan neuropathy Physical assessment			7.580±1.393	**0.036**
Nottingham Health Profile Energy Pain Emotional Reactions Sleep Social isolation Physical Abilities			 97.81±6.93 93.71±10.32 52.70±25.37 69.45±14.60 64.67±13.49 43.68±7.55	 0.747 0.221 0.499 0.998 0.065 0.270

Data was collected and analysed for 88 participants, 44.3% (39/88) male, and 55.7% (49/88) were female. Due to non-normal distribution of data Spearman Rho was applied for association between the sociodemographic variables and its association with GPX concentration. Gender, age, BMI, occupation, co-morbidities, diabetes history in years, superoxide dismutase, HbA1c, serum creatinine, haemoglobin levels, and vitamin B12 levels did not reported significant association with GPX. Levels of MDA were reported to have significant association (P=0.041), P<0.05. Michigan neuropathy physical assessment (P=0.036), P<0.05 was significant with levels of GPX in the patients Table I.

The six factors of Nottingham health profile energy levels, pain, emotional reactions, sleep, social isolation and physical abilities none reported significant association with GPX as shown in Table II.

Table II: Regression model of Glutathione peroxidase levels with Nottingham health profile and Michigan Neuropathy score

SN	variables	Intercept constant	Significance	Confidence interval	
				Lower bound	Upper bound
1	Energy level	97.452	0.554	95.064	99.545
2	Pain	91.653	0.035*	88.116	94.841
3	Emotional reaction	43.898	0.332	41.447	58.473
4	Social isolation	69.254	0.909	64.090	74.781
5	Sleep	6.446	0.002*	0.760	12.698
6	Physical abilities	42.611	0.386	39.925	45.498
7	GPX and VitaminB12	7.995	0.088	7.522	8.601
8	GPX and Superoxide dismutase	7.814	0.009	7.471	8.118

GPX was reported to have protective effect on neuropathy in patients with diabetes, in the absence of GPX the intercept constant value of 8.053 was the neuropathy score. The GPX coefficient -0.009 suggested that for every 1 unit increase in GPX levels the neuropathy score decreased by 0.009 units. The relationship was significant at P=0.036, P<0.05. Bootstrap

analysis for coefficients reported significant positive association between pain (P=0.035), P<0.05 and GPX. The sleep factor in the Nottingham health profile was reported to have significant linear association (P=0.002), P<0.05 for GPX. The combined effect of GPX and Vitaminb12 was tested for its protective role in diabetic neuropathy, which was not significant. The combined effect of GPX and Superoxide dismutase (P=0.009), P<0.05 was reported significant, lowering neuropathy scores on the Michigan scale.

Discussion

Among the studied n=88 T2DM patients laboratory reports were analysed for MAD, SOD, GPX, HBA1C, Serum creatinine, Haemoglobin and Vitamin B12 concentrations. Concentrations of GPX has been reported to 196 to 477 μmol in Plasma, 49 to 93 U/gHb in erythrocytes and 52 to 96 U/gHb in whole blood[27]. for current study GPX concentration was assessed in the whole blood thus low concentration was considered as <51 U/gHb, normal range was considered as 52 to 96 U/gHb and higher concertation was termed as >96U/gHb. Findings of the current study reported low concentrations of GPX 51.91 U/gHb, lower than the 52 to 96 U/gHb of normal range. Antioxidants activity in patients with T2DM has been reported to be lower overtime and decreased GPX has been found in T2DM after ten years of the disease[28], although in findings of the current study no significant association was reported between GPX and duration of diabetes. GPX was reported to have significant association with Michigan neuropathy physical; assessment scale (P=0.036), while for the factors of Nottingham health profile Energy (P=0.747), pain (0.221), emotional reactions (0.499), sleep (0.998), social isolation (0.065) and physical abilities (0.270), none of the values were found significant in the correlation. Although the regression model reported GPX significant association with Michigan neuropathy score (P=0.036), Nottingham pain level (P=0.035), and Sleep (P=0.002). The combined effect of GPX and vitamin B12 and GPX and SOD were not found significant. While empirical research has reported that GPX being a prominent antioxidant may have physiological processes responsible for pain modulation, and may play a critical role in pain management[29]. While the ROS leads to cellular destruction, it also initiates or exacerbates the inflammatory responses thus enabling the pain cycle[30]. while disturbed sleep patterns in the animal models have been reported to be cause of imbalance antioxidants[31], which in the context of the current study can be found decreased GPX and SOD concentrations in the patients with T2DM. While disturbed sleep patterns in the T2DM population has been found to be caused by lowered levels of GPX and increased concentrations of MDA concentrations[32], consecutively reported in the studied sample of the current study where MDA concentrations were in 93% and decreased GPX concentrations in 72% of patients.

MDA mean concentration was reported 6.92μM, IQR:2.745, with 93.7% of patients reported high and very concentrations as compared to standard range of 2.0 to 4.0 μM [33,34]. MDA concentration has been reported to be in the range of 2.0 to 4.0 μM, in different studies[33,34], for current study MDA levels were defined as low concentration (less than 2.0 μM), normal concentration (2.0-4.0 μM), high concentration (4.1-8.0 μM) and more than 8.0 μM as very high concentration. Findings of the current study reported MDA mean concentration of 8.85μM±6.48, which is higher than the standard average of very high concentration. SOD is a metalloenzymatic chemical working as antioxidant and mitigates the impacts of oxidative stress thus reported to have protective mechanism in patients with DPN, while lower levels of SOD has been reported in patients with DPN[35] Normal concentrations of SOD in healthy controls has been reported to be in the range of 149.70-207.10 U/mL with 95% of confidence interval, for current study this range was defined as the normal range, and values below or above this range were defined as low and high levels of SOD[36] in the studied sample SOD concentration was 94.45 U/mL, IQR:39.95, reported very low than the normal mean concentrations.

As Physical activities has a significant impact on T2DM and habitual aerobic exercises has been reported to be helpful in glycaemic control[37], participants of the current study were grouped in the occupation categories of strenuous, moderate and sedentary physical activities , based on the type and intensity of physical activity associated with occupation. Although HbA1c levels and GPX in the studied sample did not reported significant association with type of physical activity in the occupation categories, which is contrary to the empirical evidence as many studies has reported significant association between T2DM levels and physical activity[38].while regular physical activity has been reported to increase GPX levels, which was not found significant by current study[39]. Although, outdoor physical activities are an important aspect of glycaemic control and activities related to occupation may not be sufficient to find out the impact of physical activity on HbA1c levels or GPX [40].

SOD association with GPX was not significant (P=0.083) reported by current study, although SOD and GPX has been reported to be protectors against oxidative stress in patients with DPN [41]. in the current study the combined effect of GPX and SOD was also tested for its efficacy in preventing DPN in T2DM patients, the combined model was not found significant (P=0.009). Low concentrations of SOD and GPX has been consecutively reported in the literature to be found in patients with DPN, and it was parallel with findings of the current study, where both SOD and GPX concentrations were reported 94.45 U/mL and 51.91 U/gHb, lower than the standard concentrations of 149.70-207.10 U/mL and 52 to 96 U/gHb respectively.

There was no significant difference in the male and female gender and level of GPX (P=0.765), age categories and level of GPX (P=0.840), BMI categories and GPX level (P=0.107), and Occupation categories (P=0.621). MDA levels had significant positive association (P=0.041) with GPX levels, while the association between MDA and GPX has been reported variability in the empirical evidence. It has been reported significant and negative association in workers exposed to benzene concentrations[42]. While MDA levels has been reported to be lower than GPX levels in patients with T2DM, although no significant association was reported between MDA and GPX[43]. In children with chronic hepatitis, MDA and GPX were reported to have significant association, while results of the current study can be found relevant with findings of a study,

where diabetic rates showed positive association of MAD and GPX as compared to control groups of non-diabetic rats[44,45].

Conclusion

Patients with type 2 Diabetes mellitus has elevated concentration of the oxidative stress factors Malondialdehyde and decreased amount of Glutathione peroxidase and Superoxide dismutase. MDA and GPX were reported to have positive association, significant association of GPX with Michigan neuropathy assessment, and significant association of GPX with pain and sleep factors of the Nottingham health profile.

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Authors' Contribution

1. F.K: Concept, design, and conduct of the study. Writing of the first draft of the manuscript.
Edited, reviewed and approved the final version of the manuscript. The author confirm that no paper mill and artificial intelligence was used.
2. S.H.H: Concept and designed the study. Overall Supervision and Guarantor of the study Edited, reviewed, and approved the final version of the manuscript. The author confirm that no paper mill and artificial intelligence was used.
3. M.O.M: Data curation, formal analysis, and visualization. Edited, reviewed, and approved the final version of the manuscript. The author confirm that no paper mill and artificial intelligence was used.
4. A.H.A: Data collection and analysis. Edited, reviewed, and approved the final version of the manuscript. The author confirm that no paper mill and artificial intelligence was used.
5. A.B: Statistical analysis**.** Edited, reviewed and approved the final version of the manuscript. The author confirm that no paper mill and artificial intelligence was used.
6. A.J: Article search and literature review. The author confirm that no paper mill and artificial intelligence was used.

Human Ethics and Consent to Participate Declaration

This study was conducted in accordance with the ethical standards of the Advanced Study and Research Board of Khyber Medical University Peshawar Pakistan , and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Prior to participation, all participants were informed of the nature, purpose, and potential risks of the study. Written informed consent was obtained from all individual participants included in the study. Participation was voluntary, and participants were informed that they could withdraw from the study at any time without any negative consequences.
Confidentiality and anonymity of the participants have been preserved throughout the study. All personal data have been securely stored and used solely for the purposes of this research.
The format of the consent form signed by the participants is attached.

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