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Research Article

Serum Myelin Oligodendrocyte Glycoprotein and Myelin Protein Zero as Diagnostic Biomarkers in Diabetic Neuropathy

Abbas Mahmood Murad[1*], Maysaa Jalal Majeed[2], Rafid Badri Al-Ameri[2], Ahmed Salim AL-Haidari[3]

[1] Department of Chemistry, College of Medicine, University of Baghdad, Baghdad, Iraq
[2] Al-Imamein Al-Kadhimein Medical City, Baghdad, Iraq
[3] Allergy Center, Rusafah health Center, Baghdad, Iraq
*Corresponding author's email: abbas.mahmoud1209f@comed.uobaghdad.edu.iq

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ABSTRACT

Background: Diabetic neuropathy can affect any peripheral nerve, including sensory neurons, motor neurons, and the autonomic nervous system. Therefore, diabetic neuropathy has the potential to affect essentially any organ and can affect parts of the nervous system like the optic nerve, spinal cord, and brain. In addition, chronic hyperglycemia affects Schwann cells, and more severe patterns of diabetic neuropathy in humans involve demyelization. Schwann cell destruction might cause a number of changes in the axon. study aims to evaluate serum myelin protein level as a predicting marker in the diagnosis of diabetic neuropathy and to prevent early neuropathy complications of type 2 diabetes.

Subjects and methods: To achieve the purpose of the objective, this study involved 120 individuals divided into three groups. The first group included 40 healthy individuals; the second group included 40 type 2 diabetic patients with a diabetes duration of more than 5 years; and the last group included 40 type 2 diabetic patients with a diabetes duration of less than or equal to 5 years. The enzyme-linked immunesorbent assay (ELISA) system is used to detect serum MOG and MPZ.

Results: both groups of type 2 diabetes patients had significant ($p \leq 0.05$) increases in serum myelin protein zero P0 (MPZ) and myelin oligodendrocyte glycoprotein (MOG).

Conclusion: According to the results, myelin protein can be used to diagnose patients with diabetic neuropathy at an early stage. But it did not rise to the level of a biomarker due to a lack of sensitivity.

Introduction

According to the World Health Organization (WHO), type 2 diabetes mellitus (T2DM) (formerly called non-insulin-dependent, or adult-onset) is results from the body's ineffective use of insulin. More than 95% of people with diabetes have type2 diabetes. This type of diabetes is largely the result of excess body weight and physical inactivity (1). Symptoms may be similar to those of type 1 diabetes but are often less marked. As a result, the disease may be diagnosed several years after the onset, after complications have already arisen (1).

While according to the American Diabetes Association (ADA), Type 2 diabetes is a disorder in which the cells of the body do not respond adequately to the hormone insulin. Insulin is a hormone generated by the pancreas that allows sugar in the blood to be used for energy by the body. People with type 2 diabetes have a problem getting sugar into cells, allowing the sugar to linger in the

bloodstream and create hyperglycemia. Type 2 diabetes causes frequent urination, high amounts of urine production, fatigue, weight loss, and thirst that is more frequent than normal. A nutritious diet, frequent exercise, and serum glucose-lowering medication are used to treat type 2 diabetes (2, 3).

The myelin sheath is a greatly extended and modified plasma membrane wrapped around the nerve axon in a spiral fashion. The myelin membranes originate from and are a part of the Schwann cells in the peripheral nervous system (PNS) and the oligodendroglial cells in the central nervous system (CNS).

The myelin sheath is a multilayered membrane formed by the development of the plasmatic membrane of Schwann cells in the peripheral nervous system and central nervous system (PNS and CNS, respectively) (4, 5).

The fundamental function of this membrane is to facilitate effective nerve impulse transmission through the axons it surrounds (6).

Myelin is identified by the existence of proteins that are found only within myelin. About 60% of myelin proteins in peripheral nerves are glycoprotein's (but are less common in the central nervous system), 20%–30% are basic proteins, as well as the remaining belong to several protein families. Glycoprotein's are prominent components of cell surface membranes, they have important roles in the formation, maintenance and degeneration of myelin sheaths (4).There are many factors that can induce demyelization, including inflammation, genetics, infections, toxicity, and nutritional deficits such as some vitamins, hypoxia, copper deficiency, excessive intake of zinc, or malabsorption can affect the spinal cord and peripheral nerves (7).

Common symptoms of demyelinating diseases include: bladder and/or bowel issues, fatigue, Impaired memory Loss of or diminished vision, Numbness or tingling in the hands, feet, arms, legs, or face, Slurred speech, walking difficulties, weakness in the arms or legs (8).

The myelin sheath is a multilayered membrane produced in the peripheral nervous system by differentiation of the plasmatic membrane of Schwann cells.

Oligodendrocyte glycoprotein, also known as myelin oligodendrocyte glycoprotein, is one of numerous proteins generated by oligodendrocytes, the CNS's myelin-forming cells. MOG, along with myelin basic protein (MBP), proteolipid protein (PLP), and myelin-associated glycoprotein (MAG), is an important component of oligodendrocyte surface membranes; these glycoprotein's play critical roles in the formation, development, and breakdown of myelin sheaths.

The fundamental function of this membrane is to facilitate effective nerve impulse transmission through the axons it covers (9, 10).

Myelin oligodendrocyte glycoprotein antibody disease (MOGAD) can affect parts of the nervous system like the optic nerve, spinal cord, and brain. Chronic hyperglycemia targets Schwann cells, and more extreme forms of diabetic neuropathy in patients involve demyelization. Given the tight and intimate mutual support between axons and Schwann cells, Schwann cell destruction might cause a number of changes in the axon (11).

Myelin protein zero P0 (MPZ) is a structural element in the formation and stabilization of peripheral nerve myelin. P0 is also hypothesized to serve as a cell adhesion molecule, holding multiple layers of myelin together, which helps keep these sheets compact by serving as "glue" that keeps the layers of myelin together. Therefore, P0 is considered an essential molecule for myelin formation and maintenance in the PNS (12, 13).

Subjects and Methods

The research was conducted using an analytical cross-sectional design. was carried out between December 2021 and February 2022. age range of 40-70 years. The study involved 62 males and 58 females and involved 120 individuals divided into three groups. The first group included 40 healthy individuals, the second group included 40 type 2 diabetic patients with a diabetes duration of more than 5 years, and the last group included 40 type 2 diabetic patients with a diabetes duration of less than or equal to 5 years. Measurement of parameters that include: serum fasting blood sugar was determined by the dichromatic endpoint method; blood glycatedhaemoglobin (HbA1C) was determined based on the turbidimetric inhibition immunoassay (TINIA), serum (MOG) and P0 (MPZ), it is done by the enzyme-linked immune sorbent assay (ELISA) system.

Inclusion criteria:

Patients had type 2 DM according to WHO criteria (FBS above 126 mg/dl, HbA1c greater than 6.4%), after the physician's diagnosis.

Exclusion criteria:

Any patient with the following problems was excluded from the current study.

- Patients supplement with multivitamins or vitamin B12.
- Alcoholic patients and those with a history of strokes.
- Patient suffering from the following conditions: liver disease, tumours and leukemia, pernicious anemia, and HIV
- Malabsorption (celiac disease, inflammatory bowel disease, gastrointestinal surgery including gastrectomy and gastric bypass surgery).
- Malnutrition (pure vegans, pancreatic insufficiency, and anorexia nervosa).
- Patients with neuropathy other than diabetic neuropathy, additionally, type 1 diabetes.
- Patients on medications that may cause neuropathy, such as anticancer agents, antimicrobials, cardiovascular agents, and immunosuppressant's.

Research design:

The study design includes the total number of participants, the arrangement of the groups, and the test that was given to them. As shown in Figure 1.

Ethical approval

Ethical approval was received from the Scientific Committee Biochemistry Department, College of Medicine, and University of Baghdad, Iraq. It is worth noting that ethical commitment towards patients was obtained, and they were informed of the research objective.

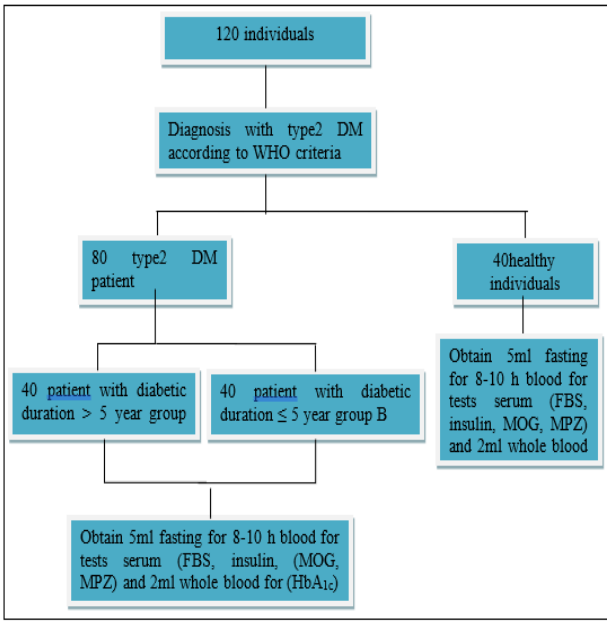


Figure 1: Study design

Statistical analyses:

The Statistical Package for Social Science (SPSS) version 27.0 was used to investigate the variations in parameters (Armonk, NY: IBM Corp).

Mean ± standard deviation was used to represent the variables. The student t-test was used to make the comparison between the groups. Person's correlation coefficient (r) was used to study correlation between two variables. The differences and correlation between values were considered statistically non-significant at the level of (P>0.05) and significant at the level of (P≤0.05). Receiver operator curve analysis (ROC) was used to find the best serum (MPZ), (MOG) Cut-off value.

Results:

As expected, serum FBS, insulin, blood HbA1c, and, as a result, HOMA-IR showed significant (p≤0.05) elevation in T2DM patients compared to the healthy individual's group, confirming the T2DM selected case's diagnosis as shown in table (1).

In this study, both groups of T2DM patients had a significant (p≤ 0.05) increase in serum (MPZ). But with a significant (p≤ 0.05) increase in patients with a type 2 diabetes period greater than 5 years, while patients with a type 2 diabetes period below or equals to 5 years showed, non-significant (p > 0.05) when compared with healthy individuals.

As for the (MOG) both groups of type2 diabetes patients showed significant (p≤ 0.05) elevation in their level of serum (MOG) when compared with the healthy group and between them.

While there was a significant (p≤ 0.05) increase in patients with a type 2 diabetes period greater than 5 years, the patients with a type 2 diabetes period below or equals to 5 years showed non-significant (p > 0.05) when compared with healthy individuals. All of this is explained in the table (2).

Table 1: Mean ± Standard deviation (SD) of serum FBS, insulin, blood HbA1C and HOMA-IR in the Healthy individuals, T2DM with diabetes duration > 5 years, and T2DM with diabetes duration ≤ 5 years patient groups

Parameters	Study groups	NO.	Mean ±SD	P-Value	LSD
S.FBS (mg/ml)	Healthy individual group (A)	40	91.99 ± 10.33	*P =0.0001	B VS A *P =0.0001
	T2DM patients having diabetes for greater than 5 yrs group (B)	40	173.20 ± 66.80		C VS A *P =0.0001
	T2DM patient having diabetes period ≤5 yrs group(C)	40	157.66 ± 62.25		C VS B **P= 0.194
B.HbA1C (%)	Healthy individual group (A)	40	5.37 ± 0.38	*P =0.0001	B VS A *P =0.0001
	T2DM patients having diabetes for greater than 5 yrs group (B)	40	8.28 ± 2.25		C VS A *P =0.0001
	T2DM patient having diabetes period ≤5 yrs group(C)	40	7.87 ± 1.90		C VS B **P= 0.287
S.Insulin (µu/ml)	Healthy individual group (A)	40	9.32 ± 4.42	*P=0.005	B VS A *P= 0.001
	T2DM patients having diabetes for greater than 5 yrs group (B)	40	13.20 ± 6.71		C VS A *P= 0.002
	T2DM patient having diabetes period ≤5 yrs group(C)	40	14.79 ± 6.49		C VS B **P=0.621
HOMA-IR	Healthy individual group (A)	40	2.75 ± 1.05	*P =0.0001	B VS A *P= 0.004
	T2DM patients having diabetes for greater than 5 yrs group (B)	40	6.11 ± 5.86		C VS A *P =0.0001
	T2DM patient having diabetes period ≤5 yrs group(C)	40	6.67 ± 4.62		C VS B **P= 0.244

*P≤0.05=significant, ** P>0.05= non-significant, LSD = fisher least significant difference, S. = serum, B. = blood

Table 2: Mean ± Standard deviation (SD) of MPZ, and MOG in healthy individuals, and patient groups

Parameters	Study groups	NO.	Mean ±SD	P-Value	LSD
S. MPZ ng/ml	Healthy individual group (A)	40	1.43 ± 0.39	*P =0.0001	A VS B *P =0.0001
	T2DM patients having diabetes for greater than 5 yrs group (B)	40	7.53 ± 4.82		A VS C **P= 0.201
	T2DM patient having diabetes period ≤5 yrs group (C)	40	2.24 ± 0.58		B VS C *P =0.0001
S.MOG ng/ml	Healthy individual group (A)	40	1.93 ± 0.29	*P =0.0001	A VS B *P =0.0001
	T2DM patients having diabetes for greater than 5 yrs group (B)	40	10.55 ± 2.11		A VS C **P= 0.315
	T2DM patient having diabetes period ≤5 yrs group (C)	40	4.51 ± 1.33		B VS C *P =0.0001

*P≤0.05=significant, ** P>0.05= non-significant

There is no significant correlation of serum P0 (MPZ) in type2 diabetic patients with type2 diabetes period greater than 5 yrs, with each of S.FBS, S.insulin, B.HbA1C,and HOMO-IR (r= - 0.02, p>0.05), (r= - 0.01, p>0.05), (r= 0.04, p>0.05), (r= 0.03, p>0.05), consequently.

Serum (MOG) also seem no significant correlation to patients with type2 diabetes period greater than 5 yrs, in each of S.FBS, S.insulin, B.HbA1C, HOMO-IR(r= 0.03, p>0.05), (r= 0.17, p>0.05), (r= 0.26, p>0.05), (r= 0.04, p>0.05), consequently, All of this is explained in the table (3).

Myelin Protein Zero (MPZ) showed non-significant correlation in patients with type2 diabetes period below or equals to 5 yrs, with each of S.FBS, S.insulin, B.HbA1c, and HOMO-IR, (r= - 0.02, p>0.05), (r= - 0.15, p>0.05), (r= 0.03, p>0.05), and (r= - 0.11, p>0.05)consequently.

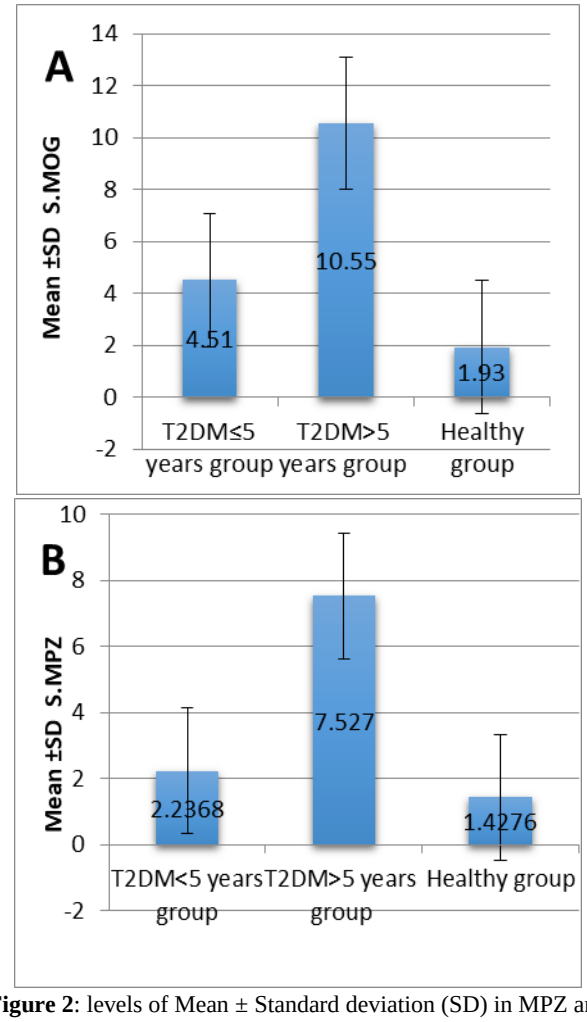


Figure 2: levels of Mean ± Standard deviation (SD) in MPZ and MOG in the study groups: Levels of **A)** MOG, **B)** MPZ, in control and diabetic patient groups

Table 3: Correlation analysis between levels of serum MPZ and MOG for studied parameters in (T2DM with diabetes duration > 5 years) group patients

	S. MPZ ng/ml		S.MOG ng/ml	
Parameters	**correlation coefficient (r)**	**p-value**	**correlation coefficient (r)**	**p-value**
S.FBS(mg/ml)	-0.02	**0.900	0.03	**0.880
S.Insulin(µu/ml)	-0.01	**0.954	0.17	**0.286
B.HbA1C (%)	0.04	**0.820	0.26	**0.167
HOMO-IR	0.03	**0.834	0.04	**0.799

** P>0.05= non-significant

Furthermore, there is no significant correlation of Serum (MOG) in patients with type2 diabetes period below or equals to 5 years, with each of S.FBS, S.insulin, B.HbA1C, and HOMO-IR, (r= -0.14, p>0.05), (r= - 0.10, p>0.05), (r= 0.03, p>0.05), (r= - 0.11, p>0.05), consequently. As shown in table (4).

Table 4: Correlation analysis between serum MPZ and MOG level for studied parameters in (T2DM with diabetes duration ≤ 5years) group patients

Parameters	S. MPZ ng/ml		S.MOG ng/ml	
	correlation coefficient (r)	p-value	correlation coefficient (r)	p-value
S.FBS (mg/ml)	-0.02	**0.924	-0.14	**0.484
S.Insulin(µu/ml)	-0.15	**0.291	-0.10	**0.540
B.HbA1C (%)	0.03	**0.840	0.03	**0.864
HOMO-IR	-0.11	**0.425	-0.11	**0.494

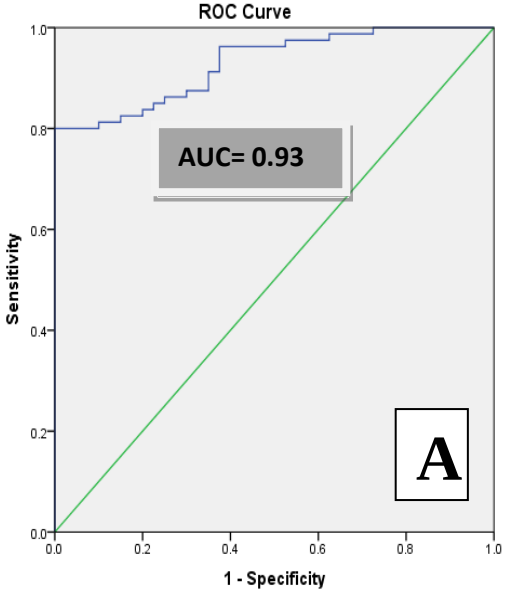
** P>0.05= non-significant

Using the receiver operator characteristic analysis (ROC) curve, to examine the diagnostic efficiency of serum MPZ and MOG levels in relation to type 2 diabetic patients, the ROC curve is a graphical representation of the relationship between clinical specificity and sensitivity.

In addition, the area under the curve (AUC) in ROC analysis indicates the advantage of using the test (s) in question. The results are tabulated in table (4) and figures (2) according to type 2 diabetic patients.

Table 5: Sensitivity and Specificity, area under curve and Cut-off value for serum (MPZ) and Serum (MOG) in type 2 diabetic Patients

parameter	Sensitivity	Specificity	AUC	Cut-off value
S. MPZ(ng/ml)	80%	100%	0.93	2.086
S.MOG(ng/ml)	81.3%	95%	0.935	2.099



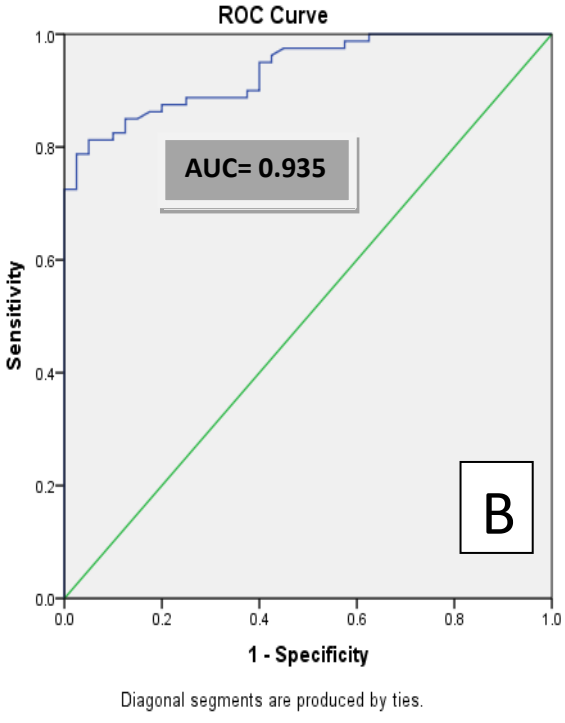


Figure 2: ROC curves for serum myelin protein in type 2 diabetic Patients **A)** ROC curves for serum MPZ **B)** ROC curves for serum MOG

Discussion

Type 2 diabetes is characterized by a relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs (14).The result of this study showed a significant increase in the mean value of FBS, Insulin and HbA1C in DM patients in both groups (T2DM with a diabetes duration of below than or equal to 5 yrs and T2DM with type2 diabetes period greater than 5 yrs) depending on fasting blood sugar level (FBS) and, according to it is the value of HbA1c and insulin. Diabetes is associated with deleterious changes in peripheral nerves, such as myelin damage and a decrease in nerve conduction velocity.

Nerve damage can cause health problems ranging from mild numbness to pain that make it hard to do normal activities and can result in associated disability resulting from foot ulceration and amputation (15). In this study, myelin protein zero and myelin oligodendrocyte glycoprotein (MOG) showed elevations in their levels in diabetic patients with both diabetes duration groups. Myelin anomalies describe diabetic peripheral neuropathy. However, the molecular processes driving such deficiencies are unknown (16). But in general, myelin basic protein levels of between 4 and 8 ng/ml may be a sign of a long-term (chronic) breakdown of myelin. It may also indicate recovery from an acute episode of myelin breakdown, if the myelin basic protein level is greater than 9 ng/ml, meaning myelin is actively breaking down (17).

A demyelinating disease is any condition that results in damage to the protective covering (myelin sheath) that surrounds nerve fibers in your brain, optic nerves, and spinal cord. When the myelin sheath

is damaged, nerve impulses slow or even stop, causing neurological problems (18).

The results showed that there was no significant association between myelin proteins and the studied markers, and this indicated myelin protein was not affected by another marker. The study's result is disagreement with the finding. Evidence from animal studies provides an underlying link between insulin signaling and the myelin sheath (19).

Conclusion:

The estimation of the level of myelin is affected by the severity and duration of type2 diabetes, which makes it a suggestion to measure it in the blood to check the condition of the neuropathy. And while measuring these proteins was beneficial in preventing early neuropathy complications of type 2 diabetes mellitus, it did not rise to the level of a biomarker due to a lack of sensitivity

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Conflict of Interest

No conflict of interest

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