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ORIGINAL ARTICLE

The Role of Serum Glutathione Peroxidase Enzyme in Relapsing-Remitting Multiple Sclerosis.

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ABSTRACT

Background: Multiple sclerosis (MS) is considered an immune-mediated disorder with different disease course., Recently, oxidative stress was reported to play a role in the pathogenesis of MS. Aim: to investigate the role of the serum glutathione peroxidase enzyme in the pathogenesis of Multiple sclerosis, especially the relapsing-remitting type (RRMS), and to assess the relationship between it and disease characteristics.

Methods: 45 patients with RRMS (23 in relapse and 22 in remission) (18 males and 27 females) and 45 age, sex, and body mass index (BMI)-matched healthy subjects were included in this study. Clinical assessment, general, and neurological examination were done. MS Severity was calculated using the expanded disability status scale (EDSS). Magnetic resonance imaging (MRI) of the brain and spine with gadolinium enhancement and visual evoked potential was done for all MS patients. Serum glutathione peroxidase (GP_X) enzyme and routine laboratory tests were assessed.

Results: reduced levels of GP in patients compared to controls. No significant difference was detected between the remitting and relapsing MS groups. In addition, there was a statistically significant negative correlation between serum GPx, disease duration, and physical MSIS. Also, an adverse correlation between serum GPx and gadolinium enhancement was recorded.

Conclusion: Our study demonstrates a significantly lower level of GPX among patients than among controls; this indicates its role in MS pathogenesis, which might be important for new therapeutic strategies based on an antioxidant approach in MS patients.

Keywords: Relapsing-Remitting Multiple Sclerosis, glutathione peroxidase, pathogenesis.

INTRODUCTION

Multiple sclerosis (MS) is characterized by inflammation, demyelination, and axonal loss in the central nervous system (CNS) **(1)**. It affects around 2.5 million individuals worldwide. Oxidative stress results from an imbalance between oxidant and antioxidant systems and is characterized by excess free radical production e.g. reactive oxygen species (ROS) and reactive nitrogen species (RNS) causing injury or cell death **(2)**. These antioxidant molecules include vitamin E, vitamin D, glutathione, antioxidant enzymes (superoxide dismutase, catalase, glutathione), and melatonin **(2)**. In MS, ROS is also considered a marker of oxidative stress as evidenced by the elevation of 7-ketocholesterol in the CSF of MS patients **(3)**. Also, Nitric oxide (NO) and its metabolites were reported to be elevated in the blood and CSF of MS patients. **(4)**Glutathione peroxidase (GPX), one of the peroxidase family, is considered one of the endogenous antioxidants that protect against oxidative damage **(5).** The main role of GPX is to reduce both free oxygen peroxide and lipid hydroperoxides to H2O**(5),** the enzyme has 8 isoenzymes: GPX1 is the highly abundant form, GPX 2 is found to be of lower levels in relapsing-remitting MS (RRMS) as lower glutathione levels point to the presence of oxidative stress in MS **(6).** This research aims to examine the role of serum glutathione peroxidase enzyme in the

pathogenesis of RRMS and to explore the relation between it and disease characteristics.

METHODS

Ethics approval and consent to participate: The study was approved by the Ethical Committee of our Faculty (ZU-IRB# 4164/22-11-2017). Written informed consent was obtained from all patients who agreed to participate in our study.

This case-control study was conducted in the neurology department and MS outpatient clinic at Zagazig University Hospitals in the period from February 2019 to October 2021. The study included 90 subjects divided into 45 patients (18 males and 27 females) and 45 age, sex, and BMI-matched nonsmoker healthy controls without any neurological diseases. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The study's Ethical approval number was (ZU-IRB# 4164/22-11-2017). Written consent was obtained from all participants in our study. RRMS was diagnosed according to the recently modified McDonald criteria 2017 **(7).**

Patients with the relapsing-remitting disease were classified into 2 groups as follows: Group (A): (Remission group): If patients presented 1 month after the relapse and when symptoms had become stable **(8)** and included 22 patients. Group (B): (Relapse group): If there were new symptoms or there was a reoccurrence of old symptoms, for at least 24 hours and occurred after 30 days or more from the previous relapse in the absence of an alteration in core body temperature or infection and included 23 patients. Expanded disability status score (EDSS) is between 1.5- 6 to include ambulatory patients **(9).** No antioxidant drugs were used by the patients.

The control group included 45 subjects in our study of age, sex, and BMI-matched nonsmoker healthy persons. We excluded patients with a history of other neurologic illnesses i.e. strokes, brain tumors, neurodegenerative disorders, and other demyelinating diseases. Other concomitant diseases such as diabetes mellitus, hypertension, hepatic, renal, and pulmonary diseases as well as patients with present infection and pregnant females were excluded also.

Patients were subjected to full medical and neurological history, complete general and neurological examination, criteria of MS (duration of disease, annualized relapse rate, severity of relapses, type of treatment used during relapse and remission) were assessed, annualized relapse rate was calculated by dividing number of relapses by duration of disease **(10).** We got annualized relapse rate by dividing the number of relapses by the duration of the disease **(10).** Assessment of disease disability was assessed using EDSS **(9).** Evidence of disease activity was assessed using the Evidence of disease activity scale and criteria which include physical and psychological Multiple Sclerosis impact scale **(11).**

Radiological investigations including magnetic resonance imaging (MRI) of the brain and spinal cord were conducted. The MS imaging protocol was performed using a 1.5 tesla superconducting MR imager (Achieva, Philips Medical System).

Complete blood count (CBC), hepatic and renal function, lipid profile, ESR, CRP, random blood sugar, and serum uric acid were done as a routine investigation. Special laboratory investigation: enzyme-linked immunosorbent assay (ELISA) for glutathione peroxidase detection using Tecan Austria GmbH 5082 Grodig, Austria SUNRISE (2002).

STATISTICAL ANALYSIS

Data were tabulated and SPSS was used for analysis **(12).** Data were presented as mean ± standard deviation (SD), frequencies, and percentages. Student t-test, ANOVA, or chi-square test was performed when suitable. Correlation analysis was performed. $P < 0.05$ was considered statistically significant (S).

RESULTS

MS was higher in females than males in a ratio of 1.5:1 nearly, with the mean age (±SD) of the remission group was 37.7 (±9.5) years and the relapse group was 34.2 (±8.7) (table 1). The GPx level was reduced in patients than control but there is no difference in its level between remitting and relapsing groups (table 1).

MS duration (M±SD) was 2.1 ± 2.4 years and the mean ARR was 2.1 (±1.9). 80% of cases had a total relapse rate (TRR) less than 5 while 20% of cases had TRR equal or more than 5. EDSS less than 5 in 82% of cases, and only 18% have EDSS equal or more than 5.

Regarding the initial manifestations, the majority of cases (44.4%) presented with pyramidal manifestations followed by visual manifestations (24%). 22.2% of cases presented with sensory manifestations. Brain stem or cerebellar manifestations were initial in 4.4% of cases (table 2).

Table (3) shows that serum GPx levels didn't differ significantly between males and females and also between patients in remission and relapse. Moreover, there is no significant difference in its level as regards ARR or treatment. In addition, GPx was statistically significantly higher in

patients treated with fingolimod and ocrelizumab (table 4).

As regard correlation, there was a negative correlation between serum GPx and disease duration, and physical MSIS. Also, there was an adverse correlation between serum GPx and gadolinium enhancement, but no significant correlation between GPX and VEP latency and amplitude and other laboratory markers (Table 5; Figures 1 and 2). No significant correlation between GPx and markers of inflammation (WBCS (total and differential), CRP) or other laboratory biomarkers could be observed (Table 6)

Table 1: Demographic data of studied groups

Demographic data	**Remission N=22**		**Relapse N=23**		**Controls N=45**		**Test of significance**	**P**
Age (Years)								
Mean±SD	37.7±9.5		34.2±8.7		33.9±10.8		F=1.06	0.34
Range	17-50		17-47		17-65			
Sex	**N**	**%**	**N**	**%**	**N**	**%**	$\chi 2$=1.36	0.5
Male	7	31.8	11	47.8	20	44.4		
Female	15	68.2	12	52.2	25	55.6		
BMI (KG/m2)								
$\overline{X}$ (±SD)	29.2±4.2		30.2±3.8		29.0±3.6		F=0.7	0.49
Range	19-35		20-35.5		19-39			
Glutathione peroxidase (ng/ ml**)**	100.5±18.7		102.4±11		120.6±29.3		F=7.47	0.001*

t: student's t-test, **X2:** chi-square test, **X:** mean, **SD:** Standard Deviation, **BMI:** Body Mass Index, **F:** Analysis Of Variance (ANOVA).

Table 2: Clinical Characteristics of MS Patients

	Range	**Mean±SD**
Duration of disease in years	0.25-8	2.1±2.4
ARR	0.5-8	2.1±1.9
Total relapse rate	**N**	**%**
<5	36	80
≥5	9	20
Initial manifestations	**N**	**%**
Pyramidal manifestation	20	44.4
sensory manifestation	10	22.2
cerebellar manifestation	2	4.4
Brain stem manifestation	2	4.4
Visual manifestation	11	24
EDSS	N	%
<5	37	82
≥5	8	18

ARR: Annualized relapse rate and **EDSS:** Expanded Disability Status Scale

Table 3: Difference between serum GPx levels in males and females, and its relation with Remission, Relapses, ARR, and treatment

Parameter	**N**	**GPx (ng/ml)** $\overline{X}$ **± SD**	**t-test**	**P**
Gender				
Male	18	106.1± 12.4	1.68	0.09
Female	27	90.4± 16.5		
Remission	22	100.5±18.8	0.42	0.67
Relapse	23	102.5±11.5		
ARR				
>1	29	100.2± 14.6	0.78	0.43
<1	16	103.97± 16.7		
Treatment				
Non-specific	18	101.2± 15.9	0.17	0.85
MS-specific therapy	27	102± 14.9		

t: student t-test**, X:** mean, SD: Standard Deviation**,** and **ARR:** Annual Relapse Rate

Table 4: Serum glutathione peroxidase in different types of disease-modifying drugs

DMD	Gpx (ng/ml) $\bar{X}$ ± SD	F	P
Nonspecific	95.8±14.	3.5	0.01*
IFN B	104.6±13.1		
Fingolimod	109.34±0.0		
Ocrelizumab	109.3±8.3		
Cyclophosphamide	97.2±4.5		
Rituximab	53.1±0.0		

DMD: disease-modifying drugs, **X**: mean, **SD:** Standard Deviation, **F:** Analysis of Variance (ANOVA)
* significant.**EDSS:** Expanded Disability Status Scale, **CRP:** C reactive protein and NS: non-significant

Table 5: Correlation of serum Glutathione peroxidase with clinical, radiological, and electrophysiological markers

Parameter	R	P
Disease duration (years)	-0.34	< 0.05 *
ARR	-0.06	NS
EDSS	-0.25	NS
MSIS physical	-0.32	<0.05*
MSIS psychological	-0.28	NS
Gadolinium enhancement	-0.33	< 0.05 *
New T2 lesions	-0.23	NS
Cervical patches	0.21	NS
Black holes	-0.05	NS
Brain atrophy	-0.04	NS
VEP latency		
.Rt	0.009	NS
.Lt	0.006	NS
VEP Amplitude		
Rt.	0.09	NS
Rt.	0.01	NS

Table 6: Correlation between GPx and laboratory biomarkers

Parameter	R	P
WBCs	0.07	NS
Neutrophils	0.08	NS
Monocytes	0.03	NS
Lymphocytes	0.02	NS
CRP	0.07	NS
Cholesterol(mg/dl)	0.1	NS
Triglyceride (mg/dl)	0.09	NS
LDL(mg/dl)	0.003	NS
HDL (mg/dl)	-0.08	NS
RBS	0.08	NS
Albumin	0.13	NS
ALT	0.07	NS
AST	0.001	NS
Uric acid	0.17	NS

WBCs: complete blood count; CRP: C-reactive protein; LDL: low-density lipoprotein; HDL: high-density lipoprotein; RBS: Random blood sugar; ALT: Alanine transaminase; AST: Aspartate transaminase

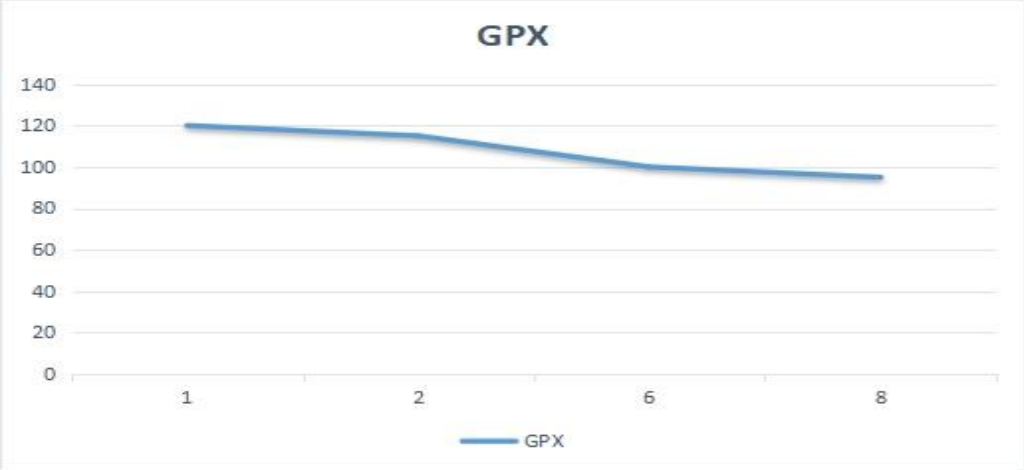

Figure 1: Correlation between GPx and disease duration.

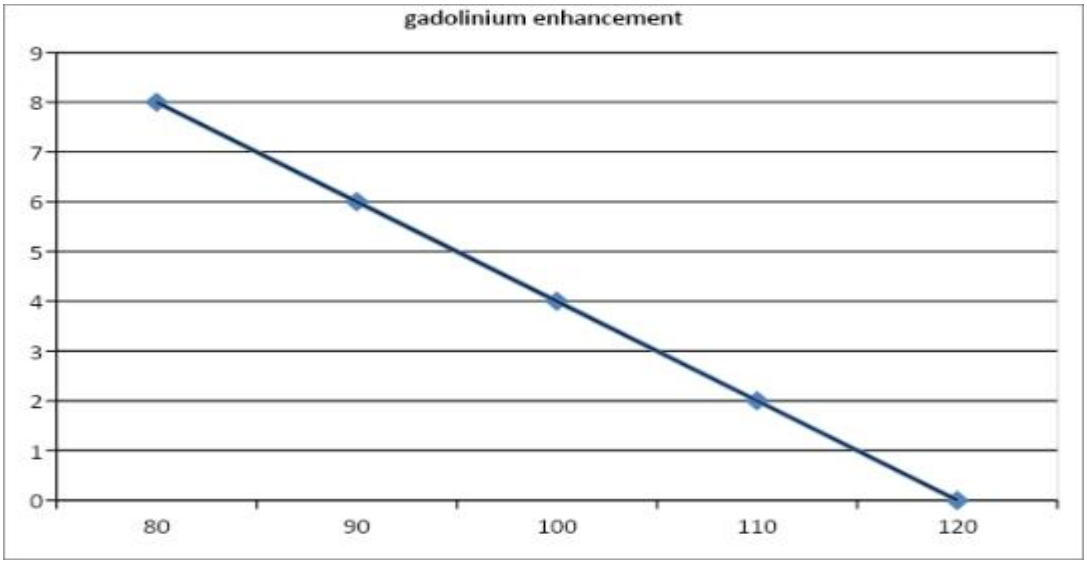

Figure 2: Correlation between GPx and gadolinium enhancement.

DISCUSSION

As a multi-factorial disease**,** multiple sclerosis (MS) characterized by an interaction between genetic predisposition, environmental factors, and aberrant immune response was reported **(13, 14).** The impact of Oxidative stress in MS pathogenesis has been reported previously as there were increased blood concentrations of the reactive oxygen species causing cell injury and death **(15, 16, 17, 18).** Glutathione (GSH), an endogenous antioxidant, is a vital agent in the detoxification of xenobiotics and their metabolites **(19),** detoxification of reactive oxidants **(20),** and preservation of the intracellular redox balance which is very important in the brain **(21).** It acts as a co-substrate to glutathione peroxidase (GPX) and glutathione reductase (GR) enzymes. (**22**). Glutathione peroxidase catalyzes the reduction of hydroperoxides such as H2O2 to oxidized glutathione (GSSG) to protect cells against oxidative damage and GSSG can also be converted back to GSH by glutathione reductase (GR) **(2).** Some studies verified normal antioxidant activity in blood, while others indicate a decrease or increase in this activity.

In our study, we found a significantly decreased serum level of glutathione peroxidase in patients than in the control group. This finding is consistent with the result of earlier studies **(5, 6, 13, 23, 24)** that reported GR and GSH concentrations were higher in sera of MS patients than controls is consequently associated with a decrease in GPX. Elevation of GSH was verified by stimulation of extracellular glutamate which represents that GSH has a neuroprotective role against glutamate toxicity and oxidative damage. Tasset and colleagues found higher activity of GR in RRMS patients compared to controls. In addition, an increased ratio of reduced glutathione to oxidized glutathione (GSH/GSSG) in these patients was recorded **(5)**. On the contrary, the results obtained by Calabrese and colleagues; Krotenko and colleagues Ortiz and colleagues, and Choi and colleagues reported decreased GSH and increased GPX **(25, 26).** However antioxidants levels increase approving of the theory that in an attempt

to protect cells, the cellular response to oxidative stress is likely to arise before the inflammatory response, and when this response is inadequate then a relapse in MS happens **(5).** Ortiz and colleagues showed that GSH level is lowered by 40–50% in RRMS patients than controls, thus GPx levels increased **(27).** However, Di Giussepe and colleagues demonstrated no change in GSH among MS patients **(28).**

Oxidative Stress gained much importance in MS throughout the disease course. Inflammatory processes are initiated by it during the acute phase, while neurodegeneration is maintained by it in the chronic phase **(1).** In this study, we noticed a negative correlation between GPX and disease duration that goes in line with Acar and colleagues **(29**); Tasset and colleagues (**5),** and Ferriera and colleagues **(2).** Fischer and colleagues reported that increased oxidative stress damage leads to more disease severity **(30)**, EDSS is the most widely used index of MS severity. In this study, we found no statistical significance correlation between GPX and EDSS. In contrast, Acar and colleagues **(29)**, Tasset and colleagues **(5),** and Girona and colleagues **(18)** found depletion of GSH, GSH/GSSG ratio, and a decline in GSSG levels and increased GPX in benign MS. This finding could suggest that antioxidant diminution is a probably causative factor not a consequence of MS severity. Miller and colleagues **(31)** and Ljubisavljevic and colleagues **(32)** found a negative correlation between oxidative stress markers and EDSS. On the other hand, we found a significant negative correlation between GPX level and physical MSIS, this coincides with Adamczyk and Adamczyk-Sowa that reported a decrease in MSIS after oxidative stress repair **(33).**

Regarding the relation between GPX and MRI imaging, we found an inverse correlation between GPX and gadolinium enhancement lesions. This matches with Miller and colleagues **(34)** and Adamczyk and Adamczyk-Sowa's results **(33).** In contrast, Ljubisavljevic and colleagues did not report such a correlation **(31).**

The effect of MS pharmacotherapy on biomarkers of oxidative stress has been studied previously, fingolimod and ocrelizumab were the highly studied medications. We found a positive correlation between GPX and treatment with fingolimod and ocrelizumab. Similarly, Yevgi and Demir found that fingolimod decreases total oxidative stress (TOS) and also decreases pre and post-treatment EDSS **(35).** In contrast, Pegoretti and colleagues found that ocrelizumab does not affect oxidative stress **(36).** Moreover, previous studies found no correlation between oxidative stress and types of drug treatment **(18, 29).**

In this study, although we observed a significant difference in WBCs between relapse and remission groups, we found a negative correlation between GPX and signs of inflammation but with no statistical significance. Similar to our results, Koch and colleagues **(37);** Miller and colleagues **(34);** Witherick and colleagues **(38);** Castegna and colleagues **(39)**, and Usatyuk and Natarajan **(40)** reported no significant correlation between oxidative stress and either disease severity or inflammatory activity. This may be explained as oxidative stress heralds the inflammatory response, thus backing the proposition that oxidative stress could modify the permeability of the blood–brain barrier and enhances the adhesion of monocytes to the vascular endothelium.

CONCLUSION

GPX is higher in patients with RRMS than control, but no statistically significant difference was observed in remission or relapse patients, this indicates its role in pathophysiology. We recommend its use as a new therapeutic strategy in the protection and treatment of MS.

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