ORIGINAL ARTICLE

THIOL-DISULFIDE HOMEOSTASIS IN MYASTHENIA GRAVIS

Myastenia Graviste Tiyol-Disülfit Homeostazisi

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No: 1, Ankara, Türkiye.

Geliş tarihi/Received: 13.06.2025
Kabul tarihi/Accepted: 14.07.2025
DOI: 10.16919/bozoktip.1716368

Bozok Tıp Derg 2025;15(3):324-330
Bozok Med J 2025;15(3):324-330

ABSTRACT

Objective: Disorders characterized by a dysfunction in neuromuscular transmission such as myasthenia gravis may be associated with oxidative stress. This study aimed to evaluate the role of thiol-disulfide homeostasis as an index of oxidative stress in adult patients with myasthenia gravis compared to healthy controls.

Material and Methods: This study included 46 patients with myasthenia gravis and 46 age- and gender-matched healthy controls. Blood samples were collected and analyzed for thiol-disulfide homeostasis parameters, total antioxidant status (TAS), and ischemia-modified albumin (IMA) using spectrophotometric and colorimetric methods. Statistical analysis was conducted using SPSS to compare oxidative parameters between groups.

Results: Mean age of patients (24 males, 22 females) was 58.45 ± 6.32 and mean age of control subjects (25 males, 21 females) was 57.22 ± 6.51. Participants in the two groups did not differ in terms of age or gender ($p>0.05$ for both). Patients showed significantly lower levels of native thiol, total thiol, and TAS, and higher levels of disulfide, disulfide/native thiol percentage ratio, and IMA compared to controls ($p<0.05$ for all). These findings indicate increased oxidative stress and disrupted antioxidant defense in patients with myasthenia gravis. There were also significant correlations between decreased antioxidant parameters and increased oxidative stress markers ($p<0.05$ for all tests).

Conclusion: This study confirms that thiol-disulfide homeostasis is significantly altered in patients with myasthenia gravis, highlighting its association with neuromuscular junction disease pathogenesis. Future research could expand on these findings by examining the effects of restoring redox balance in patients with myasthenia gravis.

Keywords: *Disulfide; Homeostasis; Myasthenia Gravis; Neuromuscular; Thiol*

ÖZET

Amaç: Myastenia gravis gibi nöromüsküler iletimde işlev bozukluğu ile karakterize bozukluklar oksidatif stresle ilişkili olabilir. Bu çalışma, yetişkin myastenia gravis hastalarında tiyol-disülfit homeostazının oksidatif stresin bir göstergesi olarak rolünü sağlıklı kontrollerle karşılaştırmayı amaçlamıştır.

Gereç ve Yöntemler: Bu çalışmaya myastenia gravis tanılı 46 hasta ve yaş ve cinsiyet açısından eşleştirilmiş 46 sağlıklı kontrol dahil edildi. Kan örnekleri toplandı ve tiyol-disülfid homeostazisi parametreleri, toplam antioksidan durumu (TAS) ve iskemi ile modifiye edilmiş albümin (IMA) açısından spektrofotometrik ve kolorimetrik yöntemler kullanılarak analiz edildi. Gruplar arası oksidatif parametrelerin karşılaştırılması için SPSS kullanılarak istatistiksel analiz yapıldı.

Bulgular: Hastaların (24 erkek, 22 kadın) yaş ortalaması 58,45 ± 6,32 ve kontrol grubunun (25 erkek, 21 kadın) yaş ortalaması 57,22 ± 6,51 idi. İki gruptaki katılımcılar yaş ve cinsiyet açısından farklılık göstermedi (her ikisi için de $p > 0,05$). Hastalar, kontrollere kıyasla önemli ölçüde daha düşük doğal tiyol, toplam tiyol ve TAS seviyeleri ve daha yüksek disülfit, disülfit/doğal tiyol yüzde oranı ve IMA seviyeleri gösterdi (tümü için $p<0,05$). Bu bulgular myastenia gravis tanısı olan hastalarda oksidatif stresin arttığını ve antioksidan savunmanın bozulduğunu göstermektedir. Azalan antioksidan parametreler ile artan oksidatif stres belirteçleri arasında da anlamlı korelasyonlar vardı (tüm testler için $p<0,05$).

Sonuç: Bu çalışma, tiyol-disülfit homeostazının myastenia gravisli hastalarda önemli ölçüde değiştiğini doğrulayarak, nöromüsküler kavşak hastalığı patogenezi ile ilişkisini vurgulamaktadır. Gelecekteki araştırmalar, myastenia gravisli hastalarda redoks dengesinin yeniden sağlanmasının etkilerini inceleyerek bu bulguları genişletebilir.

Anahtar Kelimeler: *Disülfit; Homeostazi; Myastenia Gravis; Nöromusküler; Tiyol*

INTRODUCTION

Neuromuscular disorders are a diverse group of medical conditions that affect the normal functioning of the nervous system and muscles. These disorders can involve various components of the neuromuscular system, including the nerves, neuromuscular junction, and muscles themselves. When the disorder involves the neuromuscular junction, there is a disruption of neurotransmission at the connection (synapse) between the nerve ending and the skeletal muscle fiber, leading to a variety of debilitating physical symptoms (1-3).

Neuromuscular junction disorders can arise from autoimmune, congenital, metabolic, or toxic influences. Myasthenia gravis, which is an acquired autoimmune disease, is the most common disorder of neurotransmission (1). Patients with myasthenia gravis typically exhibit weakness of the musculature involving vision, speech, swallowing, respiration, and ambulation. The locus of pathology in this condition is at the postsynaptic membrane (4). In a normally functioning neuromuscular system, motor neurons communicate with skeletal muscle via the neuromuscular junction. Axons of the motor neurons release the neurotransmitter acetylcholine into the synaptic cleft (space between the axon terminal and postsynaptic cell), which go on to bind to receptors on the muscle membrane. Acetylcholine that is released into the synaptic cleft stimulates the receptors leading to subsequent muscle contraction (4). In approximately 85% of patients with myasthenia gravis, this process is disrupted by acetylcholine receptor antibodies. The presence of these antibodies inhibits the stimulation needed to trigger muscle contraction. Muscle-specific tyrosine kinase (MuSK) antibodies and lipoprotein receptor–related protein 4 (LRP4) antibodies have been implicated in the remaining cases of myasthenia gravis (5).

The primary symptom in myasthenia gravis is proximal muscle weakness and fatigue. The classic presentation is weakness that gets progressively worse with activity and improves with rest. Patients usually report that symptoms are more prominent later in the day compared to the morning. Other characteristic symptoms of myasthenia gravis include double vision (diplopia), drooping eye lids (ptosis), dysarthria, dysphagia, and non-motor symptoms (6,7). The sensory system is spared in this disorder as junctions are not present in sensory nerves. The presence or history of a thymoma (i.e., tumor of the thymus gland) is also a common occurrence in myasthenia gravis patients (1).

Differential diagnosis of neuromuscular junction disorders usually requires a combination of comprehensive medical history, clinical and neurological examinations, electromyography (EMG), nerve conduction tests, biopsies, and genetic analysis. Single-fiber EMG testing is notably important and helpful for diagnosing myasthenia gravis (8,9). Acetylcholine antibody receptor tests and magnetic resonance or computed tomography scans (i.e. to look for a thymoma) are also common diagnostic practices (1).

One underexamined potential trigger for the immune dysfunction observed in myasthenia gravis is oxidative stress (10). Oxidative stress refers to a physiological condition that arises when there is an overabundance of reactive oxygen species (ROS) or free radicals in the body, potentially resulting in harm to cells, tissues, and biomolecules like DNA, proteins, and lipids. ROS are highly reactive particles made up of oxygen with unpaired electrons, which makes them prone to engaging in chemical reactions with other molecules present in the body (11). Furthermore, oxidative stress has been implicated in the pathogenesis of several disorders involving the central nervous system (12-14). The body naturally produces ROS as part of various metabolic processes, including energy production within mitochondria and immune responses. In healthy individuals, the production of ROS is typically balanced by the body's antioxidant defense mechanisms. These antioxidants help neutralize and eliminate excess ROS, maintaining cellular and tissue integrity. However, when the ratio between ROS and antioxidants is disrupted, oxidative stress can occur. This can occur due to various factors including inflammation, aging, genetics, and environmental conditions (15).

Oxidative stress has also been hypothesized to play a role in the pathophysiology of several neuromuscular disorders (16). Due to structural and functional damage to the nervous system and/or muscles, oxidative stress may exacerbate the severity of the disease and

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its symptoms. Specifically, oxidative stress has been linked to mitochondrial dysfunction, muscular damage, neurological damage, antioxidant deficiency, and inflammation (14).

An important indicator of oxidative stress is thiol-disulfide homeostasis, which plays a fundamental role in maintaining the delicate balance of redox reactions within living organisms (17). Thiol-disulfide homeostasis is a finely tuned biochemical process that regulates the levels of thiol and disulfide molecules, ensuring that the cell's redox environment remains stable and functional. Thiols, which are made up of a sulfur atom attached to a hydrogen atom, are often present in molecules such as cysteine and glutathione, whereas disulfides result from the bonding of two sulfur atoms together, commonly seen in proteins as disulfide bonds. An appropriate balance of thiol (SH) and disulfide (S-S) groups in the cell signifies thiol-disulfide homeostasis. Maintaining this equilibrium is crucial for various biological functions, including cellular signaling, DNA repair, and safeguarding against oxidative stress. Moreover thiol-disulfide homeostasis is critical for protein functionality and cellular mechanisms that defend against oxidative stress (17).

Thiol-disulfide homeostasis has been researched in several clinical populations including diabetes, psychiatric disorders, cardiovascular diseases, neurological disorders, and various cancers (18-24). To our knowledge, the present study is the first investigation of thiol-disulfide homeostasis in myasthenia gravis. The purpose of this study is to examine thiol-disulfide homeostasis in patients with myasthenia gravis and compare them to healthy control subjects.

MATERIALS AND METHODS

Forty-six patients with myasthenia gravis and 46 age- and gender-matched control subjects were recruited for this cross-sectional study. Patients were included in the study if they were 18 years of age or older at diagnosis; had a confirmed diagnosis of myasthenia gravis based on clinical symptoms, presence of autoantibodies, and/or electrophysiological findings that indicate a neuromuscular transmission disorder; and underwent regular follow-up and treatment. All patients were more than 1 year past initial symptoms and diagnosis. None of the patients had a history of smoking. Patients with comorbid diseases, anemia, or infection were excluded from the study. Patients were recruited to Ankara Bilkent City Hospital's Physical Medicine and Rehabilitation inpatient department. Control subjects were recruited from the same department's outpatient clinic visiting for unrelated reasons. Control subjects did not have any underlying medical conditions or neurological disease. Data collection took place between June 2023 and January 2024. This study was approved by the ethics committee of Ankara Bilkent City Hospital (Approval Code: E2-23-4412) on 06/07/2023. The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration. All participants provided written informed consent prior to enrollment in the study after the procedures were fully explained.

Blood samples were collected from both patients and control subjects, all of whom were fasting, and placed in plain tubes. After centrifugation at 1600 g for 10 minutes, the sera were separated and kept at -80 °C until the analyses were performed.

Tests for thiol-disulfide homeostasis were performed utilizing an automated spectrophotometric approach (25). Initially, disulfide bonds were reduced to generate free functional thiol groups through the use of sodium borohydride. Any excess sodium borohydride was neutralized with formaldehyde to prevent the reduction of DTNB (5,5'-dithiobis-(2-nitrobenzoic) acid). Following this reaction with DTNB, thiol groups (which include both reduced and native thiols) were quantified. The quantity of dynamic disulfide is established by computing half of the difference between the total thiols and the native thiols. After identifying the levels of native and total thiols, disulfide quantities, as well as the percent ratios of disulfide to total thiols (SS/SH+SS), disulfide to native thiols (SS/SH), and native thiols to total thiols (SH/SH+SS) were then evaluated.

A new automated colorimetric technique was utilized to assess Serum TAS levels (26). This approach converts dark blue-green 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical antioxidants in the sample into a colorless form of ABTS (reduced). The

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variation in absorbance at 660 nm is associated with the total amount of antioxidants present in the sample. This method evaluates the antioxidant properties of the sample in response to the strong free radical reactions caused by hydroxyl radicals. The results are reported as millimolar Trolox equivalents per liter.

Ischemia-modified albumin (IMA) levels were measured using venous blood samples collected within the initial hours of patient admission. The samples were kept at room temperature for 30 minutes. Subsequently, the specimens were centrifuged at a speed of 3500 rpm for 5 minutes. The resulting samples were then moved to Eppendorf tubes and stored at -80ºC until analysis was conducted. The Albumin Cobalt Binding Test was employed to identify the presence of IMA (27). To carry out this test, 50 mL of 0.1% cobalt (II) chloride (CoCl2,6H2O) (Sigma-Aldrich Chemie GmbH Riedstrasse 2, Steinheim, Germany) was added to the patient's serum and thoroughly mixed. Following this, a 10-minute incubation period was observed to facilitate the binding of albumin to cobalt. Subsequently, dithiothreitol (50 mL at a concentration of 1.5 mg/mL) was introduced and mixed in. The following step involved a 2-minute incubation, after which 1.0 mL of a 0.9% sodium chloride solution was added. This addition aimed to decrease the binding capacity. A similar methodology was employed for the blank sample, utilizing distilled water in place of dithiothreitol. The absorbance of the samples was recorded at 470 nm with a spectrophotometer. The resulting measurements were presented in absorbance units (ABSU).

The data were assessed using several statistical techniques (e.g., Kolmogorov–Smirnov test) to check for normal distribution. Descriptive statistics were reported using mean and standard deviation (mean ± SD) for variables that were normally distributed. After confirming that the data were normally distributed, an independent sample t-test was executed to compare the parameters between groups. For the correlation analysis, Pearson's correlation was applied. A 5% type 1 error rate was used to determine statistical significance. Statistical analyses were carried out using SPSS software version 20 (SPSS Inc. Chicago, IL, USA).

RESULTS

Data for 46 patients with myasthenia gravis (24 male, 22 female) and 46 age-matched healthy subjects (25 male, 21 female) were obtained for this study. Mean age of the patient group was 58.45±6.32 and mean age of the control group was 57.22±6.51. Age and gender were statistically similar between the two groups ($p>0.05$).

Results showed that the patient group had significantly reduced levels of native thiol, total thiol, and total antioxidant status (TAS) compared to the control group ($p<0.05$ for all tests). Conversely, the patient group had significantly higher levels of disulfide, disulfide/native thiol, and IMA levels ($p<0.05$ for all tests). See Table 1. Significant positive correlations were detected between tests showing antioxidant levels and significant negative correlations between antioxidant and oxidant tests ($p<0.05$ for all tests). See Table 2.

DISCUSSION

Neuromuscular junction disorders disrupt the normal communication between the nervous system and muscles by impeding neurotransmission, leading to

Table 1. Thiol-disulfide homeostasis values, total antioxidant status, and ischemia-modified albumin levels in healthy subjects and patients with myasthenia gravis

Parameter	Patient group	Control group	p-value
Native Thiol (µmol/L)	253.64±33.44	287.72±39.12	<0.001*
Total Thiol (µmol/L)	293.98±35.87	322.82±38.94	<0.001*
Disulfide (µmol/L)	20.17±3.74	17.55±3.12	<0.001*
Disulfide/Native Thiol (%)	8.05±1.66	6.24±1.57	<0.001*
TAS (mmol/L)	0.58±0.08	0.64±0.06	0.001*
IMA (ABSU)	0.74±0.19	0.59±0.15	<0.001*

Data are presented as mean ± SD, TAS: Total antioxidant status, IMA: Ischemia modified albumin, ABSU: Absorbance units, *Indicates a significant statistical difference with $p<0.05$, mmol/L: millimole/liter, µmol/L: micromoles/liter

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Table 2. Relationship between the oxidant and antioxidant parameters in the patient group

Parameter		Native Thiol (µmol/L)	Total Thiol (µmol/L)	Disulfide (µmol/L)	Disulfide/ Native Thiol (%)	TAS (mmol/L)	IMA (ABSU)
Native Thiol (µmol/L)	r		0.984	-0.126	-0.685	0.281	-0.413
	p		<0.001*	0.190	<0.001*	0.003*	<0.001*
Total Thiol (µmol/L)	r	0.984		0.053	-0.547	0.261	-0.381
	p	<0.001*		0.582	<0.001*	0.006*	<0.001*
Disulfide (µmol/L)	r	-0.126	0.053		0.793	-0.121	0.188
	p	0.190	0.582		<0.001*	0.212	0.05
Disulfide/Native Thiol (%)	r	-0.685	-0.547	0.793		-0.258	0.360
	p	<0.001*	<0.001*	<0.001*		0.007*	<0.001*
TAS (mmol/L)	r	0.281	0.261	-0.121	-0.258		-0.294
	p	0.003*	0.006*	0.212	0.007*		0.002*
IMA (ABSU)	r	-0.413	-0.381	0.188	0.360	-0.294	
	p	<0.001*	<0.001*	0.05	<0.001*	0.002*	

TAS: Total antioxidant status, IMA: Ischemia modified albumin, ABSU: Absorbance units *Indicates a significant statistical difference with p<0.05, mmol/L: millimole/liter, µmol/L: micromoles/liter

various clinical symptoms and impairments in muscle function. In the case of myasthenia gravis, dysfunction and eventual destruction of acetylcholine receptors mediated by antibodies result in life altering physical consequences for patients (1).

The present study found that antioxidant levels in serum as indexed by native thiol, total thiol, and TAS tests were significantly decreased in patients with myasthenia gravis compared to healthy subjects. The opposite pattern was found on measures of oxidative stress. Patients with myasthenia gravis had higher levels of disulfide, disulfide/native thiol percentage ratio and IMA compared to healthy subjects. Furthermore, significant positive correlations were found between antioxidant tests, and significant negative correlations were identified between antioxidant and oxidant tests. These results indicate that thiol-disulfide homeostasis is significantly disrupted in patients with myasthenia gravis. The marked imbalance in oxidant and antioxidant levels supports the hypothesis that oxidative stress contributes to the pathophysiology of myasthenia gravis.

Oxidative stress mechanisms are an important area of investigation for disorders such as myasthenia gravis as they appear to play an important role in the etiology of several related central nervous system disorders and may contribute to the progression and severity of disease symptoms (28). Oxidative stress occurs when there is an excess of ROS, which can oxidize important cellular components. Thiol-disulfide homeostasis is a vital mechanism that helps regulate the balance between reduced thiols and oxidized disulfides within cells. This balance is essential for maintaining the proper structure and function of proteins, as well as for cellular signaling and defense against oxidative stress (17).

Although more work is needed to understand the precise role that oxidative stress plays in the pathophysiology of myasthenia gravis, research on amyotrophic lateral sclerosis (ALS) has offered some insights on this issue. In ALS, oxidative stress appears to play a direct role in mitochondrial dysfunction and cellular damage, leading to subsequent nerve damage and degeneration (29). Because the level of impact is at the cellular level, it is possible that oxidative stress in myasthenia gravis damages cells through a similar mechanism. Studies on myasthenia have shown that the mechanism by which antibodies cause damage to acetylcholine receptors can be described through two processes. First, the antibody attaches to the receptor, blocking acetylcholine from binding effectively. Next, an attack results in damage of receptors and postjunctional folds. Ultimately, the binding of antibodies can lead to a significant loss of these receptors from the postsynaptic membrane. Thus, while the release of acetylcholine is takes place

normally, the receptor binding process is impaired.

The precise etiology of myasthenia gravis remains unclear also in part due to the fact that it is a rare autoimmune condition. The etiologic mechanism likely involves a complex interaction of various of genetic and environmental factors (5). The association of myasthenia gravis with thymomas and other autoimmune disorders has motivated some hypotheses. It is well recognized that thymus gland is essential in the process of producing acetylcholine receptor autoantibodies in myasthenia gravis (30). Interestingly, oxidative stress has been implicated in patients with thymus dysfunction due to other conditions (31). Whether the relationship between thymus functioning and oxidative stress is causal or correlational remains an unanswered question.

A few limitations of the present study are worth noting. First is the limited sample size. While the present study provides strong evidence for a thiol-disulfide imbalance in myasthenia gravis, the mechanism of the dysfunction is still not well-understood. A larger sample would provide more power and allow for additional analyses for understanding the exact relationship between antioxidant parameters and myasthenia gravis pathophysiology. Second, we only examined a very specific set of variables in this study. Additional laboratory tests would be beneficial to further inform existing hypotheses. The exact contribution of thiol-disulfide homeostasis to immune system function can be determined with carefully controlled studies. Furthermore, thiol-disulfide homeostasis is not an isolated process; it interacts with other cellular processes, such as energy metabolism and involves other antioxidants. Future research can investigate these interactions and elucidate specific variables to predict oxidative stress in patients with different disease severities and etiologies.

In the long-term, thiol-disulfide homeostasis may potentially serve as an early diagnostic clue or biomarker in the pathogenesis of myasthenia gravis. With more research, antioxidant-based interventions for reducing the detrimental effects of ROS and improving outcomes for patients with myasthenia may be accomplished.

CONCLUSION

The present study found that patients with myasthenia gravis have disrupted thiol-disulfide homeostasis and compromised antioxidant defense systems compared to healthy age-matched controls. Monitoring and investigating thiol-disulfide balance in patients with myasthenia gravis can provide valuable insights into mechanisms of disease pathogenesis.

Acknowledgement

The authors declare that they have no conflict of interest to disclose.

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