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GLUTATHIONE ANTIOXIDANT SYSTEM STATUS OF MEN WITH ERECTILE DYSFUNCTION DUE TO COMBAT TRAUMA

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Introduction. Most military personnel survive serious injuries, but many are left to live with long-term sexual and reproductive disorders. The injuries often result in psychological trauma and post-traumatic stress disorder, which negatively affect behavioral health and sexual function. There is emerging evidence linking erectile dysfunction (ED) to oxidative stress. Overall, combat trauma is characterized by a broad response of the body to harmful effects involving all body systems, leading to significant changes in the pro-oxidant-antioxidant balance.

Materials and Methods. The study was conducted on peripheral blood lymphocytes and serum of men with ED due to combat trauma (shrapnel and bullet wounds) and healthy men (control group). Both the study and control groups were divided into two age groups (young and middle age groups). Antioxidant activity was studied by measuring glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione S-transferase (GsT).

Results. A comparison of the groups using the Kruskal–Wallis method revealed a significant decrease in the GPx and GR activity in blood lymphocytes and serum in men with ED due to combat trauma compared with healthy men of corresponding age groups. It was shown that GPx activity in peripheral blood lymphocytes of patients of the young age group was 1.64-fold lower, and in patients of the middle age group 1.70-fold lower than in the control group ($P < 0.001$). Similar changes were observed in blood serum. GR activity in blood lymphocytes in patients of the young and middle age groups was 1.42-fold lower than in healthy men ($P < 0.001$). In blood serum,

GR activity in patients of the young age group was 1.70-fold (P <0.001) and in patients of the middle age group 1.56-fold lower than in healthy men (P <0.001). GsT activity in blood lymphocytes in both age groups increases by 1.2-fold, however these changes were not significant (P >0.05).

Conclusion. Erectile dysfunction caused by combat trauma is accompanied by a significant decrease in the activities of antioxidant defense enzymes – glutathione peroxidase and glutathione reductase. There is no difference between age groups of patients with erectile dysfunction due to combat trauma. However, the activity of glutathione S-transferase practically does not change, although there is a tendency for its increase.

Keywords: glutathione peroxidase, glutathione reductase, glutathione S-transferase, erectile dysfunction, combat trauma

INTRODUCTION

In modern wars, particularly the Russian-Ukrainian conflict, most soldiers are exposed to severe injuries, which are mostly complex multisystem polytrauma. Many of them remain to live with long-term sexual disorders (Breyer *et al*., 2014; Bird *et al*., 2021). The injuries often result in psychological trauma from war, which has long-lasting effects on behavioral health and post-traumatic stress disorder (PTSD), which negatively impacts sexual function (Banti *et al*., 2016; Castillo *et al*., 2022). In men, sexual dysfunction may include erectile dysfunction (ED), delayed ejaculation, hypoactive sexual desire, premature ejaculation. ED is also a predictor of cardiovascular disease, dementia, Parkinson's disease, and premature mortality from various causes.

The connection between ED and oxidative stress was demonstrated (Chen *et al*., 2024). In general, combat trauma is characterized by a broad response of the body to harmful effects involving all body systems, which leads to significant changes in the prooxidant-antioxidant balance. The content and activity of endogenous antioxidants in cells and the body decreases, and the intensity of free radical processes increases sharply (Fishman *et al*., 2013; Frati *et al*., 2017; Schwarz *et al*., 2017). During the development of traumatic shock, the hyperproduction of free radicals and reactive oxygen species not only causes direct cell damage, but also many indirect effects. A number of studies have shown that the degree of free radical damage has a positive correlation with the severity of the injury and the inflammatory process (Ince & Mik, 2016; Forrester *et al*., 2018).

Post-traumatic stress disorder can also lead to negative impacts on quality of life and functional impairments in various areas, including sexual dysfunction (Danielsson *et al*., 2018; Highfill-McRoy *et al*., 2022). Post-traumatic stress disorder is associated with higher rates of ED, decreased sexual desire, and premature ejaculation. Combat-related injuries can have significant consequences for the fertility of military personnel, as they typically serve during their peak sexual activity years (Castillo *et al*., 2022). Oxidative stress, primarily through the accumulation of reactive oxygen species, disrupts endothelial function, reduces NO bioavailability, and contributes to vascular dysfunction, which determines all key mechanisms of the onset and progression of ED (Kaltsas *et al*., 2024). Cell protection from free radicals, in particular reactive oxygen species and lipid peroxidation products, is extremely important for ensuring proper functioning of the body. Studies have shown that the use of antioxidants and antihypoxants leads to a progressive improvement in survival rates due to a significant reduction in oxidative stress, inflammatory reactions and normalization of homeostasis (Bjugstad *et al*., 2016; Matsumoto *et al*., 2019).

The glutathione antioxidant system is one of the most important systems which protects cell against oxidative stress. It includes enzymatic (glutathione peroxidase GPx, glutathione reductase GR, glutathione S-transferase GsT) and non-enzymatic components (reduced glutathione GSH). The glutathione system plays an important role in suppressing the pathophysiological process, and its depletion (decrease in GSH content and enzyme activities) can lead to severe cytotoxic and destructive damage. GSH is able to quickly mobilize with an increase in the content of reactive oxygen species, which provides cell resistance to lipid peroxidation, free radicals, protein alkylation, and prevents damage to the DNA structure (Georgiou-Siafis *et al*., 2023; Lapenna, 2023).

Our previous studies have shown an increase in the MDA content in the blood serum of patients with ED injured as a result of combat. At the same time, no significant changes in the concentration of oxidized glutathione in the serum and blood lymphocytes were found between men with ED due to combat injury and healthy men (Onufrovych *et al*., 2024). Literature data on the activity of glutathione antioxidant system status in men with ED are practically absent.

The aim of our work was to assess the activities of glutathione-dependent enzymes: glutathione S-transferase (GsT), glutathione peroxidase (GPx) and glutathione reductase (GR) in lymphocytes and blood serum of men with erectile dysfunction who suffered as a result of hostilities.

MATERIALS AND METHODS

Study design. The study was conducted on blood lymphocytes and peripheral blood serum of men with ED who suffered from combat injuries (shrapnel and bullet wounds) in the Russian-Ukrainian conflict and who were treated at the Military Medical Clinical Center of the Western Region. The research was conducted in September–December 2023 and January 2024. The research group of men with combat injuries was divided into two age subgroups: men aged 20–39 years (young age group, n = 42) and men aged 40–53 years (middle age group, n = 26). Exclusion criteria: clinically significant comorbidities cardiovascular, hepatic, thromboembolic, neurological, oncological or endocrine, history of retroperitoneal surgery or radiotherapy, consumption of medications that affect ejaculation, abuse or dependence on psychoactive substances.

The control group consisted of 48 practically healthy men without complaints of sexual dysfunction or cardiac, neurological or endocrinological pathology. The control group included two subgroups: the young age group (20–39-year-olds, n = 30) and the middle age group (40–53-year-olds, n =18). The collection of peripheral blood was carried out after the preliminary completion of their clinical examination, before assigning them a course of treatment. The distribution of patients with ED by groups was quite homogeneous in terms of body weight, severity of injuries and severity of the condition upon admission to the clinic, the amount of blood loss, tactics of surgical correction.

Lymphocytes isolation. Peripheral blood lymphocytes were isolated according to the method of A. Boyum. Lymphocytes were collected from men in the study groups after their clinical examination was completed and before the treatment course was prescribed. Blood, diluted in a ratio of 1:1 with physiological solution, was layered in a density gradient of ficol-triumbrast (ρ = 1.08 g/cm^3) and centrifuged for 20 min at 500 g. The removed interphase rings of mononuclear cells were washed twice for 10 min with physiological solution. After the last centrifugation, a small amount of

physiological solution was added to the sediment; it was resuspended and, with the help of trypan blue, the number of live and dead cells was counted in the Goryaev chamber. The integrity and viability of blood lymphocytes in all experiments was at least 95 %. Saponin was added to the suspension to permeabilize blood lymphocyte membranes and reveal latent enzymatic activities. Blood lymphocytes were incubated for 10 min with moderate shaking in a solution containing saponin at a concentration of 0.2 % (optimal concentration).

Enzyme assay. The antioxidant activity in blood lymphocytes and serum was analyzed at the time of admission to the urology clinic. The activity of glutathione-dependent enzymes was determined in blood serum and in saponin-permeabilized peripheral blood lymphocytes. GPx activity was determined by the amount of reduced glutathione (GSH), which was used to neutralize hydrogen peroxide in the glutathione peroxidase reaction, considering the dilution of the biological material in the sample and the micromolar absorption coefficient of the thionitrophenyl anion at a wavelength of 412 nm (11.4 cm^2/μM) (Tramer *et al*., 2004). GR activity was determined spectrophotometrically by the decrease in optical density as a result of NADPH oxidation at a wavelength of 340 nm. GsT activity was assessed by the rate of formation of the conjugate with 1-chloro-2,4 dinitrobenzene, which is characterized by an absorption maximum at 346 nm (Raijmakers *et al*., 2003).

Statistical analysis. Experimental data were processed by methods of variation statistics using MS Office and BioStat LE software. Inter-group differences were determined using non-parametric Kruskal–Wallis ANOVA with Dann's post-hoc test. P values of <0.05 or lower were interpreted as statistically significant.

RESULTS AND DISCUSSION

A comparison of the groups using the Kruskal–Wallis method revealed a significant decrease in the GPx activity in blood lymphocytes and serum between men with ED due to combat trauma and healthy men of corresponding age groups. Specifically, the GPx activity in peripheral blood lymphocytes of patients of the young age group was 1.64-fold lower, and in patients of the middle age group 1.70-fold lower than in the control group (P <0.001) (**Fig. 1*A***). Similar changes were observed in blood serum (**Fig. 1*B***). Specifically, the GPx activity in blood serum in patients of the young age group was 1.52-fold lower and in patients of the middle age group 1.54-fold lower than in healthy men (P <0.001). No significant difference in GPx activity between age groups both in men with ED due to combat trauma and healthy men was detected.

GR activity in blood lymphocytes and serum in patients with ED due to combat trauma of both age groups was significantly lower than in the control group (**Fig. 2**). Specifically, GR activity in blood lymphocytes in patients of the young and middle age group was 1.42-fold lower than in healthy men (P <0.001). In blood serum, GR activity in patients of the young age group was 1.70-fold (P <0.001) and in patients of the middle age group 1.56-fold lower than in healthy men (P <0.001). No significant difference in GR activity between age groups both in men with ED due to combat trauma and healthy men was detected.

Another important GSH-dependent enzyme is GsT. In patients with ED due to combat trauma, the enzyme activity in blood lymphocytes in both age groups increased by 1.2-fold, however these changes were not significant (P >0.05) (**Fig. 3*A***). Also, no significant increase in GsT activity was detected in serum (**Fig. 1*B***).

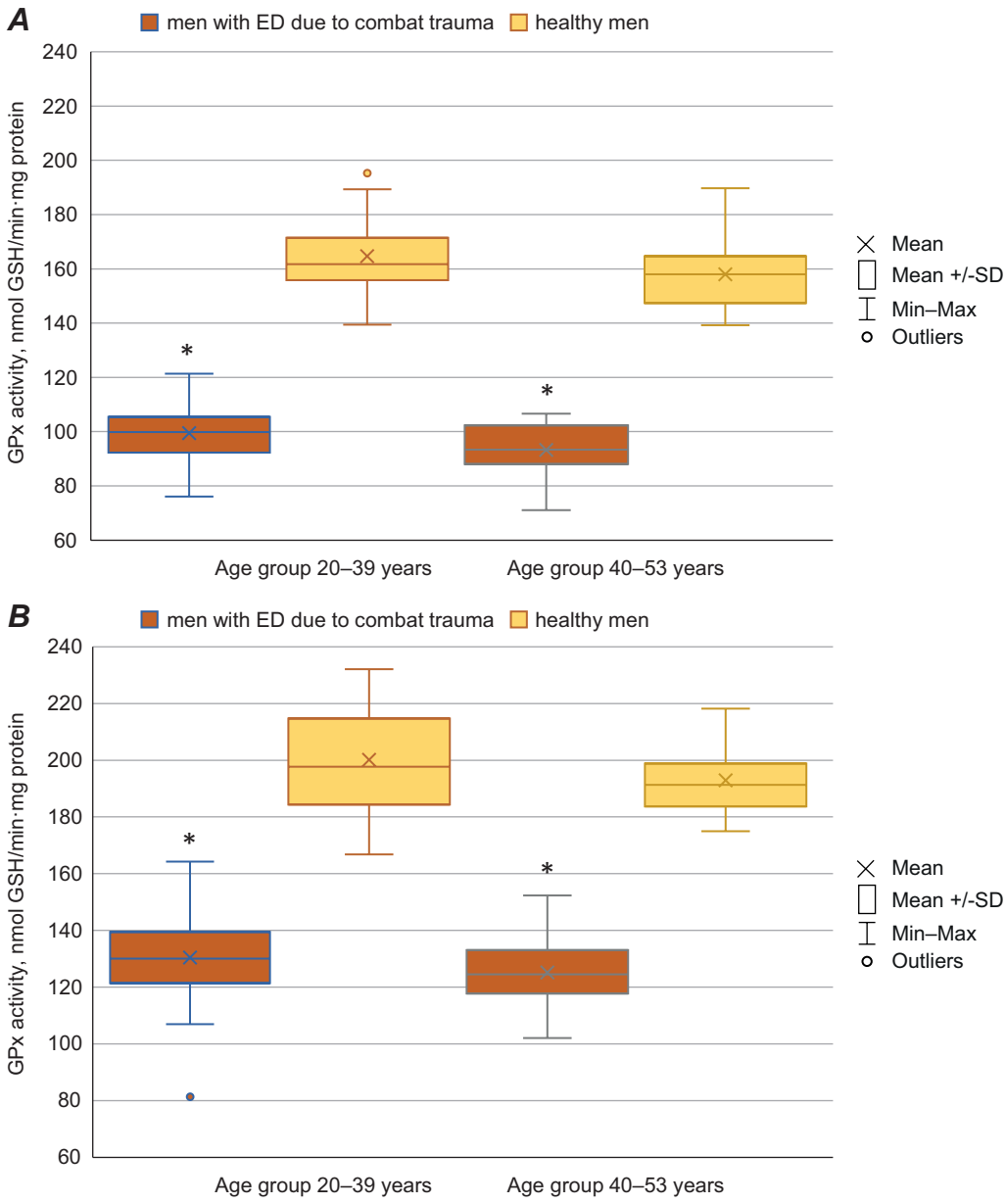

Fig. 1. Glutathione peroxidase activity of peripheral blood lymphocytes (***A***) and blood serum (***B***) in men with erectile dysfunction due to combat trauma and healthy men, graphical interpretation of the Kruskal–Wallis test, n = 18–42, * P <0.001

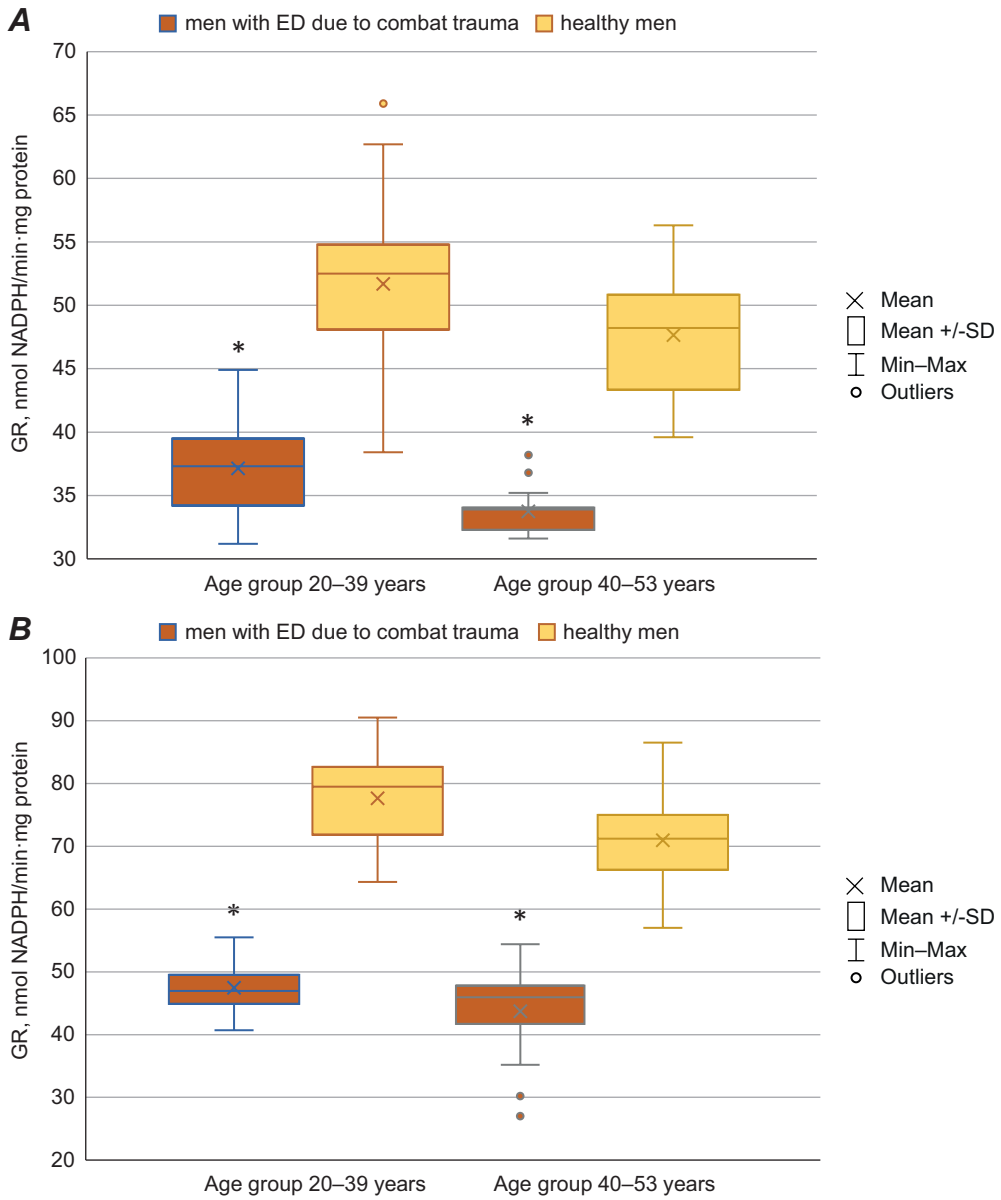

Fig. 2. Glutathione reductase activity of peripheral blood lymphocytes (***A***) and blood serum (***B***) in men with erectile dysfunction due to combat trauma and healthy men, graphical interpretation of the Kruskal–Wallis test, n = 18–42, * P <0.001

Alongside the intensification of lipid peroxidation processes, as previously reported regarding membrane-bound ATPase activity (Onufrovych *et al.*, 2024; Vorobets *et al.*, 2024), our present study identified changes in the activity of enzymes in the glutathione antioxidant system in men with erectile dysfunction due to combat trauma. The decrease in the GPx activity, which reduces lipid hydroperoxides, is apparently associated with the intensification of lipoperoxidation processes in membrane structures. The level of

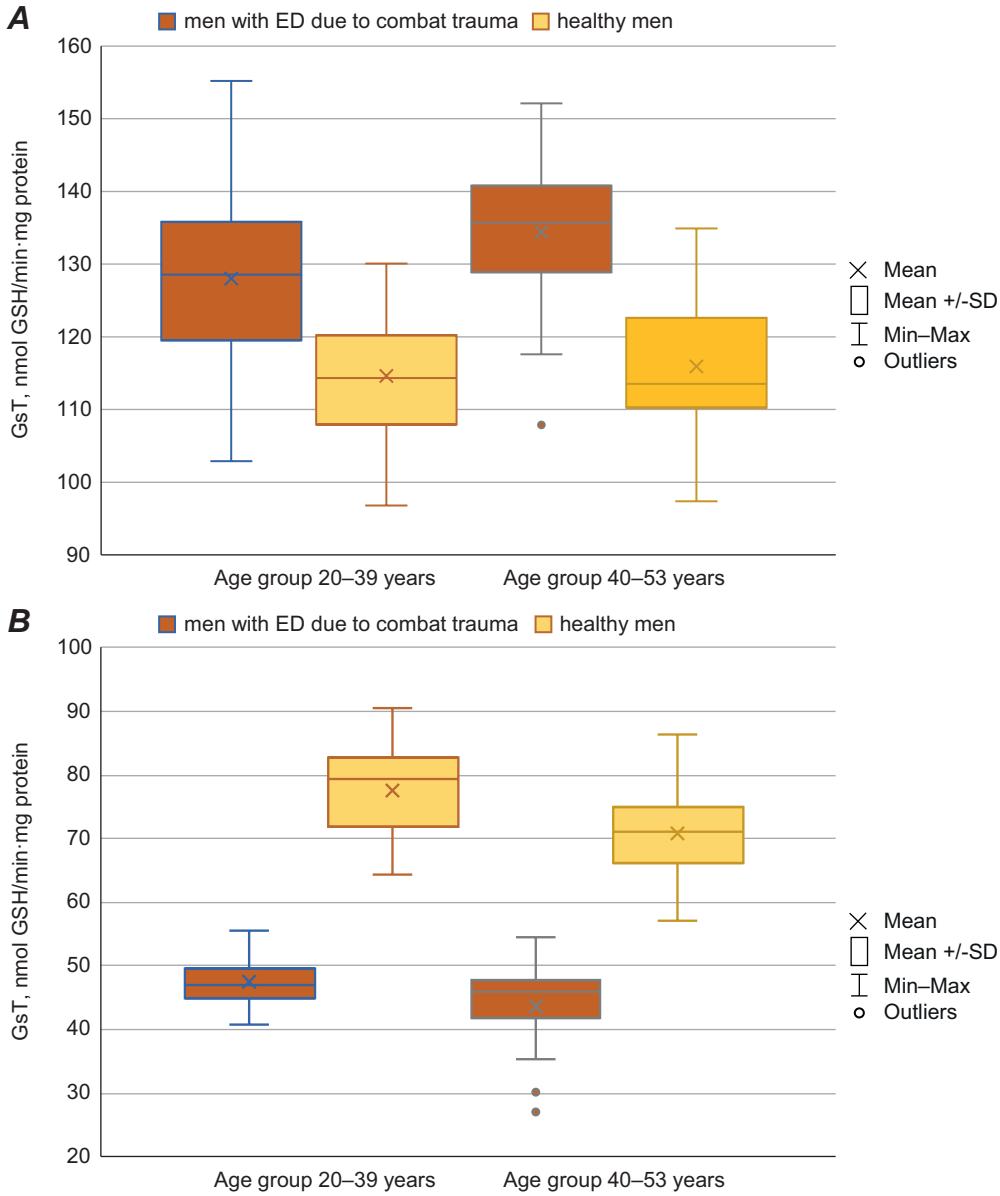

Fig. 3. Glutathione S-transferase activity of peripheral blood lymphocytes (***A***) and blood serum (***B***) in men with erectile dysfunction due to combat trauma and healthy men, graphical interpretation of the Kruskal–Wallis test, n = 18–42

GPx activity in the cell depends on the functioning of GR, which catalyzes the reduction of oxidized glutathione (GSSG) to its reduced form. Since GR is an NADPH-dependent enzyme its activity is inhibited as a result of accumulation of the oxidized form of the nucleotide. Thus, a decrease in GR activity may also be caused by a decrease in NADPH content under pathological conditions. The normal functioning of NADPH-dependent GR is extremely important for preventing oxidative damage to biomembranes that are

unable to synthesize GSH *de novo*, and therefore depends on the intensity of reduction of oxidized glutathione by GR and its influx from the cytosol. The decrease in GSH content is apparently due to dysfunction of CR, which requires NADPH as a source of reducing equivalents (Kand'ar & Hajkova, 2014; Vašková *et al*., 2023).

Given the important role of GSH in numerous biochemical and physiological processes, including differentiation, proliferation, apoptosis, disruption of its homeostasis may indicate the development of pathological changes. Researchers have shown that a decrease in GSH content, due to both an increase in free radical formation caused by hyperglycemia and a decrease in NADPH levels, can impair endothelial cell function (Reyes *et al*., 2015). This condition may play an important role in the etiology of some clinical signs, such as ED (Tagliabue *et al*., 2005).

GSH and GSH-dependent enzymes are known to play an important role in the inactivation of free radicals. The reduced form of glutathione (GSH) is the most important cellular antioxidant and is also a necessary cofactor for nitric oxide (NO) synthase, which synthesizes NO from L-arginine. Therefore, depletion of GSH may lead to a decrease in NO synthesis and, consequently, to impaired vasodilation in the corpora cavernosa (Tagliabue *et al*., 2005).

In our study, the enzyme activity of GPx and GR was significantly reduced in men with ED who were injured as a result of combat trauma. The decrease in the GR activity may be due to the fact that its functioning depends on the content of intracellular GSH. The latter is not only a substrate of reactions, but also a factor important for the constant restoration of selenol groups located in the catalytic center of the enzyme, which are oxidized during the reaction catalyzed by the enzyme.

A significant decrease in the GPx and GR activity is directly related to an increase in the level of lipid peroxidation products and a deterioration in the state of redox balance in the studied groups of men. These changes indicate that under conditions of injury and the development of ED in men, the compensatory mechanisms of the glutathione antioxidant system are depleted, as evidenced by the suppression of GPx and GR activity (Jomova *et al*., 2023).

It should be noted that GPx can prevent the accumulation of secondary peroxidation products, however it is not able to neutralize them, unlike GsT. Since GsT plays a critical role in defense mechanisms against oxidative stress in all life forms, GSTs activity also has been widely used as a biomarker to detect stress (Farombi *et al*., 2007). In our previous study, it was shown that sperm GSTs enzyme assays can be used as a bioindicator for impaired male fertility (Vorobets *et al*., 2018). A slight increase in GsT activity in the serum and blood lymphocytes of men with ED due to combat trauma, demonstrated in the present study, can be considered a compensatory reaction to a decrease in GPx activity under conditions of prolonged oxidative stress. However, changes in GsT activity were not significant.

The present study proves the importance of glutathione antioxidant system in the etiology and pathophysiology of ED due to combat trauma. The results of the present study should be considered in the context of its limitations. Patients of both studied groups represent a highly heterogeneous population. The present study investigated the enzyme activity of GPx, GR and GsT only with 66 patients with ED due to combat trauma. The possible role of other factors (for example lifestyle factors, diseases history etc.) should be taken into account.

CONCLUSION

Erectile dysfunction due to combat trauma is accompanied by a significant decrease in the activity of such antioxidant defense enzymes as glutathione peroxidase and glutathione reductase in both blood lymphocytes and serum. The study did not reveal any differences between age groups of patients with erectile dysfunction due to combat trauma. In men with erectile dysfunction caused by combat trauma, glutathione S-transferase activity remains largely unchanged.

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COMPLIANCE WITH ETHICAL STANDARTS

Conflict of interest: the authors declare that the study was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Animal rights: this article does not include animal studies.

Human rights: all studies were conducted in accordance with the Declaration of Helsinki guidelines. Approval for the study was taken from the ethics committee of Danylo Halytsky Lviv National Medical University (protocol No 7 from 26 June 2023).

AUTHOR CONTRIBUTIONS

Conceptualization, [F.R.; O.O.; V.Z.; N.G.; A.S.]; methodology, [M.V.; O.O.; V.D.; V.Z.]; validation, [M.V.; F.Z.; B.A.]; formal analysis, [V.M.; F.Z.; B.A.].; investigation, [M.O.; V.D.; B.A.]; resources, [F.R., V.D.]; data curation, [F.R.; O.O.; F.Z.; B.A.]; writing – review and editing, [V.M.; F.R.; O.O.; V.D.; N.G.; A.S.]; visualization, [M.O.; F.Z.] supervision, [F.R.; V.D.; V.Z.; O.C.]; project administration, [F.R.; V.Z.; O.C.]; funding acquisition, [F.R.; V.Z.].

All authors have read and agreed to the published version of the manuscript.

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СТАН ГЛУТАТІОНОВОЇ АНТИОКСИДАНТНОЇ СИСТЕМИ У ЧОЛОВІКІВ З ЕРЕКТИЛЬНОЮ ДИСФУНКЦІЄЮ, ОБУМОВЛЕНОЮ БОЙОВОЮ ТРАВМОЮ

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Вступ. Більшість військових виживають після важких поранень, однак багато з них залишаються жити з тривалими сексуальними та статевими розладами. Унаслідок поранень часто виникають психологічні травми і посттравматичний стресовий розлад, що негативно впливають на поведінкове здоров'я та сексуальну функцію. З'являються дані про зв'язок між еректильною дисфункцією (ЕД) і розвитком оксидативного стресу. Загалом, бойова травма призводить до загальної реакції організму на шкідливий вплив із залученням усіх систем організму, що значно змінює показники прооксидантно-антиоксидантного балансу.

Матеріали та методи. Дослідження проводили на лімфоцитах периферичної крові та сироватці крові чоловіків з ЕД унаслідок бойової травми та здорових чоловіків (контрольна група). Основна та контрольна групи були поділені на дві вікові групи (молодша та середня вікові групи). Антиоксидантну активність досліджували за визначенням активності глутатіонпероксидази (GPx), глутатіонредуктази (GR) та глутатіон S-трансферази (GsT).

Результати. Порівняння груп за допомогою непараметричного критерію Крускала–Волліса виявило достовірне зниження активності GPx і GR у лімфоцитах крові та сироватці крові між чоловіками з ЕД внаслідок бойової травми та здоровими чоловіками відповідної вікової групи. Виявлено, що активність GPx у лімфоцитах периферичної крові пацієнтів молодшої вікової групи була в 1,64 раза нижчою, а у пацієнтів середньої вікової групи в 1,70 раза нижчою, ніж у контрольній групі чоловіків ($P < 0,001$). Схожі зміни спостерігали і в сироватці крові. Активність GR у лімфоцитах крові у пацієнтів молодшої та середньої вікових груп була в 1,42 раза нижчою, ніж у здорових чоловіків ($P < 0,001$). У сироватці крові активність GR у пацієнтів молодшої вікової групи була в 1,70 раза ($P < 0,001$), а у пацієнтів середньої вікової групи в 1,56 раза нижчою, ніж у здорових чоловіків ($P < 0,001$). Активність GsT у лімфоцитах крові в обох вікових групах підвищується в 1,2 раза, однак ці зміни не є достовірними ($P > 0,05$).

Висновки. Еректильна дисфункція, спричинена бойовою травмою, супроводжується значним зниженням активності ферментів антиоксидантного захисту – глутатіонпероксидази та глутатіонредуктази. Різниці між віковими групами пацієнтів з еректильною дисфункцією внаслідок бойової травми не виявлено. Активність глутатіон S-трансферази практично не змінюється, хоча є тенденція до її підвищення.

Ключові слова: глутатіонпероксидаза, глутатіонредуктаза, глутатіон S-трансфераза, еректильна дисфункція, бойова травма

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