Glutathione-Dependent Mechanisms of Antioxidant Defense in Men with Pathozoospermia after COVID-19 Infection

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Abstract

The article presents results of studying the influence of COVID-19 infections on glutathione metabolism in men with pathozoospermia and COVID-19. In erythrocyte cytolysate, we determined concentration of reduced (GSH) and oxidized (GSSG) glutathione and the GSH/GSSG ratio as the main indication of cell redox-status and an important factor in cell redox-dependent signaling control along with the effect GSH-dependent enzymes. Results of our study allowed us to determine the peculiarity of the influence of COVID-19 infection on the glutathione metabolic pathway. The understanding of the influence mechanisms of SARS-CoV-2 on metabolic processes in the body of men with pathozoospermia has been expanded. The data obtained give grounds and opportunities for a more reasonable approach to the organization of preventive, curative, and rehabilitative measures for COVID-19 infection. (**International Journal of Biomedicine. 2021;11(4):543-545.**)

Key Words: infertility • men • COVID-19 • glutathione • oxidative stress

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Introduction

The infectious factor accounts for about 15% of the whole structure of reasons for men's infertility.⁽¹⁾ The appearance of new infections with COVID-19 made careful study of its possible consequences necessary. Men and women are equally susceptible to contracting COVID-19, but there is some evidence that men could be at risk for more complications.⁽²⁻⁴⁾ Frequently, COVID-19 is diagnosed in reproductive-age men.⁽⁴⁻⁶⁾ This fact dictates the importance of a thorough study of the potential impact and possible consequences of this disease on the male reproductive system.

The generation of a certain count of free radicals in cells promotes implementation of cell functions.^(5,6) The majority of disturbances in reactions of free radical molecules with

different peptides, lipids, and signal factors are determined in nosological forms.⁽⁷⁻⁹⁾ Pathological changes in the glutathione status for a wide range of diseases can play an important role in determining the symptoms and severity of the process. The glutathione system provides a protective effect with the help of three components: antioxidant protection, detoxification, and immunostimulation.⁽¹⁰⁻¹²⁾ The sulfhydryl group (SH) is the main tool of glutathione in implementing antioxidant and detoxification effects, and it is used as an electron donor in antioxidant neutralization reactions of more than 3,000 toxic oxidized substrates in the body. The most important role of glutathione as an antioxidant is explained by the high reducing potential of the molecule and the high intracellular concentration. The glutathione system restores peroxides, as well as products of peroxidation of lipids, membrane phospholipids, proteins, and nucleic acids and removes them from the body in the form of non-toxic conjugates.^(12,13)

In addition, it regulates the synthesis and recovery of vitamins A, C, and D, and also acts as an immunomodulator, taking part in the activation of natural killer cells (NK cells) and T-lymphocytes.^(4,6,14)

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The aim of this research was to study the effect of COVID-19 infection on glutathione metabolism in men with pathozoospermia.

Materials and Methods

The results of the examination of men ($n=30$; average age of 29.9 ± 5.3 years) with pathozoospermia after COVID-19 infection from infertile married couples (Group 1) were analyzed retrospectively. The comparison group included 38 men (average age of 30.2 ± 3.6 years) with pathozoospermia who did not have COVID-19 infection (Group 2).

Semen was analyzed in accordance with the WHO recommendations⁽¹⁵⁾ (twice with a minimum interval of 2 weeks). Hemolysate prepared from red blood cells was used as the material for biochemical studies. Blood was sampled from the ulnar vein, on an empty stomach from 8 a.m. to 9 a.m., in accordance with the generally accepted procedure—two months after the patient received a negative PCR test for SARS-CoV-2. The concentration of GSH (mmol/L), GSSG (mmol/L) was determined in the erythrocyte cytolysate (Hissin P. Y. et al., 1976). The measurements were carried out on a spectrofluorimeter 02 ABFF-T (Russia).

Statistical analysis was performed using STATISTICA 6.1 software (Stat-Soft Inc., USA).

The study was carried out in compliance with Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. The study was approved by the Ethics Committee of the Scientific Center for Family Health and Human Reproduction Problems. Written informed consent was obtained from each patient.

Results and Discussion

Currently, in relation to more than 60 illnesses, a pathogenetic association with oxidative stress has been established.⁽¹⁶⁾ Paying to attention the significance of glutathione in forming an antioxidant potential for the whole organism and support functional tone for the immune system in the active phase, we studied the influence of COVID-19 on the metabolic pathway of glutathione in men with pathozoospermia.

As a result of the study, a statistically significant increase in the level of GSH by 8% ($P=0.001$) and GSSG by 16% ($P=0.000$) was found in Group 1, compared to Group 2. In turn, the GSH/GSSG ratio in Group 1 was 10% lower than in Group 2 ($P=0.01$) (Fig.1).

Disturbances in the activity of thiol-dependent ensembles, according to modern concepts, are an indispensable companion of anomalies of spermatogenesis.⁽⁸⁾ Specific features of glutathione activity are caused by a character of virus impact on the body when there is a quick need for large amounts of glutathione and its precursors.

The data obtained show that oxidative stress leads to a significant accumulation of GSSG in the body and its release into the blood. A lower level of GSH in Group 2 may be due

to increased activity of glutathione peroxidase or a decrease in the activity of glutathione reductase. Glutathione peroxidase forms the first response to oxidative stress and performs the function of a scavenger during the leakage of ROS and the development of chains of uncontrolled processes. The increased content of GSSG in the blood of men of Group 1, in turn, can cause the oxidation and activation of the thiol groups of blood proteins and proteins of the basolateral membranes of tissue cells. In this regard, the process of catabolization and removal of an excessive accumulation of GSSG from the blood circulation is of particular biological importance. The concentrations of GSH and GSSG depend on the body's condition. In many pathological conditions, the GSH/GSSG rate changes towards the growth of oxidized forms, which was revealed in men with pathozoospermia after COVID-19 infection. Oxidative stress leads to a significant accumulation of GSSG in the body and its release into the blood, as evidenced by the data obtained. Numerous publications indicate that maintaining glutathione at a high level provides reliable, non-specific antiviral protection regardless of the type of virus and demonstrates immunomodulatory properties. There is evidence that glutathione inhibits the replication of various types of viruses at different stages of their life cycle, thereby reducing the viral load on the body and preventing a massive release of inflammatory cells in the lungs, including those due to glutathione's own anti-inflammatory properties.⁽¹⁷⁾

Fig. 1. The level of GSH, GSSG, and the GSH/GSSG ratio in the study groups. *- $P<0.05$

In conclusion, the analysis of the literature data indicates that among all the antioxidants in the body, it is glutathione that provides a stable basis for the normal functioning of the antioxidant system, and disturbances in the thiol-disulfide metabolism can cause serious disorders of various organs and systems. The study of the potential impact of the new coronavirus infection COVID-19 on the reproductive health of men is an extremely relevant topic. Further large-scale studies of various aspects of the pathogenesis of COVID-19 are needed. Determination of the total activity of the enzymes of the thiol-disulfide system is currently acquiring great diagnostic significance, since many proteins localized in various tissues and intracellular compartments have glutathione-S-transferase activity. The results of the conducted studies allowed us to determine the peculiarities

of the impact of a COVID-19 infection on the metabolism of glutathione – the main component of the body's antioxidant system. The data obtained give grounds and opportunities for a more reasonable approach to the organization of preventive, curative, and rehabilitative measures for COVID-19 infection.

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Competing Interests

The authors declare that they have no competing interests.

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