

OXIDATIVE STRESS IN INFERTILE MEN WITH CONCOMITANT PATHOLOGY

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SUMMARY. According to modern ideas, the development of pathological processes in the body, in particular related to infertility, is accompanied by a violation of the mechanisms of antioxidant protection of cells. Hyperproduction of reactive oxygen species (ROS) is found in many pathological conditions, both related to the reproductive system and not directly related to it. Excessive ROS production, is thought, to be caused by an imbalance between prooxidants and the antioxidant system and causes damage to the sperm membrane, chromosome DNA, and initiates sperm apoptosis that leading to infertility.

The aim – to study of the functional state of the pro- / antioxidant system in the seminal fluid and serum of infertile men with concomitant pathology.

Material and Methods. The studies were performed on the serum and seminal fluid of infertile men aged 22–48 years with diagnosed idiopathic infertility ($n=23$) and rheumatoid arthritis ($n=22$). The control group consisted of 27 men of the same age. The ejaculate was analyzed according to WHO recommendations (2010). Determination of malonic dialdehyde (MDA) concentration was performed based on its interaction with 2-thiobarbituric acid. The state of the antioxidant system of semen and blood serum was concluded based on determining the total antioxidant activity by enzyme-linked immunosorbent assay using a commercial test system manufactured by Elabscience (ELISA, USA).

Results. It was found that in patients with autoimmune pathology, the concentration of MDA in the serum exceeded the control group by 2.25 times, and in idiopathic infertility – by 2.16 times. In semen, the content of MDA in men with infertility due to autoimmune pathology is likely to exceed 4 times the control values. In patients with idiopathic infertility, the content of MDA in the seminal fluid was within normal limits. Against the background of intensification of lipid peroxidation processes, the overall antioxidant activity decreases. At autoimmune pathology it decreases in 8.1 times.

Conclusion. Oxidative stress is one of the immunopathogenetic mechanisms of development of male infertility against the background of autoimmune pathology and idiopathic infertility.

KEY WORDS: idiopathic infertility; rheumatoid arthritis' oxidative stress; malonic dialdehyde' antioxidant activity.

Introduction. According to modern ideas, the development of pathological processes in the body, in particular related to infertility, is accompanied by a violation of the mechanisms of antioxidant protection of cells [1-7]. Intensification of lipid peroxidation leads to the accumulation of toxic products, which leads to a decrease in the body's resistance [3, 6, 8-10]. At the same time, the buffer capacity of the antioxidant system (AOC) is quite large and is provided by various components. An important place among the AOC of the cell is occupied by the glutathione system [1, 5, 11-13].

It is believed that the oxidative stress of sperm, which leads to a decrease in their fertility, develops when the dynamic balance between oxidants and the antioxidant system in the seminal fluid, which neutralizes active free radicals. Increasing the concentration of reactive oxygen species (ROS) and decreasing the activity of the antioxidant system can cause significant DNA damage in sperm [12, 14]. Hyperproduction of reactive oxygen species – free radicals – can be detected in many pathological conditions, both related to the reproductive system and not directly related to it [15, 16]. In ejaculate, the sources of ROS are immature sperm (appear in the case of improper cell differentiation during the stages of spermatogenesis) and leukocytes [180]. Insignificant generation of reactive oxygen species is required for normal regulation of

sperm function (capacitance and acrosomal response). However, excess ROS production causes damage to the sperm membrane, chromosome DNA, and initiates sperm apoptosis, leading to infertility [11, 12, 18].

Lipids as components of the membrane play an important role in the performance of sperm functions. In addition, impaired spermatogenesis as a cause of infertility is associated with dyslipidemia, which can lead to damage to the testosterone-synthesizing function of Leydig cells. Oxidative stress leads to the activation of lipid peroxidation processes. The concentration of free radical oxidation products, in particular, malonic dialdehyde (MDA) in the blood and tissues increases. This substance is formed constantly, but in minimal quantities and it plays an important role in the synthesis of prostaglandins, progesterone and other steroids [10]. Increased oxidative stress mediates testicular damage and spermatogenesis [7, 11, 18]. Oxidative stress also plays a crucial role in the dysfunction of the reproductive system as a whole. Therefore, the analysis of the functional state of the pro- / antioxidant system will reveal its role in the pathogenesis and prognosis of the disease.

Purpose – to study of the functional state of the pro- / antioxidant system in the seminal fluid and serum of infertile men with comorbidities.

Material and research methods. The set of material – blood and ejaculate – was conducted in the

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rheumatology and urology departments of the Lviv Regional Clinical Hospital. A detailed medical history was collected, as well as medical and surgical treatment. The men underwent a thorough examination of the genitourinary system to establish exclusion criteria. The study included individuals with normally developed urogenital organs. The study included individuals diagnosed with rheumatoid arthritis (RA) without concomitant inflammatory diseases of connective tissue, other inflammatory diseases, cancer at the time of the study. The duration of the patient's disease ranged from 6 to 360 months. All RA patients were diagnosed with asthenozoospermia or leukocytospermia. An idiopathic form of infertility characterized by unexplored etiopathogenesis has been diagnosed by the lack of fertilization during a couple's regular sexual life and the inability to determine the cause of the disease. This form of infertility included men with oligozoospermia, oligoasthenozoospermia, asthenozoospermia, and leukospermia.

All studies were conducted with the appropriate permission of the Commission on Bioethical Expertise of Danylo Halytsky Lviv National Medical University and with the written consent of patients.

We examined 45 infertile men aged 22–48 years, which were divided into 2 groups: 1 group – 22 men with systemic autoimmune disease – rheumatoid arthritis (RA); Group 2 – 23 somatically healthy patients with idiopathic infertility. The control group included 27 fertile healthy men aged 22–48 years.

Ejaculate analysis was performed according to WHO recommendations (2010) [19]. Semen plasma was obtained by centrifuging ejaculate samples at 3000 g for 10 min and precipitating sperm. Blood collection, by venipuncture, was performed from the elbow vein in the morning, under conditions of physiological rest, on an empty stomach, for 20 ml in test tubes stabilized with heparin (final dilution 1:100).

Determination of the concentration of malonic dialdehyde (MDA) was performed on the basis of its interaction with 2-thiobarbituric acid with the formation of chromogen with a maximum absorption in the red spectrum at a wavelength of 532 nm [20]. The state of the antioxidant system of semen and blood serum was concluded based on determining the total antioxidant activity by enzyme-linked immunosorbent assay using a commercial test system manufactured by Elabscience (ELISA, USA). The protein content in the lymphocyte mixture was determined by a modified Lowry method [21].

Variational and statistical data processing was performed using the software package for Microsoft Excel personal computers. The results are presented as the arithmetic mean (M) \pm standard error of the mean (m). The number of experiments (n) corresponds to the number of subjects studied in each case (each time using samples obtained from one patient or a virtually healthy donor). The reliability of changes between the statistical characteristics of two alternative sets of parametric data was determined by Student's t-test. The critical levels of reliability in testing statistical hypotheses in the studies were taken as 0.95, 0.99 and 0.999. The relationship between the two traits in the presence of a normal distribution was assessed by Pearson correlation analysis (r). The probability of correlation coefficients was evaluated by comparing the calculated coefficients with the critical ones.

Results and Discussion. Malonic dialdehyde (MDA), which is formed as a result of metabolism of arachidonic and other polyunsaturated fatty acids, is currently considered as a marker of oxidative stress and lipid peroxidation [9, 10, 20]. In the serum of infertile men, the MDA content was significantly higher than the control values in all surveyed groups. At the same time, in patients with autoimmune pathology, it exceeded the control group by 2.25 times, and in idiopathic infertility – by 2.16 times (Table 1).

Table 1. MDA content and total antioxidant activity in the serum of infertile men with various concomitant pathologies, $M \pm m$

Control / pathology	MDA content ($\mu\text{mol} / \text{l}$)	Total antioxidant activity ($\mu\text{mol} / \text{l}$)
Control ($n=27$)	3.80 \pm 0.41	1.48 \pm 0.21
Idiopathic infertility ($n=23$)	8.22 \pm 0.86***	0.79 \pm 0.08**
Autoimmune pathology (rheumatoid arthritis) ($n=22$)	8.51 \pm 0.83***	0.78 \pm 0.08**

Note: ** – $p < 0.01$; *** – $p < 0.001$ – the probability of the difference compared to the control.

It should be noted that the mean serum MDA content among all infertile men was highest in patients with autoimmune pathology, which is probably due to the underlying pathological process. Increased

lipid peroxidation at the general level found in the study groups may affect reproductive function locally. Therefore, it was important to investigate the level of MDA in semen and determine its effect on sperm

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motility and morphological features. Human semen contains antioxidants and an enzymatic antioxidant system that protects sperm from oxidative damage. When oxidants suppress the antioxidant defense system, oxidative stress occurs. It induces apoptosis, peroxidation of membrane lipids and DNA fragmentation, which impairs sperm function.

MDA, which is a marker of oxidative stress, may be a diagnostic indicator for the prognosis of infertility in patients with pathospermia [13, 22, 23]. It is known that the level of MDA in seminal fluid is negatively

correlated with the viability of sperm, their motility [17, 24]; and positively - with acrosome abnormalities and the presence of residual cytoplasmic droplets [8]. In the analysis of semen, we found that the content of MDA in it in men with infertility due to autoimmune pathology probably exceeds the control values by 4 times (Table 2). In patients with idiopathic infertility, the content of MDA in the seminal fluid was within the norm, which indicates other immune mechanisms than the activation of oxidative stress involved in the pathogenesis of infertility.

Table 2. MDA content and total antioxidant activity in the seminal fluid of infertile men with various comorbidities, $M \pm m$

Control / pathology	MDA content ($\mu\text{mol/l}$)	Total antioxidant activity ($\mu\text{mol/l}$)
Control (n=27)	2.31 \pm 0.30	2.11 \pm 0.21
Idiopathic infertility (n=23)	2.53 \pm 0.37	1.82 \pm 0.19
Autoimmune pathology (rheumatoid arthritis) (n=22)	9.17 \pm 1.04***	1.13 \pm 0.12***

Note: *** – $p < 0.001$ – the probability of the difference compared to the control.

Correlation analysis was performed to establish the relationship between pro- and antioxidant indicators and spermogram indicators. No significant correlation was found between serum MDA and semen in all men examined. It should be noted that the highest level of MDA in seminal fluid was determined in patients with inflammatory joint disease. This may be due to leukocytospermia, which is observed in this group, which is confirmed by the results of correlation analysis. A direct statistically significant correlation between the content of MDA in seminal fluid and the concentration of leukocytes ($r=0.84$; $p < 0.05$) was recorded (Fig. 1).

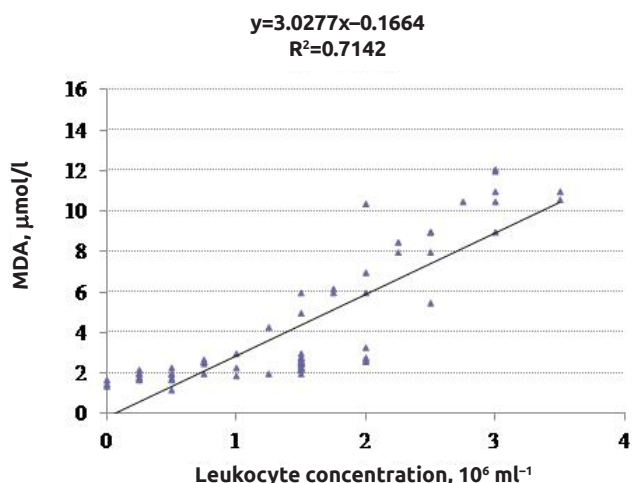


Fig. 1. Correlation between the content of MDA and the number of leukocytes in the seminal fluid of men with idiopathic infertility and infertility on the background of autoimmune diseases.

The presence of an inverse statistically significant correlation between the content of MDA in seminal fluid and sperm motility ($r=-0.66$; $p < 0.05$), which indicates a predictor of intensification of lipid peroxidation in reducing sperm motility (Fig. 2).

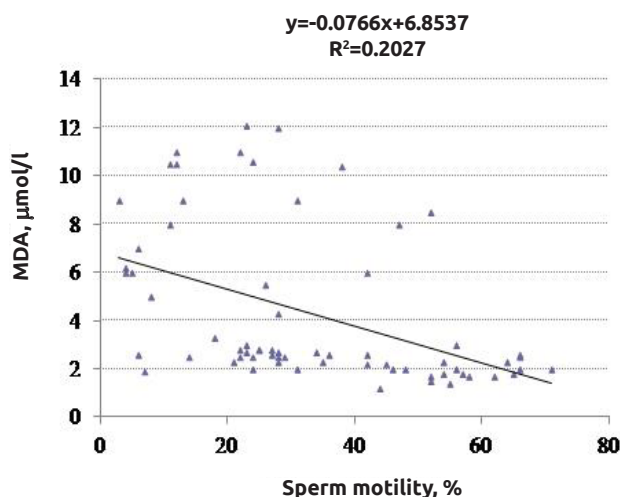


Fig. 2. Correlation between the content of MDA in seminal fluid and sperm motility in men with idiopathic infertility and infertility on the background of autoimmune diseases.

Against the background of intensification of lipid peroxidation processes, the total antioxidant activity decreases, which is confirmed by the inverse statistically significant correlation between the MDA content in seminal fluid and total antioxidant activity ($r=-0.65$; $p < 0.05$) (Fig. 3).

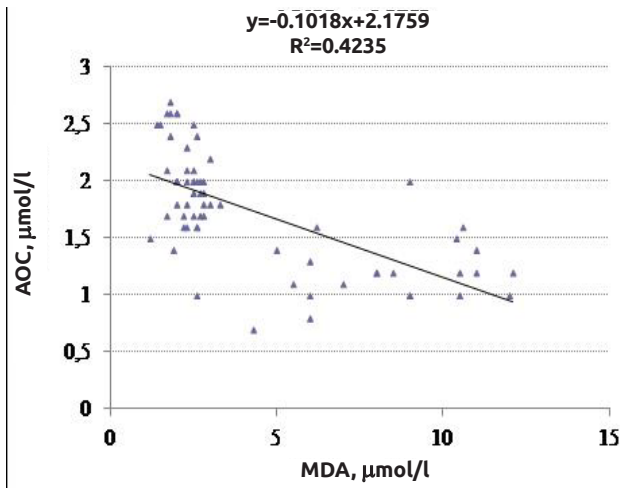


Fig. 3. Correlation between the content of MDA in seminal fluid and total antioxidant activity in men with idiopathic infertility and infertility on the background of autoimmune diseases.

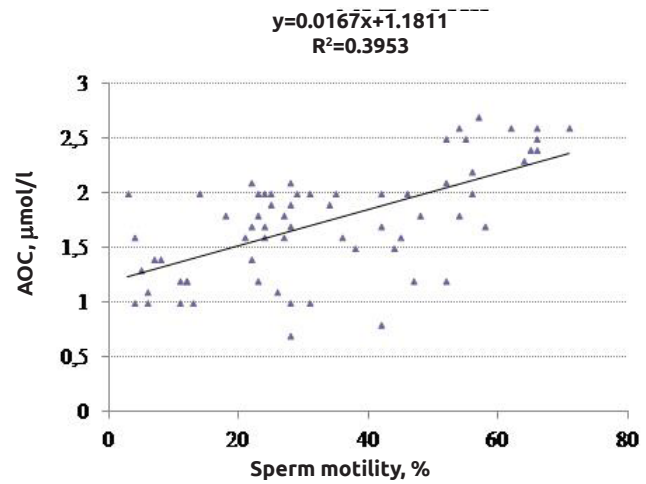


Fig. 4. Correlation between total antioxidant activity and sperm motility in men with idiopathic infertility and infertility on the background of autoimmune diseases.

There is also a direct correlation between total antioxidant activity and sperm motility ($r=0.62$; $p<0.05$), which indicates the important role of protective resources of the antioxidant defense system in maintaining sperm motility (Fig. 4).

The fact that we found a significant inverse correlation between the content of MDA in semen and the concentration of IL-1 β in it was interesting, while the percentage of motile sperm increased with increasing levels of IL-1 β . This is probably a reflection of the physiological connection, as IL-1 β is involved in lipid metabolism. There were no significant correlations between sperm counts and malonic dialdehyde levels in semen in men with idiopathic infertility. An evaluation of all infertile men found that patients with serum asthenozoospermia had higher levels of MDA than those with oligozoospermia, which again indicates a possible primary effect of lipid peroxidation on sperm motility.

Conclusion. Determination of the main product of lipid peroxidation, malonic dialdehyde, has shown that its level in semen is elevated in infertile men with autoimmune diseases. This suggests that oxidative stress is one of the immunopathogenetic mechanisms of infertility in the context of autoimmune pathology. In men with idiopathic infertility, the content of MDA in the seminal fluid was within normal limits, which indicates other mechanisms of infertility formation than the activation of oxidative stress.

Prospects for further research. The next step is to elucidate changes in the activities of Ca²⁺, Mg²⁺-ATP-dependent hydrolase systems of spermatozoa in infertile men with idiopathic infertility and autoimmune pathology, as Ca²⁺ is an intracellular messenger and regulates virtually all cellular processes.

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ОКСИДАТИВНИЙ СТРЕС В ІНФЕРТИЛЬНИХ ЧОЛОВІКІВ ІЗ СУПУТНЬОЮ ПАТОЛОГІЄЮ

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РЕЗЮМЕ. Згідно із сучасними уявленнями, розвиток патологічних процесів в організмі, зокрема пов'язаних із неплідністю, супроводжується порушенням механізмів антиоксидантного захисту клітин. Гіперпродукція активних форм кисню виявляється при багатьох патологічних станах, як пов'язаних із репродуктивною системою, так і не пов'язаних з нею безпосередньо. Вважають, що надлишкова продукція АФК, яка виникає внаслідок порушення рівноваги між прооксидантами та антиоксидантною системою, спричиняє пошкодження мембрани сперматозоїдів, ДНК хромосом та ініціює апоптоз сперматозоїдів, що призводить до непліддя.

Мета – вивчення функціонального стану про-/антиоксидантної системи в сім'яній рідині та сироватці крові інфертильних чоловіків із супутньою патологією.

Матеріал і методи. Дослідження проводили на сироватці крові та сім'яній рідині інфертильних чоловіків віком 22–48 років із діагностованим ідіопатичним непліддям (n=23) та автоімунною патологією (ревматоїдним артритом) (n=22). Контрольну групу складали 27 чоловіків такого ж віку. Аналіз еякуляту проводили згідно із рекомендаціями ВООЗ (2010). Визначення концентрації малонового діальдегіду (МДА) проводили на основі його взаємодії з 2-тіобарбітуровою кислотою. Про стан антиоксидантної системи сім'яної рідини та сироватки крові робили висновок на основі визначення загальної антиоксидантної активності імуноферментним методом із використанням комерційної тест-системи виробництва фірми «Elabscience» (ELISA, США).

Результати. З'ясовано, що у пацієнтів із автоімунною патологією концентрація МДА у сироватці крові перевищувала показники контрольної групи в 2,25 рази, а при ідіопатичному неплідді – у 2,16 рази. У сім'яній рідині вміст МДА у чоловіків із непліддям на ґрунті автоімунної патології вірогідно перевищує контрольні значення у 4 рази. У пацієнтів з ідіопатичним непліддям вміст МДА у сім'яній рідині був у межах норми. На тлі інтенсифікації процесів пероксидного окиснення ліпідів знижується загальна антиоксидантна активність. При автоімунній патології вона знижується в 8,1 рази.

Висновок. Оксидативний стрес є одним із імунопатогенетичних механізмів розвитку інфертильності чоловіків на тлі автоімунної патології та ідіопатичного непліддя.

КЛЮЧОВІ СЛОВА: ідіопатичне непліддя, ревматоїдний артрит, оксидативний стрес, малоновий діальдегід, антиоксидантна активність.

Отримано 03.09.2022

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