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OXYGEN-BINDING PROPERTIES OF BLOOD IN INSULIN RESISTANCE WITH DIFFERENT ASPROSIN CONTENT

V.V. Zinchuk[1]*, J.S.O. Al-Jebur[2], N.V. Glutkina[1]

[1]Grodno State Medical University,
80 Gorky str., Grodno, 230009 Belarus; *e-mail: zinchuk@grsmu.by
[2]Yanka Kupala State University of Grodno,
22 Elizy Ozheshko str., Grodno, 230023 Belarus

The oxygen-binding properties of blood were studied in male patients with insulin resistance (IR) with different levels of asprosin. The content of asprosin, parameters of blood oxygen transport function, as well as gas transmitters, nitrogen monoxide and hydrogen sulfide, were determined in the venous blood plasma. In the studied IR patients with increased blood asprosin content, impaired blood oxygenation was noted; IR patients with normal body weight had increased hemoglobin affinity for oxygen, while in IR patients with overweight and the 1st degree obesity, this parameter decreased. The detected increase in the concentration of nitrogen monoxide and the decrease in hydrogen sulfide may be important for the oxygen-binding properties of the blood and the development of metabolic imbalance.

Key words: asprosin; insulin resistance; affinity of hemoglobin for oxygen; gas transmitter; nitrogen monoxide; hydrogen sulfide; blood

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INTRODUCTION

Obesity and metabolic disorders, including the development of carbohydrate metabolism disorders and insulin resistance (IR), represent an important problem for people of different ages, with different levels of physical activity [1, 2]. It has been shown that IR with obesity is characterized by a decrease in the insulin-stimulated glucose transport and metabolism in adipocytes, skeletal muscles, and the liver. This is associated with impaired insulin signal transduction in target tissues, inhibition of translocation and regulation of the action of type 4 glucose transporters (GLUT4), a decrease in the number of insulin receptors in myocytes and adipocytes, impaired insulin receptor autophosphorylation (with a decrease in their tyrosine kinase activity) and phosphorylation of insulin receptor substrates (IRS) [3]. Dysfunction of adipose tissue leads to the development of overweight and, as a consequence, development of IR and a number of concomitant diseases. In this regard, understanding the molecular mechanisms of IR induction under conditions of obesity is important for the development of new, more effective therapeutic agents to prevent endocrine complications [4, 5].

Adipose tissue is now considered as a trigger in the development of metabolic disorders leading to overweight is given to adipose tissue; this metabolically active endocrine organ produces a class of special signaling molecules, adipokines [6]. An imbalance in the levels of pro- and anti-inflammatory adipokines is one of the triggers that affect the decrease in the functionality of the cardiorespiratory system [7]. These include, in particular, the recently discovered hormone asprosin; its content in the blood affects the total amount of energy resources in adipose tissue, and this, in turn, changes the regulation of energy homeostasis, neuroendocrine functions, and metabolism [8]. An increase in the concentration of asprosin has a significant impact on many important functions of the body and causes infertility, obesity, IR, metabolic syndrome, and autoimmune diseases [9].

Asprosin influences energy metabolism of the body and, accordingly, its oxygen supply. In a cardiomyoblast cell culture, this hormone prevented cell death caused by hypoxia and stimulated mitochondrial respiration [10]. It has been shown that asprosin inhibited H_2O_2-induced apoptosis, generation of reactive oxygen species (ROS) by activating the ERK1/2 signaling kinase pathway, and increased the level of superoxide dismutase (SOD) in stromal cells of cardiac muscle tissue during ischemia [11]. It can be assumed that regulating energy-dependent cell processes, asprosin can affect the intracellular oxygen content and, accordingly, mechanisms of oxygen transport by blood, in particular, its oxygen-binding properties. It has been shown that in healthy individuals with different body weights, this hormone influenced oxygen transport function of the blood [12].

Thus, the aim of the study was to investigate the oxygen-binding properties of blood during IR with different levels of asprosin.

MATERIALS AND METHODS

The study was conducted on males in the age range of 40-60 years with different body weights. The inclusion criterion for patients (n=60) in the study was the presence of IR, determined by the criterion

of the HOMA-IR index (Homeostasis Model Assessment of Insulin Resistance). The studied persons were non-smokers, had no bad habits. The exclusion criterion was the presence of diseases in the acute form or the chronic stage of exacerbation. The control group included 20 people of the same age range.

The body mass index (BMI) was calculated by the formula $BMI = P/H^2$, where BMI is the body mass index, arb. units; P — mass (kg); H — height (cm). The body shape index (BSI) was calculated using the formula $BMI = WC/(BMI^{2/3} \times H^{1/2})$, where WC is waist circumference (m) [13]. The characteristics of the participants by these criteria are given in Table 1.

Venous blood sampling from the cubital vein was performed on an empty stomach in the morning without previous dietary correction. Plasma samples were stored at -20°C before assays. Asprosin concentration was determined by enzyme immunoassay using the ELISA Kit for Asprosin test system (Biobase, China). The content of cholesterol, triglycerides (TG), high density lipoproteins (HDL) and low density lipoproteins (LDL) was determined using a biochemical analyzer (Roche Diagnostics GmbH, Germany). Concentrations of insulin, insulin-like growth factor 1, coenzyme Q_{10} were measured by enzyme immunoassay using kits (Biobase). The glucose concentration and the level of glycated hemoglobin were determined spectrophotometrically using a COBAS 111 analyzer (Roche). The HOMA-IR index was calculated using the formula: HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5.

The partial pressure of oxygen (pO_2) and carbon dioxide (pCO_2), pH, and the degree of blood oxygen saturation (SO_2) were determined in venous blood samples using an ABL80 gas analyzer (Radiometer, Germany). Indicators of the acid-base balance, deficiency (excess) of buffer bases (ABE), bicarbonate (HCO_3^-), were calculated using the Siggaard-Andersen nomogram. The affinity of hemoglobin to oxygen was assessed by p50 (pO_2 of blood at 50% oxygen saturation), determined by the spectrophotometric method ($p50_{real}$). The p50 values at standard pH, pCO_2, and temperature ($p50_{stand}$) and the position of the oxyhemoglobin dissociation curve were calculated using the Severinghaus formulas [14].

The plasma samples were also used for determination of gas transmitters: nitrogen monoxide (NO) and hydrogen sulfide (H_2S). The NO content was evaluated by the concentration of nitrates/nitrites (NO_3^-/NO_2^-), which were measured spectrophotometrically at 540 nm using the Griess reagent [15]. The H_2S content was determined by a spectrophotometric method based on the reaction between the sulfide anion and an acidic solution of the reagent *N,N*-dimethyl-*para*-phenylenediamine hydrochloric acid in the presence of ferric chloride at 670 nm [16].

The data obtained were analyzed by nonparametric statistics using the Statistica 10.0 program. All parameters were checked for compliance with the normal distribution using the Shapiro-Wilk test. Three or more independent groups were compared using Kruskal-Wallis rank analysis of variance. Taking into account a small sample size and multiple comparisons the reliability of the data obtained was assessed using the Mann-Whitney U-test. Results are presented as median (Me), 25th and 75th quartile range. Differences were considered as statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

The metabolic profiles of the examined persons are given in Table 2. IR patients with overweight and the 1st degree obesity had higher values of lipid and carbohydrate metabolism (including HOMA-IR) in comparison with healthy individuals. In addition, persons with overweight and the 1st degree obesity had increased levels of insulin. The plasma

Table 1. General characteristics of IR patients and healthy volunteers

Parameters	Healthy volunteers	IR		
		Normal body weight	Overweight	1st degree obesity
n	20	20	20	20
Age, years	49.0 (41.5; 55.23)	44.5 (40.0; 54.5)	45.0 (38.0; 52.5)	44.0 (39.5; 56.0)
Body weight, kg	69.5 (65.8; 72.5)	69.5 (65.0; 72.0)	82.0 (76.0; 87.0)$^{\Psi\#}$	101.0 (94.5; 115.5)$^{\Psi\#}$*
Height, cm	175.0 (173.8; 176.5)	174.5 (172.8; 177.3)	172.5 (169.8; 175.3)	172.0 (169.0; 174.3)
Waist circumference, cm	87.5 (86.0; 89.5)	87.5 (86.0; 89.5)	98.0 (95.5; 103.0)$^{\Psi\#}$	118.5 (116.5; 121.0)$^{\Psi\#}$*
Hip circumference, cm	93.0 (88.75; 94.50)	93.0 (87.50; 97.00)	102.5 (99.50; 108.00)$^{\Psi\#}$	126.5 (122.50; 130.00)$^{\Psi\#}$*
BMI, kg/m^2	22.1 (19.5; 24.8)	22.9 (22.4; 23.5)	26.9 (25.6; 29.1)$^{\Psi\#}$	35.3 (32.84; 38.4)$^{\Psi\#}$*
DSI, $m^{11/6}kg^{-2/3}$	0.084 (0.081; 0.086)	0.083 (0.081; 0.085)	0.082 (0.079; 0.086)$^{\Psi}$	0.081 (0.079; 0.089)$^{\Psi}$

Here and in subsequent tables (2 and 3) changes are statistically significant as compared with healthy individuals – Ψ, IR patients with normal – # and overweight – *.

Table 2. The main parameters of metabolic profiles in IR patients and healthy volunteers

Parameter	Healthy volunteers	IR		
		Normal body weight	Overweight	1st degree obesity
n	20	20	20	20
Insulin, μU/ml	6.34 (5.78; 7.17)	10.35 (9.25; 11.97)$^{\Psi}$	18.06 (17.39; 20.77)$^{\Psi\#}$	15.58 (14.57; 16.55)$^{\Psi\#}$*
Insulin like growth factor 1, ng/ml	20.45 (19.06; 21.94)	16.01 (14.86; 16.87)$^{\Psi}$	13.23 (12.74; 15.83)$^{\Psi\#}$	11.52 (9.91; 12.56)$^{\Psi\#}$*
Coenzyme Q_{10}, μmol/l	1.94 (1.65; 2.00)	0.39 (0.38; 0.40)$^{\Psi}$	0.37 (0.36; 0.38)$^{\Psi\#}$	0.38 (0.36; 0.39)$^{\Psi}$
Total cholesterol, mg/dl	168.0 (165.0; 170.0)	209.0 (203.8; 212.5)$^{\Psi}$	216.0 (210.0; 225.0)$^{\Psi\#}$	229.5 (222.5; 241.3)$^{\Psi\#}$*
Glucose, mmol/l	4.36 (4.21; 4.51)	6.25 (6.10; 6.46)$^{\Psi}$	6.61 (6.26; 6.83)$^{\Psi}$	6.75 (6.56; 7.00)$^{\Psi\#}$*
Glycated hemoglobin, %	5.40 (5.05; 5.65)	6.20 (6.05; 6.40)$^{\Psi}$	6.00 (5.80; 6.20)$^{\Psi\#}$	6.15 (5.90; 6.40)$^{\Psi}$*
HOMA-IR	1.24 (1.09; 1.41)	2.81 (2.63; 3.33)$^{\Psi}$	5.35 (4.98; 6.06)$^{\Psi\#}$	4.63 (4.27; 5.03)$^{\Psi\#}$*
TG, mg/dl	99.5 (85.0; 120.0)	150.0 (142.5; 162.0)$^{\Psi}$	167.5 (162.8; 173.3)$^{\Psi\#}$	173.5 (169.0; 178.3)$^{\Psi\#}$*
HDL, mg/dl	52.5 (46.8; 57.0)	41.0 (38.0; 42.3)$^{\Psi}$	41.0 (36.0; 48.3)$^{\Psi}$	39.0 (35.8; 43.0)$^{\Psi}$
LDL, mg/dl	96.0 (85.0; 104.3)	132.0 (130.0; 134.0)$^{\Psi}$	135.5 (130.0; 136.3)$^{\Psi\#}$	133.5 (131.3; 139.0)$^{\Psi\#}$

concentration of asprosin (Fig. 1) in IR patients with normal BMI was significantly higher than in healthy subjects: 20.95 (18.87; 25.11) pmol/l (p<0.05). In IR patients with overweight, this parameter higher 40.26 (37.36; 41.26) pmol/l (p<0.05), and in IR patients with the 1st degree of obesity it reached 66.81 (62.33; 69.6) pmol/l (p<0.05). IR is a pathological condition in which the sensitivity of tissues (fat, muscle, and liver) to insulin decreases [17]. IR is most often detected in obesity; its development is obviously associated with increased synthesis of adipose tissue hormones (adipokines) [18, 19], including asprosin, which was observed in our study.

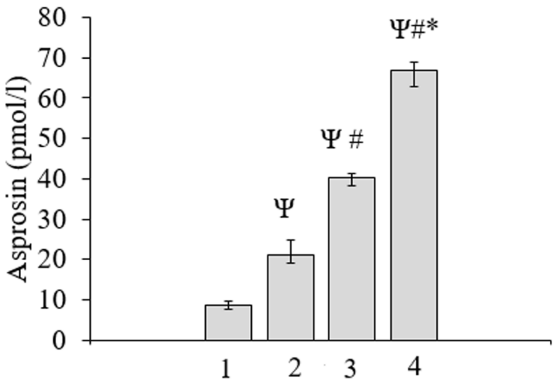

Figure 1. Plasma asprosin concentration in healthy individuals (1) and IR patients with: normal (2), overweight (3) and the 1st degree obesity (4): changes are statistically significant as compared with healthy individuals – Ψ, IR patients with normal – # and overweight – *.

Table 3 shows parameters of the blood oxygen-binding properties of IR patients. In patients with the 1st degree obesity (and the most pronounced in the asprosin content), there was a decrease in the venous blood SO_2 and pO_2 (by 11.2%, p<0.05 and 7.9%, p<0.05) as compared with IR patients with normal and overweight. An increase in the affinity of hemoglobin to oxygen $p50_{real}$ (mm Hg) was found in IR patients with normal body weight up to 26.3 (22.4; 30.0) (p<0.05) in comparison with healthy 24.5 (23.8; 26.7); it was characterized by a rightward shift of the hemoglobin-oxygen dissociation curve (Fig. 2). This increase in p50 contributes to the mass transfer of oxygen in tissues under conditions of normoxia or moderate hypoxia. However, it should be noted that in IR patients with overweight and the 1st degree obesity there was a decrease in $p50_{real}$ (mm Hg) (up to 25.7 (23.2; 27.0) (p<0.05) and 25.1 (24.1; 27.4) (p<0.05), respectively) as compared with persons with normal body weight. A leftward shift in the hemoglobin-oxygen dissociation curve (Fig. 2) obviously reflects impairments of the compensatory mechanisms of oxygen delivery to tissues. The concentration of glycated hemoglobin was less than 7%, which was not significant for a direct change in the affinity of hemoglobin for oxygen. It is known, the aerobic potential of the body is determined by the efficiency of the circulatory system functioning at the level of both macro- and microcirculation and the effective fluidity of blood with its oxygen transport potential [20]. At high affinity of hemoglobin for oxygen in individuals during hypoxia and physical activity, an imbalance in the mechanisms of regulation of the cardiorespiratory system is observed [21].

Table 3. The oxygen-binding properties of blood in IR patients with different BMI values and healthy volunteers

Parameter	Healthy volunteers	IR		
		Normal body weight	Overweight	1st degree obesity
n	20	20	20	20
SO_2, %	74.5 (71.75; 77.00)	71.0 (66.70; 77.21)$^{\Psi}$	65.5 (62.00; 74.00)$^{\Psi}$	62.5 (54.70; 69.00)$^{\Psi\#}$*
pO_2, mm Hg	38.0 (37.00; 40.00)	38.0 (36.75; 40.00)	37.5 (34.75; 38.25)$^{\Psi}$	35.0 (32.00; 37.00)$^{\Psi\#}$*
pH, units	7.41 (7.38; 7.42)	7.37 (7.36; 7.40)$^{\Psi}$	7.35 (7.34; 7.36)$^{\Psi\#}$	7.34 (7.33; 7.35)$^{\Psi\#}$*
pCO_2, mm Hg	38.0 (37.00; 39.25)	39.0 (38.75; 42.00)$^{\Psi}$	43.0 (40.00; 44.25)$^{\Psi\#}$	44.0 (42.00; 47.00)$^{\Psi\#}$
HCO_3^-, mmol/l	26.50 (25.00; 27.00)	23.50 (21.75; 26.00)$^{\Psi}$	23.48 (20.00; 25.25)$^{\Psi}$	21.50 (19.75; 23.00)$^{\Psi\#}$
ABE, mmol/l	2.0 (0.49; 4.00)	-1.05 (-2.95; 0.87)$^{\Psi}$	-1.35 (-4.70; 0.27)$^{\Psi}$	-3.60 (-5.45; -2.10)$^{\Psi\#}$
$p50_{real}$, mm Hg	24.5 (23.8; 26.7)	26.3 (22.4; 30.0)$^{\Psi}$	25.7 (23.2; 27.0)$^{\Psi\#}$	25.1 (24.1; 27.4)$^{\Psi\#}$*
$p50_{stand}$, mm Hg	25.4 (23.8; 26.5)	25.9 (22.6; 29.6)$^{\Psi}$	23.9 (21.9; 25.6)$^{\Psi\#}$	23.2 (21.9; 25.7)$^{\Psi\#}$*

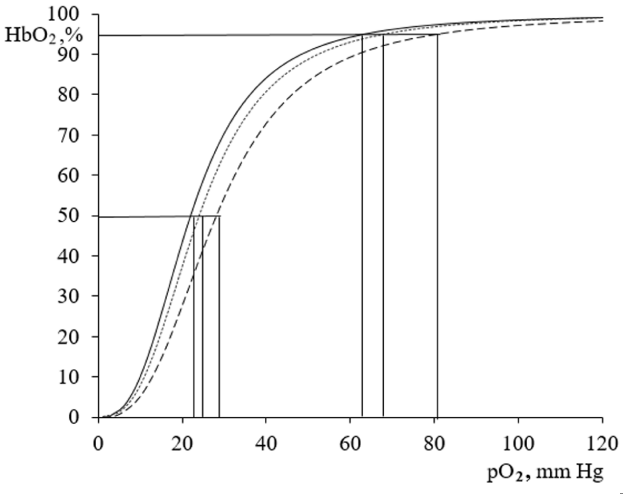

Figure 2. Oxyhemoglobin dissociation curve in healthy individuals (——) and IR patients with normal body weight (– – –) and 1st stage obesity (·····). The y-axis shows hemoglobin saturation with oxygen, %. The abscissa shows the partial pressure of oxygen in the blood, mm Hg.

Obesity-associated IR induces inflammation, adipocyte dysfunction, oxidative stress, and hypoxia [3]. Adaptation processes during hypoxia, controlled by both central and intercellular and intracellular regulatory mechanisms, provide maintenance of the proper level of metabolism, and asprosin makes a certain contribution to this regulation. An important pathogenetic link of IR is that reduces insulin sensitivity of skeletal muscles due to the activation of protein kinase C/Ca^{2+}-ATPase of the sarco/endoplasmic reticulum (SERCA2)-mediated pathways, and is also able to bind to the Toll-like receptor-4 (TLR4) thus increasing the production of ROS and pro-inflammatory cytokines through the TLR4/JNK-mediated pathway and causing impairments in the mechanisms of oxygen supply [11]. In this context it is especially interesting that asprosin concentration increased in patients with type 2 diabetes mellitus and coronavirus infection with decreased blood oxygen saturation (up to 70%) [22]. This increase in the asprosin concentration may be due to the release of glucose from the liver to meet the body's energy needs [22]. The oxygen-binding properties of blood, determining the degree of its deoxygenation, are an important link in the regulation of the energy of the body, and vice versa, modification of the oxygen-transport function of the blood in response to a change in the level of asprosin influences metabolic processes.

Asprosin reduces the ROS production, reduces apoptosis, and increases production of the gas transmitter NO in cardiac microvascular endothelial cells [23]. The system of gas transmitters has a modulating effect on the oxygen transport function of the blood under various conditions of oxygen supply, accompanied by the development of hypoxia [24]. These effects are realized through various levels of regulation of erythrocyte and systemic mechanisms. The gas transmitter NO contributes to the pathogenesis of IR: inhibition of the inducible isoform of NO synthase prevents, while inhibition of the endothelial isoform of this enzyme, on the contrary, contributes to the occurrence of this pathology [25].

In our study we found an increase in NO and a decrease in H_2S concentrations in the blood of IR patients (Fig. 3) as compared with healthy volunteers. In persons with the 1st degree obesity and a high level of asprosin, the NO content demonstrated the highest increase to 29.52 (27.24; 32.85) μmol/l. The H_2S concentration in this group decreased to 9.38 (8.64; 10.81) μmol/l (p<0.05); this was significantly lower than in IR patients with normal

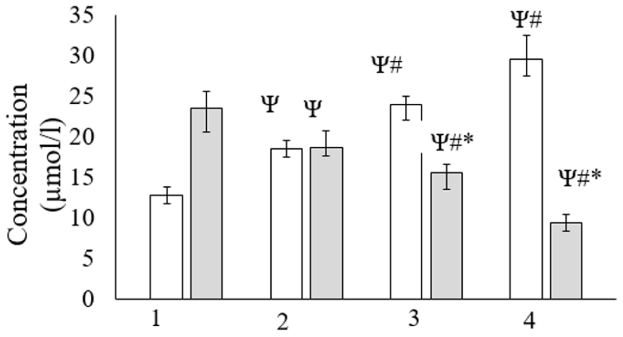

Figure 3. Concentrations of plasma nitrates/nitrites (□) and H_2S (■) concentration in healthy individuals (1) and IR patients with: normal (2), overweight (3) and the 1st degree obesity (4): changes are statistically significant as compared with healthy individuals – Ψ, IR patients with normal – # and overweight – *.

body weight. It should be noteed that in patients of this group, as well as in patients with overweight, a more significant change in the content of these gas transmitters was found in comparison with healthy volunteers.

Being endogenous active mediators of inflammation, adipokines, secreted by adipocytes, regulate intercellular and intersystem interactions, determine cell survival, stimulation or suppression of their growth, differentiation, functional activity of cells and their apoptosis processes, ensure the coordination of the action of the immune, endocrine and nervous systems in response to various effects [26]. These molecules are also involved in the regulation of the signaling pathway of the L-arginine-NO system [27], by regulating expression of the endothelial isoform of NO synthase, which is important for the formation of a certain level of metabolic processes. Adipokines (leptin) are important for the formation of the mechanisms of oxygen transport by blood in the metabolic syndrome and myocardial infarction; these effects are mediated by the action on the mechanisms of external respiration and blood circulation, the L-arginine-NO system, and indirectly through the modification of the oxygen transport function of blood (hematopoiesis) [28]. This suggests that other adipokines, particularly, asprosin, also contribute to these processes.

Gasotransmitters (NO and H_2S) can have a synergistic effect, but in some cases, for example, under the action of ozone, multidirectional changes in their content are observed [29]. This influences the mechanisms of regulation of hemoglobin affinity for oxygen. The interaction of NO- and H_2S-dependent signaling cascades can lead to various physiological reactions of certain individual cells, organs, and systems. In particular, the suppression of NO production in diabetes mellitus and arterial hypertension leads to a decrease in H_2S effects, which also occurs in cardiovascular disorders appearing in the metabolic syndrome [30]. Opposite changes in the content of these gasotransmitters may be due to competition for the binding sites of cysteine SH groups during S-nitrosylation and S-sulfhydration, or the interaction of H_2S with NO with thionitrous acid formation [31].

Thus, the changes in the activity of the gasotransmitter system (NO and H_2S) in IR patients with different concentrations of asprosin, found in this study, are important for the formation of the mechanisms of oxygen transport by the blood. The contribution of asprosin to the regulation of the oxygen-binding properties of blood is important for the formation of oxygen supply and adaptive reserves in persons with metabolic disorders.

CONCLUSIONS

IR patients with increased asprosin concentrations are characterized by impaired blood oxygenation (as evidence by a decrease in SO_2 and pO_2); the manifestation impaired blood oxygenation is more pronounced with an increase in the concentration of this hormone.

In IR patients with normal body weight, an increase in the affinity of hemoglobin to oxygen is noted, while in IR patients with overweight and the 1st degree obesity of the first degree, this parameter decreased thus indicating a decrease in the adaptive reserves of oxygen homeostasis mechanisms.

IR patients with increased concentrations of asprosin (especially IR patients with the 1st degree obesity) are characterized by an increase in the concentration of the gasotransmitter NO and a decrease in the H_2S level; this is important for the formation of oxygen-binding properties of the blood and the development of a metabolic imbalance.

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COMPLIANCE WITH ETHICAL STANDARDS

Experimental procedures were carried out in accordance with the requirements of the Directive of the European Union 2010/10/63 EU, approved by the Ethics Committee of the Grodno State Medical University (No. 2 of February 12, 2021). All participants of this study signed an informed voluntary consent to the use of their biological material.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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КИСЛОРОДСВЯЗЫВАЮЩИЕ СВОЙСТВА КРОВИ ПРИ ИНСУЛИНОРЕЗИСТЕНТНОСТИ С РАЗЛИЧНЫМ СОДЕРЖАНИЕМ АСПРОСИНА

В.В. Зинчук[1]*, Д.Ш.О. Аль-Джебур[2], Н.В. Глуткина[1]

[1]Гродненский государственный медицинский университет,
230009, Беларусь, Гродно, ул. Горького, 80; *эл. почта: zinchuk@grsmu.by
[2]Гродненский государственный университет им. Янки Купалы,
230023, Беларусь, Гродно, ул. Элизы Ожешко, 22

Исследовали кислородсвязывающие свойства крови у пациентов мужского пола при инсулинорезистентности (ИР) с различным содержанием аспросина. В плазме венозной крови определяли содержание аспросина, показатели её кислородтранспортной функции, а также газотрансмиттеры монооксид азота и сероводород. У исследуемых пациентов с ИР при повышенном содержании аспросина отмечено ухудшение оксигенации крови, при нормальной массе тела выявлено увеличение сродства гемоглобина к кислороду, а при избыточной массе тела и ожирении I степени — его уменьшение. Выявленное увеличение концентрации монооксида азота и снижение сероводорода, по-видимому, имеет значение для кислородсвязывающих свойств крови и развития метаболического дисбаланса.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: аспросин; инсулинорезистентность; сродство гемоглобина к кислороду; газотрансмиттер; монооксид азота; сероводород; кровь

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