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Insulin-like growth factors and their transporter proteins in the liver of rats with experimental diabetes, adenocarcinoma of the uterine corpus, and their combination

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ABSTRACT

Aim. To investigate the content of insulin-like growth factor (IGF)-1, IGF-2, and their transporter proteins IGFBP-1 and IGFBP-2 in the liver of rats with experimental diabetes, Guerin's carcinoma, and their combination.

Materials and methods. The experiment was carried out on 64 white outbred rats of both sexes, which were divided into 4 groups of 8 animals each: group 1 – intact animals, group 2 – animals with experimental diabetes, group 3 – animals with subcutaneously inoculated Guerin's carcinoma, group 4 – animals with experimental diabetes and subcutaneously inoculated Guerin's carcinoma. In the study, biochemical and statistical analyses and enzyme immunoassays were performed.

Results. In the liver of the outbred rats, sex specificity in the content of insulin-like growth factors and IGFBP-1 was established: the levels of IGF-1, IGF-2, and IGFBP-1 in males were lower than in females. It was shown that the development of diabetes mellitus and the growth of Guerin's carcinoma led to changes in the sex-specific components in the rat liver.

Conclusion. The growth of Guerin's carcinoma and the progression of diabetes mellitus cause multidirectional changes in IGF and IGFBP levels in the liver of females and unidirectional changes in the liver of males. Following the growth of Guerin's carcinoma against the background of diabetes mellitus, sex-specific differences in the content of the studied parameters were minimized. It was shown that diabetes mellitus changed the metabolic profile of the liver in the animals of both sexes.

Keywords: Guerin's carcinoma, diabetes mellitus, liver, IGF, IGFBP

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Инсулиноподобные факторы роста и их белки-переносчики в печени крыс при экспериментальном диабете, злокачественном росте аденокарциномы тела матки и их сочетании

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РЕЗЮМЕ

Цель. Исследовать содержание инсулиноподобных факторов роста (IGF) 1 и 2, их белков-переносчиков IGFBP-1 и IGFBP-2 в печени крыс с сахарным диабетом, аденокарциномой Герена и при их сочетании.

Материалы и методы. Эксперимент проводился на 64 белых беспородных крысах обоего пола, которые были разделены на 4 группы по 8 особей: 1-я – интактные животные, 2-я – животные с экспериментальным диабетом, 3-я – животные с подкожной перевивкой карциномы Герена, 4-я – животные с экспериментальным диабетом и с подкожной перевивкой опухоли Герена. В работе осуществляли биохимический, иммуноферментный и статистический анализы.

Результаты. В печени беспородных крыс установлена половая специфичность содержания инсулиноподобных факторов роста и IGFBP-1: у самцов уровень IGF-1, IGF-2 и IGFBP-1 оказался ниже, чем у самок. Развитие сахарного диабета и рост перевивной карциномы Герена в самостоятельных вариантах приводили к изменению половых особенностей изученых компонентов в печени крыс.

Заключение. Рост карциномы Герена и сахарный диабет вызывают разнонаправленные изменения IGF и IGFBP в печени самок, но однонаправленные – в печени самцов. В результате развития карциномы Герена на фоне сахарного диабета половые различия в содержании изученных показателей нивелируются, сахарный диабет изменяет метаболический профиль печени у животных обоего пола.

Ключевые слова: карцинома Герена, сахарный диабет, печень, IGF, IGFBP

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INTRODUCTION

The incidence of diabetes mellitus (DM) and cancer has increased significantly in recent years. In addition, there are many common risk factors for both DM and cancer. Much epidemiological evidence indicates that DM is considered an independent risk factor for increased incidence of different cancers and death from them. Morbidity and mortality from various types of cancer, such as cancer of the pancreas, liver, colon, breast, endometrium, and bladder, are slightly increased in DM patients. Although the underlying biological mechanisms are not fully understood, studies have confirmed that the growth hormone / insulin-like growth factor (IGF) 1 axis, hyperglycemia, and sex hormones create favorable conditions for cancer cell proliferation and metastasis. The growth hormone / IGF-1 axis activates several metabolic and mitogenic signaling pathways; hyperglycemia provides energy for the growth of cancer cells. Thus, these factors affect all cancers, while sex hormones play an important role only in breast cancer, endometrial cancer, and prostate cancer [1].

The most common types of DM are type 1 and type 2 diabetes. On the one hand, an autoimmune disorder of insulin-producing beta cells causing absolute insulin deficiency leads to type 1 diabetes mellitus (T1DM) and accounts for about 5% from 10% of all DM cases. On the other hand, type 2 diabetes mellitus (T2DM) is associated with metabolic disorders in which cells become insensitive to insulin and, therefore, exhibit relative insulin deficiency. Several studies have shown that although both T1DM and T2DM are associated with higher risks of cancer, T2DM has a stronger association with cancer, both epidemiologically and biologically [2, 3].

Endometrial cancer (EC) is the most common gynecologic cancer. Compared with other cancers, EC is often diagnosed earlier and has a better prognosis. However, mortality from it has increased significantly over the past 20 years. An association between DM and EC has been consistently confirmed by cohort studies and meta-analyses [4]. In addition, a systematic review and meta-analysis summarized results of 29 cohort studies and found the incidence of EC in women with and without DM. The cumulative relative risk was 1.89 (95% confidence interval (CI): 1.46–2.45; $p < 0.001$), and the cumulative incidence rate was 1.61 (95% CI: 1.51–1.71; $p < 0.001$), which again confirms that DM is an independent risk factor for higher incidence of EC [5].

Insulin is a peptide hormone that regulates the metabolism of carbohydrates and fats and improves glucose absorption. Insulin loses the function of increasing cellular uptake and utilization of glucose in DM patients, which is clinically defined as insulin resistance [6]. High insulin levels are a sign of hyperinsulinemia, which stimulates liver cells to produce IGF-1, when insulin binds to the insulin receptor on the surface of target cells. IGF-1 binds to the IGF-1 receptor (IGF-1R), receptor tyrosine kinase, to activate several metabolic and mitogenic signaling pathways that regulate cancer cell proliferation, differentiation, and apoptosis [7].

Insulin-like growth factors (IGFs) and IGF-binding proteins (IGFBPs) are fundamental mediators of cell growth, development, and survival and are expressed in most tissues. Epidemiological data indicate the relationship of IGF and IGFBP with the risk of prostate, breast, colorectal, and thyroid cancers [8]. DM patients show higher IGF-1 levels, which makes them more susceptible to an increased risk of many cancer types. In addition, many studies have demonstrated that IGF-1 is more often expressed in cells of hormone-dependent cancer than in other types of cancer [9].

An experiment on a mouse model of HER2-mediated breast cancer confirmed that hyperinsulinemia promotes enhanced growth of breast tumors through the growth hormone / IGF-1 axis [10]. Epidemiological evidence suggests that DM is associated with a higher risk of development and death from many cancer types. The underlying mechanisms linking DM and cancer are not yet fully understood; however, hyperglycemia as a sign of DM was suggested to contribute to tumor progression [11].

The aim of this study was to analyze the levels of IGF-1 and IGF-2 and their transporter proteins IGFBP-1 and IGFBP-2 in the liver of rats with DM, Guerin's carcinoma, and their combination.

MATERIALS AND METHODS

The study included white outbred rats of both sexes weighing 180–220 g obtained from the Research Center for Biomedical Technologies of FMBA, Andreevka branch, the Moscow region. The animals were kept under natural light conditions with free access to water and food. The animals were used in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Directive 86/609/EEC), the International Recommendations for Biomedical Research

Involving Animals, and the order of the Ministry of Health of Russia No. 267 "On the Approval of the Rules of Laboratory Practice", dated June 19, 2003. The study was approved by the Ethics Committee at the National Medical Research Center of Oncology (Protocol No. 21/99 of 01.09. 2020).

Animals of each sex were divided into 4 groups of 8 rats each: group 1 – intact animals, group 2 – animals with experimental diabetes, group 3 – animals with subcutaneously inoculated Guerin's carcinoma (control group), group 4 – animals with experimental diabetes and subcutaneously inoculated Guerin's carcinoma growing in presence of alloxan-induced diabetes (treatment group). Experimental diabetes was reproduced by an intraperitoneal alloxan injection at the dose of 150 mg / kg of body weight. Blood levels of glucose were monitored for one week. High blood glucose in the range of 15–30 nmol / l indicated the development of DM.

The rats from the control group and the animals from the main group after 1 week of persistent hyperglycemia received subcutaneous injections of 0.5 ml suspension of Guerin's tumor cells diluted in saline 1:5. The procedure was performed as follows: the assistant shaved off the animal's hair and treated the skin with an iodine alcohol solution 5% downward from the corner of the right shoulder blade; then, using all aseptic techniques described above, the assistant fixed the rat with its back up. The experimenter grasped the treated skin fold with a sterile gloved hand, pierced the skin with a syringe needle and injected the tumor cell suspension. Then the needle was removed, and the injection site was pressed tightly for 1 minute with a cotton swab dipped in 70% alcohol with a small addition of iodine in order to exclude the outflow of the injected suspension. Subcutaneous tumor growth could be recorded three days after the injections of the tumor cell suspension.

At the time of the Guerin's carcinoma inoculation, the average blood glucose values in the animals of the main group (n = 8) were 25.4 ± 1.2 mmol / l, while in the control group of intact animals (n = 8), the values were 5.2 ± 0.3 mmol / l.

10 days after, the animals were decapitated using a guillotine. The levels of IGF-1, IGF-2, IGFBP-1, and IGFBP-2 (Cusabio, China) were measured in the liver of all animals by ELISA using the Infinity F50 TECAN analyzer (Austria). The results were statistically processed using the Statistica 6.0 software. The results were checked for normality of distribution by the Shapiro – Wilk test. The significance of differences between the samples was assessed using the Student's t-test and the Mann – Whitney test. The data were presented as the mean and the standard error of the mean $M \pm m$. The differences were considered significant at $p < 0.05$.

RESULTS

The blood levels of glucose in the intact animals did not have significant sex differences and were on average 5.4 ± 0.5 mmol / l. In the rats with inoculated Guerin's carcinoma, the blood glucose levels were on average 5.1 ± 0.43 mmol / l. In the animals with alloxan-induced T1DM, the blood glucose averaged 22.5 ± 2.1 mmol / l; in the rats of the main group, the blood glucose levels were 25.3 ± 2.4 mmol / l at the time of tumor onset.

The levels of IGF-1 and IGF-2 in the liver of male outbred white rats were 1.4 times lower than in females, and the levels of IGFBP-1 in male rats were 1.8 times lower than in female ones ($p < 0.05$) (Table 1).

Table 1

Levels of insulin-like growth factors and transporter proteins in the rat liver, ng / g of tissue, $M \pm m$

Groups	IGF-1	IGFBP-1	IGF-2	IGFBP-2
Females				
Intact	1166.5 ± 98.7[4]	123.2 ± 11.4[4]	14.6 ± 1.2[4]	230.1 ± 21.4
Диабет	1480.4 ± 120.1[1, 3]	200.5 ± 17.6[1, 3, 4]	32.9 ± 2.9[1, 3]	454.0 ± 43.6[1, 3, 4]
Guerin's carcinoma	903.5 ± 87.4[2, 4]	77.4 ± 6.7[1, 2, 4]	16.0 ± 1.4[2]	197.4 ± 18.5[2, 4]
DM + carcinoma	1322.2 ± 113.5	140.1 ± 12.0[2, 3]	39.8 ± 3.5[1, 3]	425.7 ± 39.2[1, 3, 4]
Males				
Intact	843.6 ± 81.3	66.6 ± 5.8	10.8 ± 0.9	202.9 ± 19.1
DM	1269.2 ± 97.8[1]	140.5 ± 10.3[1, 3]	51.0 ± 4.3[1, 3]	704.8 ± 65.7[1, 3]
Guerin's carcinoma	1233.7 ± 101.6[1]	93.8 ± 8.3[1, 2]	18.7 ± 1.6[1, 2]	298.2 ± 21.4[1, 2]
DM + carcinoma	1526.3 ± 132.5[1]	152.1 ± 11.4[1, 3]	43.0 ± 3.7[1, 3]	726.7 ± 64.3[1, 3]

Note: [1] statistically significant differences compared with intact animals; [2] statistically significant differences compared with animals with DM; [3] statistically significant differences compared with animals with carcinoma; [4] statistically significant differences compared with males of the corresponding groups, $p < 0.05$ (here and in Table 2).

Female rats with DM showed an increase in the levels of IGF-1 and IGF-2 in the liver samples by 1.3 and 2.3 times, respectively ($p < 0.05$), and a rise in IGFBP-1 and IGFBP-2 by 1.6 times and by 2 times, respectively, compared with the values in the intact animals. The growth of inoculated Guerin's carcinoma downregulated only the levels of IGF-1 and IGFBP-1 in the liver by 1.3 and 1.6 times, respectively ($p < 0.05$), and did not affect the levels of IGF-2 and IGFBP-2. As a result of the growth of Guerin's carcinoma in the presence of DM, the levels of IGF-1 in the liver did not differ from those in the animals with DM and were 1.5 times higher ($p < 0.05$) than in the animals with malignant tumors only, while the levels of IGF-2 were 2.5 times higher than the values in the animals with Guerin's carcinoma.

As for IGF-binding proteins, the levels of IGFBP-1 and IGFBP-2 in the liver of the animals from the treatment group exceeded the values in the animals with independent tumor growth by 1.8 times and 2.2 times, respectively, while IGFBP was 1.4 times lower than in the rats with DM.

In male rats, DM upregulated the levels of both IGF-1 and IGF-2 by 1.5 times and 4.7 times, respectively ($p < 0.05$), compared with the values in the intact animals, as well as the levels of IGFBP-1 and IGFBP-2 by 2.1 times and 3.5 times, respectively (Table 1).

The growth of Guerin's carcinoma also increased the levels of IGF-1 and IGF-2 by 1.5 and 1.7 times, respectively ($p < 0.05$), and the levels of IGFBP-1 and IGFBP-2 by 1.4 and 1.5 times, respectively ($p < 0.05$), compared with the values in the intact animals. The studied parameters were elevated in the animals with malignant tumors or DM alone; the combined growth of Guerin's carcinoma in the presence of DM demonstrated quite similar changes, compared with independent processes.

Changes in the IGF / IGFBP ratios were found in all the groups of animals (Table 2) despite the fact that elevated levels of IGF-1, IGF-2, and IGF-binding proteins were determined in the liver of both male and female animals with independent and combined pathologies, except for the growth of Guerin's carcinoma in females. Thus, in females with DM, all ratios decreased: IGF-1 / IGF-2 – by 1.8 times ($p < 0.05$), IGF-1 / IGFBP-1 – by 1.8 times ($p < 0.05$), IGF-1 / IGFBP-2 – by 1.5 times ($p < 0.05$), IGF-2 / IGFBP-1 – by 1.4 times ($p < 0.05$), and IGF-2 / IGFBP-2 – by 1.3 times ($p < 0.05$) (Table 2).

Females with growing Guerin's carcinoma showed a decrease in the IGF-1 / IGFBP-1 ratio in the liver by 1.4 times ($p < 0.05$), IGF-2 / IGFBP-1 – by 1.8 times ($p < 0.05$), and IGF-2 / IGFBP-2 – by 1.3 times ($p < 0.05$). In combined pathologies, the ratios of IGF-1 / IGFBP-1 and IGF-2 / IGFBP-1 decreased by 1.4 and 1.7 times, respectively ($p < 0.05$), compared with DM, and by 1.7 and 1.4 times, respectively ($p < 0.05$), compared with independent growth of Guerin's carcinoma.

Table 2

Ratios of insulin-like growth factors and transporter proteins in the liver of rats, $M \pm m$

Groups	IGF-1/IGFBP-1	IGF-1/IGFBP-2	IGF-2/IGFBP-1	IGF-2/IGFBP-2
Females				
Intact	79.9 ± 7.1	5.1 ± 0.45	8.4 ± 0.76	0.5 ± 0.04
DM	45.0 ± 4.2[1, 4]	3.3 ± 0.27[1, 3, 4]	6.1 ± 0.52[1, 3, 4]	0.4 ± 0.03[1, 4]
Guerin's carcinoma	56.5 ± 5.5[1]	4.6 ± 0.42[2]	4.8 ± 0.33[1, 2]	0.4 ± 0.03[1, 4]
DM + carcinoma	33.2 ± 2.9[1, 2, 3]	3.1 ± 0.29[1, 3]	3.5 ± 0.31[1, 2]	0.3 ± 0.02[1, 2, 3, 4]
Males				
Intact	78.1 ± 6.7	4.2 ± 0.38	6.2 ± 0.54	0.3 ± 0.02
DM	24.9 ± 2.3[1, 3]	1.8 ± 0.15	2.8 ± 0.27[1, 3]	0.2 ± 0.019[1, 3]
Guerin's carcinoma	66.0 ± 5.8[2]	4.1 ± 0.34	5.0 ± 0.43[1, 2]	0.3 ± 0.02[2]
DM + carcinoma	35.5 ± 3.1[1, 2, 3]	2.1 ± 0.19	3.5 ± 0.32[1, 2, 3]	0.2 ± 0.018[1, 3]

The IGF-1 / IGFBP-2 ratio decreased by 1.5 times ($p < 0.05$) compared with animals with Guerin's carcinoma, and the IGF-2 / IGFBP-2 ratio decreased by 1.3 times ($p < 0.05$) compared with the animals with solitary pathologies.

In males, the ratio of IGF to IGF-binding proteins decreased by 1.5–3.1 times ($p < 0.05$) in the DM group, but not in the group with independent tumor growth, compared with the intact animals (Table 2). The IGF / IGFBP ratio in the treatment group was 1.5–2 times lower ($p < 0.05$) than in the group with independent tumor growth. Compared with the group of males with DM, the ratios in the treatment group did not differ significantly, except for IGF-1 / IGFBP-1, which was 1.4 times higher.

DISCUSSION

The levels of IGFs and IGFBP-1 in the liver of outbred white rats were sex-specific. The levels of IGF-1, IGF-2, and IGFBP-1 in the liver of males were lower than in females. Changes in the sex specificity of IGF and IGF-binding proteins were revealed in the liver of rats with DM: the levels of IGF-1 in males did not differ from those in females, and the levels of IGF-2 and IGFBP-2 exceeded those in the liver of females. The differences in the content of IGF and IGFBP in healthy and pathological tissues of the liver in females and males are associated with the main sex steroids – estrogens and androgens. Studies have shown that biologically available estrogen and testosterone are elevated in women with DM [12], while the total testosterone concentration in men with DM is lower than in men without DM [13]. Although the mechanism remains unclear, it may be explained by different affinities of steroids to sex hormone-binding globulin (SHBG) [14, 15]. SHBG synthesis declines with an increase in the blood levels of glucose and insulin, which elevates the levels of free estrogen and testosterone. This is the main reason why DM may play an important role in protecting men from prostate cancer, but not protecting women from breast and endometrial cancers. High levels of free estrogens and androgens are associated with a higher risk of developing many types of cancer, such as breast, endometrial, and prostate cancers [16]. The subcutaneous transplantation of Guerin's carcinoma leveled the initially existing sex specificity of IGF and IGFBP-1 in the liver, and the levels of IGF-1 and IGFBP-2 in males exceeded those in females, while the values of IGF-2 and IGFBP-1 did not differ from those in females.

IGFs and proteins that affect their bioavailability act in an autocrine / paracrine manner, reducing inflammation and fibrosis in the liver and inhibiting the activation of hepatic stellate cells [17]. High insulin levels stimulate liver cells to produce IGF, and IGF bind to IGF receptors (IGF-R) to activate some metabolic and mitogenic signaling pathways that regulate proliferation, differentiation, and apoptosis of cancer cells [7]. Our study established that IGF levels in the liver increased in both male and female rats with DM, but only in males with Guerin's carcinoma. It is worth noting that IGFs bind to IGFBP, including IGFBP-2 [18]. Our study revealed an increase in IGFBP levels in the liver of animals of both sexes with DM. Elevated levels of IGFBP-1 and IGFBP-2, in particular in older men, were suggested to be associated with a decline in insulin sensitivity [8].

The significant increase in IGFBP-2 in the liver of rats under the influence of DM, both alone and in a combination with developing malignant process, was worth noting. The role of IGFBP-2 in physiological and pathological conditions is still not fully understood. However, IGFBP-2 has been related to metabolic syndrome, T2DM, and fatty liver disease. Altered IGFBP-2 secretion may indicate cellular dysfunction of hepatocytes [19]. IGFBP-2 is believed to be a non-invasive biomarker of lipid accumulation in the liver indicating the disease progression [1].

Changes in the levels of IGF and IGFBP during the growth of Guerin's carcinoma in the presence of DM are unidirectional in animals of both sexes and characterized by increasing levels of the studied substances compared with the values in the intact animals. DM as an endocrine disease induced in experimental animals determines the status of the IGF-1 axis. This fact was confirmed in female rats, as the growth of Guerin's carcinoma alone caused a decrease in IGF-1 in the liver, while in the presence of DM, its levels, as well as the levels of IGFBP, increased.

Thus, Guerin's carcinoma and DM cause multidirectional changes in IGF and IGFBP in the liver of females, but unidirectional changes in males. The development of Guerin's carcinoma in the presence of DM reduces sex differences in the studied parameters, and DM changes the metabolic profile of the liver in animals of both sexes. Only experimental studies can solve a number of issues related to the pathogenesis of cancer in presence of comorbid diseases [20].

The global incidence of DM and cancer is believed to be growing rapidly due to changes in lifestyle and increasing life expectancy. Since the internal heterogeneity of DM and cancer complicates research, many questions remain, and the main ones are how endocrine comorbidity affects the risk, course and outcome of malignant disease and what the main biological mechanisms of the malignant development in the presence of such a serious concomitant pathology as DM are. Further research is required to provide a broader range of preventive and therapeutic options for treating cancer patients with DM.

REFERENCES

1. Wang M., Yang Y., Liao Z. Diabetes and cancer: Epidemiological and biological links. *World Journal of Diabetes*. 2020;11(6):227–238. DOI: 10.4239/wjd.v11.i6.227.
2. Arneth B., Arneth R., Shams M. Metabolomics of type 1 and type 2 diabetes. *Int. J. Mol. Sci.* 2019;20(10):2467. DOI: 10.3390/ijms20102467.

3. Yaribeygi H., Bo S., Ruscica M., Sahebkar A. Ceramides and diabetes mellitus: an update on the potential molecular relationships. *Diabet. Med.* 2020;37(1):11–19. DOI: 10.1111/dme.13943.
4. Saltzman B.S., Doherty J.A., Hill D.A., Beresford S.A., Voigt L.F., Chen C. et al. Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. *Am. J. Epidemiol*. 2008;167(5):607–614. DOI: 10.1093/aje/kwm333.
5. Liao C., Zhang D., Mungo C., Tompkins D.A., Zeidan A.M. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. *Gynecol. Oncol*. 2014;135(1):163–171. DOI: 10.1016/j.ygyno.2014.07.095.
6. Godsland I.F. Insulin resistance and hyperinsulinaemia in the development and progression of cancer. *Clin. Sci. (Lond.)*.2009;118(5):315–332. DOI: 10.1042/CS20090399.
7. Liao Z., Tan Z.W., Zhu P., Tan N.S. Cancer-associated fibroblasts in tumor microenvironment - Accomplices in tumor malignancy. *Cell Immunol*. 2019;343:103729. DOI: 10.1016/j.cellimm.2017.12.003.
8. Watts E.L., Perez-Cornago A., Appleby P.N., Albanes D., Ardanaz E., Black A. et al. The associations of anthropometric, behavioural and sociodemographic factors with circulating concentrations of IGF-I, IGF-II, IGFBP-1, IGFBP-2 and IGFBP-3 in a pooled analysis of 16,024 men from 22 studies. *Int. J. Cancer*. 2019;145(12):3244–3256. DOI: 10.1002/ijc.32276.
9. Collins K.K. The diabetes-cancer link. *Diabetes* Spectr. 2014;27(4):276–280. DOI: 10.2337/diaspect.27.4.276.
10. Ferguson R.D., Gallagher E.J., Cohen D., Tobin-Hess A., Alikhani N., Novosyadlyy R. et al. Hyperinsulinemia promotes metastasis to the lung in a mouse model of Her2-mediated breast cancer. *Endocr. Relat. Cancer*. 2013;20(3):391–401. DOI: 10.1530/ERC-12-0333.
11. Mansor R., Holly J., Barker R., Biernacka K., Zielinska H., Koupparis A. et al. IGF-1 and hyperglycaemia-induced FOXA1 and IGFBP-2 affect epithelial to mesenchymal transition in prostate epithelial cells. *Oncotarget.* 2020;11(26):2543–2559. DOI: 10.18632/oncotarget.27650.
12. Muka T., Nano J., Jaspers L., Meun C., Bramer W.M., Hofman A. et al. Associations of steroid sex hormones and sex hormone-binding globulin with the risk of type 2 diabetes in women: A population-based cohort study and meta-analysis. *Diabetes.* 2017;66(33):577–586. DOI: 10.2337/db16-0473.
13. Ding E.L., Song Y., Malik V.S., Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA.* 2006;295(1):1288–1299. DOI: 10.1001/jama.295.11.1288.
14. Liu S., Sun Q. Sex differences, endogenous sex-hormone hormones, sex-hormone binding globulin, and exogenous disruptors in diabetes and related metabolic outcomes. *J. Diabetes*. 2018;10(6):428–441. DOI: 10.1111/1753-0407.12517.
15. Gambineri A., Pelusi C. Sex hormones, obesity and type 2 diabetes: is there a link? *Endocr. Connect.* 2019;8(1):R1–R9. DOI: 10.1530/EC-18-0450.
16. Felix A.S., Yang H.P., Bell D.W., Sherman M.E. Epidemiology of Endometrial Carcinoma: Etiologic Importance of Hormonal and Metabolic Influences. *Adv. Exp. Med. Biol*. 2017;943:3–46. DOI: 10.1007/978-3-319-43139-0_1.
17. Takahashi Y. The role of growth hormone and insulin-like growth factor-I in the liver. *Int. J. Mol. Sci.*2017;18(7):E1447. DOI: 10.3390/ijms18071447.
18. Bach L.A., Headey S.J., Norton R.S. IGF-binding proteins – the pieces are falling into place. *Trends Endocrinol. Metab*. 2005;16(5):228–234. DOI: 10.1016/j.tem.2005.05.005.
19. Fahlbusch P., Knebel B., Hörbelt T., Barbosa D.M., Nikolic A., Jacob S. et al. Physiological disturbance in fatty liver energy metabolism converges on IGFBP2 abundance and regulation in mice and men. *Int. J. Mol. Sci.* 2020;21(11):4144. DOI: 10.3390/IJMS21114144.
20. Kit O.I., Frantsiyants E.M., Dimitriadi S.N., Shevchenko A.N., Kaplieva I.V., Trepitaki L.K. Neoangiogenesis and fibrinolytic system biomarkers expression in the dynamics of experimental kidney ischemia in rats. *Experimental and Clinical Urology*. 2015;(1):20–23 (in Russ.).

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Frantsiyants E.M., Kotieva I.M., Kaplieva I.V. – conception and design of the experiment. Surikova E.I., Neskubina I.V., Pogorelova Yu.A. – analysis and interpretation of the results. Frantsiyants E.M., Bandovkina V.A., Shaposhnikov A.V. – preparation and editing of the manuscript, critical revision of the manuscript for important intellectual content. Trepitaki L.K., Morozova M.I., Nemashkalova L.A., Sheiko E.A. – carrying out of the experiment. Pogorelova Yu.A., Cheryarina N.D. – carrying out of the ELISA analysis. Frantsiyants E.M., Bandovkina V.A., Kaplieva I.V. – final approval of the manuscript for publication.

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