УДК 616.379-008.64-021.6-092.6:616.61:577.125.722.032
https://doi.org/10.20538/1682-0363-2022-3-112-119

Insulin-like growth factors and their carrier proteins in kidneys of rats with experimental diabetes, malignant tumor, and their combination

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ABSTRACT

Persistent hyperglycemia resulting from diabetes mellitus causes microvascular lesions and long-term diabetic complications, such as nephropathy.

The aim of the study was to analyze the levels of insulin-like growth factors (IGFs), their carrier proteins (IGFBP), and markers of kidney tissue damage (IL-18, L-FABP, cystatin C, NGAL, and KIM-1) in male rats with diabetes mellitus, tumor growth, and their combination.

Materials and methods. The study included white outbred male rats (n = 32) weighing 180–220 g. The animals were divided into four groups (n = 8 each): group 1 – intact animals; controls (2) – animals with diabetes mellitus; controls (3) – animals with Guerin carcinoma; experimental group (4) – animals with Guerin carcinoma against the background of diabetes mellitus. Levels of IGF-1, IGF-2, IGFBP-1, IGFBP-2 and markers of acute kidney injury (IL-18, L-FABP, cystatin C, NGAL, and KIM-1) were determined in the kidney homogenates using enzyme-linked immunosorbent assay.

Results. Increased levels of acute kidney injury markers were found in the kidneys of male rats with diabetes mellitus alone and in combination with Guerin carcinoma. In the animals with diabetes mellitus, the levels of IGF-1, IGFBP-1, and IGFBP-2 were decreased on average by 1.3 times, and the level of IGF-2 was increased by 2.1 times compared with the values in the intact male rats. The elevation of IGF-2 / IGF-1 on average by 2.8 times indicated increasing hypoglycemia in the kidney tissue of the animals with diabetes mellitus and in the experimental group with diabetes mellitus and Guerin carcinoma. In the kidney tissues of the rats with Guerin carcinoma, IGF-1 and IGF-2 were elevated on average by 1.5 times, and IGFBP-2 was decreased by 1.7 times. In the animals with malignant tumors growing against the background of diabetes mellitus, IGF-2 and IGFBP-1 were increased by 2.3 and 1.7 times, respectively, and the levels of IGF-1 and IGFBP-2 were similar to those in the intact animals.

Conclusion. The study demonstrated abnormalities in the metabolic profile of the kidneys in male rats with experimental diabetes mellitus, Guerin carcinoma, and their combination.

Keywords: diabetes mellitus, Guerin carcinoma, markers of acute kidney injury, IGF, IGFBP

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

Source of financing. The authors state that they received no funding for the study.

Conformity with the principles of ethics. The study was approved by the Animal Bioethics Committee at National Medical Research Center of Oncology (Protocol 21/99 of 01.09.2020).

For citation: Frantsiyants E.M., Bandovkina V.A., Kaplieva I.V., Surikova E.I., Neskubina I.V., Pogorelova Yu.A., Trepitaki L.K., Cheryarina N.D., Kotieva I.M., Morozova M.I. Insulin-like growth factors and their carrier proteins in kidneys of rats with experimental diabetes, malignant tumor, and their combination. *Bulletin of Siberian Medicine.* 2022;21(3):112–119. https://doi.org/10.20538/1682-0363-2022-3-112-119.

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Инсулиноподобные факторы роста и их белки-переносчики в почках крыс при экспериментальном диабете, злокачественном росте и их сочетании

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РЕЗЮМЕ

Устойчивая гипергликемия в результате сахарного диабета вызывает повреждение микрососудов и долгосрочные диабетические осложнения, такие как нефропатия.

Целью настоящего исследования явилось изучение уровня инсулиноподобных факторов роста (IGF), их белков-переносчиков (IGFBP) и маркеров повреждения (IL-18, L-FABP, цистатина С, NGAL, КИМ-1) в ткани почек самцов крыс при сахарном диабете, опухолевом росте и их сочетании.

Материалы и методы. В исследование включены самцы белых беспородных крыс (n = 32) массой 180–220 г, разделены на четыре группы по 8 особей в каждой. Группа 1–интактные животные, контрольная группа (2) –животные с сахарным диабетом, контрольная группа (3) – животные с карциномой Герена, основная группа (4) – животные с карциномой Герена на фоне сахарного диабета. В гомогенатах почек методом иммуноферментного анализа определяли IGF-1, IGF-2, IGFBP-1, IGFBP-2 и маркеры острого повреждения почек: IL-18, L-FABP, цистатин С, NGAL, KIM-1.

Результаты. При сахарном диабете в самостоятельном варианте и сочетанном с ростом карциномы Герена у самцов крыс в почках установлено повышение уровня маркеров острого повреждения почек. При развитии сахарного диабета уровень IGF-1, IGFBP-1 и IGFBP-2 был снижен в среднем в 1,3 раза, а уровень IGF-2 повышен в 2,1 раза относительно показателя у интактных самцов. Повышение IGF-2/IGF-1в среднем в 2,8 раза свидетельствовало о нарастании гипогликемии ткани почек животных при сахарном диабете и в группе с сахарным диабетом и опухолью Герена. При опухоли Герена в ткани почек самцов уровень IGF-1 и IGF-2 был повышен в среднем в 1,5 раза, а уровень IGFBP-2 снижен в 1,7 раза. При сочетанном развитии злокачественной опухоли на фоне сахарного диабета содержание IGF-2 и IGFBP-1 было повышено в 2,3 и 1,7 раза соответственно, а IGF-1 и IGFBP-2 не отличались от показателей у интактных животных.

Заключение. Обнаружены нарушения метаболического состояния ткани почек самцов при развитии сахарного диабета, опухоли Герена и их сочетания.

Ключевые слова: сахарный диабет, карцинома Герена, маркеры острого повреждения почек, IGF, IGFBP

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Исследование одобрено биоэтическим комитетом по работе с животными ФГБУ «Ростовский научно-исследовательский онкологический институт» (протокол № 21/99 от 01.09.2020).

Для цитирования: Франциянц Е.М., Бандовкина В.А., Каплиева И.В., Сурикова Е.И., Нескубина И.В., Погорелова Ю.А., Трепитаки Л.К., Черярина Н.Д., Котиева И.М., Морозова М.И. Инсулиноподобные факторы роста и их белки-переносчики в почках крыс при экспериментальном диабете, злокачественном росте и их сочетании. *Бюллетень сибирской медицины.* 2022;21(3):112–119. https://doi.org/10.20538/1682-0363-2022-3-112-119.

INTRODUCTION

The growing incidence of diabetes mellitus (DM) and chronic kidney disease (CKD) worldwide has prompted research efforts to overcome the growing prevalence of diabetic nephropathy (DN), which has become a global disaster due to the limited effectiveness of existing treatments [1]. Persistent hyperglycemia resulting from DM causes microvascular damage and long-term diabetic complications, such as nephropathy, also known as diabetic kidney disease (DKD) [2]. The kidneys play an important role in maintaining blood glucose homeostasis. In normal conditions, about 180 g of glucose is filtered through the glomeruli every day and almost completely reabsorbed by the renal tubules, of which about 90% is reabsorbed by the proximal tubules of the kidneys [3]. Both DM and CKD are known to be associated with aging. The incidence of DM in people over 65 years more than doubles that in people over 20 years [1], and aging is a key factor explaining the loss of nephrons and leading to CKD [4].

DM is believed to be an inducer of accelerated cellular aging and is associated with cardiovascular and kidney diseases due to high glucose levels [5]. However, tissue-specific aging remains poorly understood. DM is the leading cause of end-stage renal disease worldwide, especially in the elderly [6]. Accelerated kidney aging in DM is associated with multiple stressors, such as accumulation of advanced glycation end products, hypertension, oxidative stress, and inflammation [7].

IGF, a peptide growth factor secreted by the collecting duct of the adult kidney, binds to IGF1R and phosphorylates insulin receptor substrate proteins, thereby initiating downstream pathways, including PI3K-Akt-mTOR, to participate in the regulation of cell proliferation and apoptosis [8]. IGF-1 infusion improves hemodynamic parameters, such as renal plasma flow, inulin clearance, and renal vascular resistance in fasted rats. Studies have shown that IGF signaling is significantly involved in kidney development and various kidney diseases [9]. IGF-1 decreases after ischemic injury, and treatment with exogenous IGF-1 accelerates recovery by limiting cell apoptosis and promoting cell proliferation [10]. These findings were further supported by a study showing that administration of rhIGF-1 2 hours after injury suppressed the inflammatory response in the kidneys and increased EGF levels. IGF-1 also promotes tubular regeneration after acute kidney injury (AKI) by transactivating EGFR [7]. In addition to ligands, receptors, insulin, and IGF, there is a family of high affinity insulin-like growth factor binding proteins (IGFBPs). These proteins primarily counteract IGF function and can serve as independent biomarkers [11].

The DKD-affected kidney is believed to be particularly prone to hypoxic medullary injury [12]. The use of biomarkers of AKI for detection and assessment of its severity is expanding, and combined analyzes of several biomarkers increase their sensitivity and specificity [13]. However, although elevated markers in young and stable patients with intact kidneys are a strong sign of AKI, they are less predictable in elderly patients with comorbidities, especially with DM and pre-existing renal failure [13]. A study [14] measured serum and urine KIM-1 levels in addition to liver fatty acid binding protein (L-FABP), another marker of proximal renal tubular damage, in DM patients to clarify the relationship between these parameters. Experimental studies *in vivo* can reveal characteristics of cancer development in the presence of comorbid diseases [15].

The aim of this study was to analyze the levels of IGF, their carrier proteins (IGFBP), and markers of kidney tissue damage (IL-18, L-FABP, cystatin C, NGAL, and KIM-1) in the kidneys of male rats with DM, tumor growth, and their combination.

MATERIALS AND METHODS

The study included white outbred male rats weighing 180–220 g obtained from the Research Center for Biomedical Technologies of FMBA (Andreevka branch, 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 Guiding Principles for Biomedical Research Involving Animals, and the order of the Ministry of Health of Russia No. 267 of 19.06.2003 “On the approval of the rules of laboratory practice”.

The animals were divided into four groups, with 8 rats in each: intact animals (1); two control groups: with alloxan-induced diabetes (2) and Guerin carcinoma (3); experimental group (4) with Guerin carcinoma growing in presence of alloxan-induced diabetes. Experimental diabetes was reproduced by an intraperitoneal alloxan injection (150 mg / kg of body weight). Blood levels of glucose were monitored daily for one week. The blood glucose levels in intact animals

were 5.2 ± 0.3 mmol / l, in rats with induced DM – 27.3 ± 2.6 mmol /l, and in the experimental group – 25.4 ± 2.2 mmol / l. The rats from groups 3 and 4 after 1 week of persistent hyperglycemia received subcutaneous injections (downward from the corner of the right shoulder blade) of 0.5 ml suspension of Guerin carcinoma cells diluted 1 : 5 in saline. The experimental animals were monitored daily; subcutaneous tumor growth could be recorded 3 days after the injections of Guerin carcinoma cell suspension. Examinations carried out after 10 days of the malignant tumor growth corresponded to the exponential phase of Guerin carcinoma growth. 10 days after, the animals were decapitated using a guillotine. The levels of IGF-1, IGF-2 IGFBP-1, and IGFBP-2, as well as AKI markers (IL-18, L-FABP, cystatin C, NGAL, and KIM-1) were measured by ELISA in kidney homogenates in all animals (Cusabio, China).

The results were statistically processed using the Statistica 13.0 software package. The results were presented as the mean and the standard error of the mean $M \pm SE$. Normality of data distribution was checked by the Shapiro – Wilk test. The significance of differences between the independent variables was assessed using the Mann – Whitney test. The differences were considered significant at $p < 0.05$.

RESULTS

The results of the analysis of IGFs and their carrier proteins in the kidney tissue of male rats with DM, Guerin carcinoma, and Guerin carcinoma growing in the presence of DM are presented in Table 1.

Table 1

Levels of IGF and IGFBP (ng / g of tissue) in the kidneys of male rats, $M \pm SE$

Parameter	IGF-1	IGF-2	IGF-2/IGF-1	IGFBP-1	IGFBP-2
Group 1 (intact), $n = 8$	125.1 ± 10.8	66.6±5.9	0.5 ± 0.06	63.0 ± 6.7	456.79 ± 54.2
Group 2 (DM), $n = 8$	93.5 ± 8.4[1]	140.5±13.2[1]	1.5 ± 0.14[1]	46.2 ± 4.1[1]	349.3 ± 31.5[1]
Group 3 (Guerin carcinoma), $n = 8$	197.6 ± 16.3[1,2]	93.8 ± 9.5[1,2]	0.5 ± 0.05[2]	56.1 ± 5.8	274.3 ± 26.9[1,2]
Group 4 (DM + Guerin carcinoma), $n = 8$	120.6 ± 11.8[2]	152.1 ± 13.7[1]	1.3 ± 0.15[1]	105.6 ± 11.2[1,2]	372.0 ± 33.8

Note: statistically significant ($p < 0.05$) compared with: 1 – levels in intact animals; 2- levels in group 2 (here and in Table 2).

The levels of IGF-1, IGFBP-1, and IGFBP-2 in the animals with DM were decreased on average by 1.3 times ($p < 0.05$) compared with the values in the intact males, while IGF-2, on the contrary, was increased by 2.1 times. IGF-1 and IGF-2 in the kidney tissues of the male rats with Guerin carcinoma were increased by 1.6 and 1.4 times ($p < 0.05$), respectively, IGFBP-2 was decreased by 1.7 times ($p < 0.05$), and IGFBP-1 did not differ significantly from the levels in the intact males. In the animals with combined DM and Guerin carcinoma, the levels of IGF-1 and IGFBP-2 in the kidney tissues did not differ significantly from those in the intact males, and IGF-2 and IGFBP-1 were increased by 2.3 and 1.7 times ($p < 0.05$), respectively.

Clinical application of IGF-2 measurement in the diagnosis of non-islet cell tumor hypoglycemia was shown. Recent advances in understanding the pathophysiology of IGF-2 in cancer revealed new clinical potential of its use [16]. An increase in the IGF-2 / IGF-1 ratio indicated increasing tissue hypoglycemia.

The tumor tissue was not the subject of the study, nevertheless, we considered it reasonable to calculate the IGF-2 / IGF-1 ratio in the kidney tissue of the animals. IGF-2 / IGF-1 in the kidney tissue increased only in the male rats with DM and with Guerin carcinoma growing in presence of DM by 3 and 2.6 times, respectively. This indicated an increase in kidney tissue hypoglycemia in the animals precisely in conditions associated with an increase in the blood glucose level.

The bioavailability of the IGF-1 / IGFBP-1 and IGF-2 / IGFBP-1 ratios is also worth noting. IGF-1 / IGFBP-1 in the kidney tissue was elevated only in the animals with Guerin carcinoma (3.5 ± 0.4 vs. 2.0 ± 0.1). The IGF-2 / IGFBP-1 ratio was increased in all studied processes: in DM from 1.1 ± 0.09 to 3.0 ± 0.2; in Guerin carcinoma from 1.1 ± 0.09 to 1.7 ± 0.08; in DM + Guerin carcinoma from 1.1 ± 0.09 to 1.4 ± 0.07 ($p < 0.05$).

We studied AKI markers in the kidney tissue of rats with DM, Guerin carcinoma, and Guerin carcinoma growing in the presence of DM (Table 2).

The level of all markers, except for cystatin C, were increased in DM, compared with the values in the intact male frats: IL-18 – by 1.6 times ($p < 0.05$), L-FABP – by 1.9 times ($p < 0.05$), NGAL – by 2.3 times, and KIM-1 – by 1.6 times ($p < 0.05$). The male rats with Guerin carcinoma were characterized by elevated levels of some markers, compared with the intact animals: IL-18 – by 1.8 times ($p < 0.05$), cystatin C – by 1.3 times ($p < 0.05$), and KIM-1 – by 1.3 times

($p < 0.05$). In the kidney tissue of the male rats with Guerin carcinoma growing in the presence of DM, the level of IL-18 was increased by 1.5 times ($p < 0.05$), L-FABP – by 1.4 times ($p < 0.05$), cystatin C – by 1.8 times ($p < 0.05$), NGAL – by 2 times ($p < 0.05$), and KIM-1 – by 1.4 times ($p < 0.05$).

Table 2

Levels of AKI markers in the kidneys of male rats

Parameter	IL-18 (pg / g of tissue)	L-FABP (pg / g of tissue)	cystatin C (ng / g of tissue)	NGAL (ng / g of tissue)	KIM-1 (pg / g of tissue)
Group 1 (intact), $n = 8$	5,415.1 ± 398.6	2,319.4 ± 251.7	960.8 ± 83.5	0.12 ± 0.02	679.1 ± 58.4
Group 2 (DM), $n = 8$	8,520.4 ± 611.8[1]	4,365.2 ± 369.5[1]	828.4 ± 77.1	0.28 ± 0.03	1,058.5 ± 84.9[1]
Group 3 (Guerin carcinoma), $n = 8$	9,536.3 ± 842.5[1]	2,883.6 ± 334.6[2]	1,267.9 ± 113.5[1,2]	0.13 ± 0.015[2]	904.9 ± 76.3[1]
Group 4 (DM + Guerin carcinoma), $n = 8$	8,253.4 ± 731.2[1]	3,298.7 ± 248.3[1,2]	1,717.5 ± 99.4[1,2]	0.24 ± 0.028[1]	935.5 ± 81.7[1]

DISCUSSION

DM is an increasingly dangerous public health problem both due to its high prevalence and incidence and poor outcomes of vascular complications, such as DKD. Acute hyperglycemia occurs in diabetic ketoacidosis, and hyperglycemia can cause a series of metabolic disorders. Does it mean that rapidly elevated blood glucose may also lead to "acute hyperglycemic renal toxicity" [3]?

IGFs are essential for normal pre- and postnatal kidney development. IGF-1 mediates many growth hormone effects, and both excess and deficiency of growth hormone are associated with impaired renal function. IGFs affect renal hemodynamics both directly and indirectly by interacting with the renin – angiotensin system. In addition to IGF ligands, the IGF system includes IGF-1, IGF-2 / mannose-6-phosphate, and insulin receptors, as well as a family of 6 high affinity IGFBP that modulate the IGF effect. Dysregulation of the IGF system causes a number of kidney diseases.

Our results are consistent with the results from a number of studies showing that abnormal IGF levels are found in diabetic nephropathy and chronic renal failure [9]. In addition, IGF-1 can induce proliferation and differentiation of renal tubular epithelial cells and modulate immune cells, reducing the production of proinflammatory cytokines [17]. Obviously, decreased IGF-1 levels in the kidney tissues could lead to an increase in the production of proinflammatory cytokines and greater susceptibility of the organ to their action. However, our study did not reveal a decrease in the level of IGF-1 in the kidney tissues (both in the control and in the experimental groups), although elevated IL-18 levels were found in all studied tissue samples.

IL-18 is a proinflammatory cytokine produced by the proximal tubular epithelium after the action of nephrotoxic factors. Interleukins are important mediators of the immune response in the innate and adaptive immunity. All cytokines are freely filtered and then reabsorbed and metabolized in the proximal tubules; therefore, an increase in the level of IL-18 indicates damage to these tubules [18]. The determination of IL-18 in urine allows for identification of renal damage caused by ischemia at the earliest stage. IGF-1 controls the anti-apoptotic Bcl-2 protein, which is the main mechanism of protection and survival of the renal epithelium during injury, and Bcl-2 is regulated by IGF-1 at the post-transcriptional level [19].

In contrast to IGF-1, the levels of IGF-2 were increased in all kidney tissue samples, although in the animals with DM, i.e. in the experimental and control groups, these changes were more pronounced, compared with the rats with the independent growth of Guerin carcinoma. IGF-2 is a 7.5 kDa mitogenic peptide hormone expressed by the liver and many other tissues. It is three times more abundant in serum than IGF-1, but our understanding of its physiological and pathological roles is insufficient compared with IGF-1. Expression of the IGF-2 gene is strictly regulated. Its overexpression is observed in many cancers and associated with a poor prognosis. Elevated serum IGF-2 levels are also associated with an increased risk of developing various cancers [16].

In this study, IGF-2 / IGF-1 demonstrated increasing hypoglycemia in the kidney tissue of animals precisely in conditions associated with an increase in blood glucose levels, i.e. in the experimental group and in the control group with DM. The increased IGF-2 / IGFBP-1 ratio showed, on the one hand, an increase in the bioavailability of IGF-2 in all studied pathological processes, and, on the other hand, that this factor is pathognomonic in both malignant growth and DM. There are many common risk factors

for DM and cancer [20]. Obviously, IGF-2 is one of such pathognomonic factors.

In recent decades, new methods for studying kidney diseases have been proposed, such as tubular enzymes and new AKI biomarkers. Very promising new AKI biomarkers have been termed "renal troponins" and have suggested early detection of kidney disease.

Numerous studies on urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C (CysC), liver fatty acid binding protein (L-FABP), and interleukin (IL)-18 have been carried out. Elevated levels of NGAL, a biomarker of distal tubular segments, may indicate that these segments are affected by inflammation. After ischemic or nephrotoxic AKI, intrarenal NGAL is dramatically upregulated at the transcriptional and protein levels. In contrast, unaltered KIM-1, a proximal tubular biomarker, may reflect improved cortical oxygenation [12].

Biomarkers can be localized in certain nephron segments. A recent study [21] suggested that IL-18, NGAL, L-FABP, and KIM-1 can help characterize the function of glomeruli or tubules; glomerular, tubular or interstitial damage, inflammation. At the same time, NGAL levels can be elevated in sepsis, CKD or urinary tract infections, and no specific threshold values were noted for it [22]. The levels of KIM-1 can be elevated in chronic proteinuria and inflammatory diseases [23]. L-FABP can be closely associated with anemia in patients without DM [24].

CysC is produced by nucleated cells at a constant rate, filtered by glomerular cells, and almost completely reabsorbed and catabolized (but not secreted) in the proximal tubules. Over the past decade, CysC was revealed to be a stronger death risk predictor in older people than creatinine [25].

L-FABP is a 14 kDa protein from a large fatty acid-binding protein superfamily. It is predominantly localized in the proximal tubules [25]. The described studies make it obvious that the kidneys of males with DM, Guerin carcinoma, and the combined pathology were subject to any kind of damaging effects, be it hyperglycemia or stress associated with tumor growth. The L-FABP protein levels were increased only in the samples of the animals with DM, alone or with concomitant disease. CysC, on the contrary, increased in the kidney tissues of the animals with Guerin carcinoma, alone or with concomitant disease. The IL-18 and NGAL levels were increased in the kidney tissues of the male rats with both pathological processes. Thus, male rats with different pathologies showed glomerular, tubular or interstitial damage. The glomerular filtration was affected only in the animals with independently growing tumors (control group) or in combination with DM (experimental group). Similar results associated with kidney ischemia and cancer were earlier obtained in the experiment and in clinical practice [26, 27].

CONCLUSION

DM as a concomitant process in malignant growth increases the levels of IGF-2, IGF-1 / IGF-2, and IGFBP-2 in kidney samples of nonlinear male rats with a rise in the local level of AKI markers. Perhaps the reason for it should be sought in the predictive role of sex hormones.

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Received 16.03.2021;
approved after peer review 05.04.2021;
accepted 05.10.2021