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IMPACT OF THE GROWTH HORMONE AND IGF-1 ON GRAFT FUNCTION AND IMMUNE RESPONSE IN PEDIATRIC LIVER RECIPIENTS

R.M. Kurabekova[1], O.M. Tsirulnikova[1, 2], S.Yu. Oleshkevich[1], I.E. Pashkova[1], G.A. Olefirenko[1]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Sechenov University, Moscow, Russian Federation

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are the most important regulators of growth, regeneration and metabolism. The influence of GH and IGF-1 on pediatric liver transplant outcomes is mediated through growth and body weight regulation, specific effects on hepatocyte function and immune system activity. In recent years, the blood levels of these factors and life expectancy, both in healthy individuals and liver recipients, have been shown to be correlated. In pediatric liver recipients, neurohumoral regulation of graft function and other functions of the growing organism, has not been studied enough. The results of studies on the levels and dynamics of GH and IGF-1 in the blood of liver recipients can serve as a basis for assessing the state of graft using new minimally invasive methods and identifying therapeutic targets for personalized therapy. This review summarizes the current understanding of the significance of GH/IGF-1 hormones in hepatobiliary diseases and pediatric liver transplantation (LTx).

Keywords: biomarker, pediatric liver transplantation, liver disease, liver fibrosis.

GH and IGF-1 are the key links in neurohumoral regulation of metabolism. They can affect tissues through different intracellular signaling pathways. GH stimulates IGF-1 synthesis, which, in turn, influences GH production by the principle of negative feedback, inhibiting its synthesis [1].

GH is synthesized in the anterior pituitary lobe and secreted into the blood, with maximum blood concentrations every 3–5 hours. The nature of GH secretion differs in men and women and depends on age. The highest level of the hormone in the blood is observed during fetal development. With age, the baseline level, frequency, and amplitude of hormone secretion peaks decrease. The range of reference values of GH in the blood of children aged 1–3 years is 2–10 ng/mL, and in adults it is 1–5 ng/mL [2].

IGF-1 is a polypeptide hormone produced by many tissues. More than 90% of IGF-1 circulating in the systemic circulation is synthesized by hepatocytes [3]. Plasma IGF-1 levels, in contrast to GH, practically do not change during a day. The range of reference values of plasma IGF-1 levels in children aged 1–3 years is 5–300 ng/mL [3]. The maximum plasma IGF-1 level in children is observed during puberty and gradually decreases over the years.

The significance of growth hormone and IGF-1 in pediatric liver transplantation (LTx) may be related to their role in regulation of growth and body weight, their influence on hepatocyte function and immune system activity [4, 5].

The physiological effects of GH and IGF-1 on cells are mediated through transmembrane receptors found on the surface of many cell types, including hepatocytes and lymphocytes [6]. The effect of GH and IGF-1 is largely determined by the level of receptor expression, which depends on cell type and may change under the influence of various factors. The GH/IGF-1 effect depends on GH and IGF-1 production, on one hand, and on IGF-1-binding proteins, proteases that degrade the IGF-1-binding protein complex, and GH and IGF-1 receptors, on the other hand [7].

Growth regulation is one of the main functions that GH and IGF-1 have in common. In addition, both in children and adults, GH plays an important role in metabolic regulation. IGF-1 is the main mediator of anabolic and mitogenic effects of GH in peripheral tissues and is a key factor in regulation of body weight. On the other hand, they have different effects on glucose and lipid metabolism: GH increases the blood glucose level and promotes lipolysis, while IGF-1 has the opposite effects [8, 9].

GROWTH HORMONE AND INSULIN-LIKE GROWTH FACTOR 1 IN LIVER DISEASES

IGF-1 synthesis by hepatocytes is impaired in liver disease leading to increased GH secretion. Despite high

Corresponding author: Rivada Kurabekova. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (499) 190-53-44. E-mail: transplant2009@mail.ru

serum GH levels in patients with chronic liver disease (CLD), low IGF-1 levels can also result from hepatocyte resistance to GH [10, 11]. It is supposed that metabolic disorders frequently found in patients with liver diseases – insulin resistance, malnutrition, osteopenia, etc. – are associated with impaired neurohumoral regulation caused by IGF-1 deficiency [12–14].

The degree of decrease in IGF-1 levels in patients with CLD correlates with the severity of hepatocyte dysfunction [15, 16]. Administration of recombinant IGF-1 leads to the arrest of liver fibrous degeneration [17, 18]. In an experiment on animals with nonalcoholic steatohepatitis (NASH), treatment with recombinant IGF-1 has been shown to improve liver function in cirrhosis. It was also found in the experiment that the degree of hepatic ischemia/reperfusion injury is less when IGF-1 levels are higher [19, 20]. Some experimental studies have suggested the possibility of using IGF-1 in clinical practice. It has been shown that recombinant IGF-1 in patients with cirrhosis increases serum albumin levels and improves energy metabolism [21].

GH levels are significantly higher in adult patients with cirrhosis than in healthy individuals. This is associated with impaired IGF-1 synthesis by the liver in the end stage of hepatobiliary diseases [9]. GH levels in recipients decrease to normal values in adults as early as on day 7 after LTx, while IGF-1 levels increase [12].

Our studies have shown that in young children with severe hepatobiliary diseases, as in adults, GH levels are elevated and IGF-1 is reduced, which is combined with stunted growth and weight retardation. The degree of increased GH levels in these children is not correlated with IGF-1 levels and anthropometric indices, but is associated with the Pediatric End-stage Liver Disease (PELD) score for liver disease severity and liver fibrosis severity. After LTx, GH and IGF-1 levels in children are comparable with the levels of these hormones in healthy children and significantly correlate with the growth of recipient children [22].

Previously, it was believed that IGF-1 does not directly affect hepatocyte function because in a healthy liver, a small number of IGF-1 receptors are expressed on the surface of hepatocytes. However, further studies have shown that in some liver diseases, there is increased expression of these receptors [4]. In acute viral hepatitis and chronic hepatitis B and C, expression of IGF-1 receptors on hepatocytes is higher than in a healthy liver. There is also increased IGF-1 levels, which is believed to accelerate regeneration of damaged hepatocytes [23].

The antifibrotic effect of IGF-1 is realized both directly through the GH/IGF-1 system and indirectly through regulation of other profibrogenic factors [24, 25]. Stellate cells play a key role in liver fibrosis. Their activation, caused by chronic trauma, oxidative stress, increased inflammatory cytokines and lipopolysaccharides, leads to their transformation into fibroblasts [26]. It has been shown that IGF-1 can inactivate hepatic stellate cells and induce their aging, thus limiting fibrosis [27]. The above results indicate that decreased IGF-1 production in the liver is not only the result of liver dysfunction, but also plays an important role in fibrosis.

It is known that life expectancy is closely related to the GH/IGF-1 system, which may be of some importance for the development of techniques for predicting recipient and graft survival [28, 29].

In an experiment, it was shown that IGF-1 can improve survival rates in rats with acute liver failure induced by D-galactosamine and lipopolysaccharide administration. Prophylactic administration of IGF-1 to animals prevented an increase in bilirubin levels and transaminase activity [18].

Clinical studies have established an association between GH and IGF-1 levels in adult LTx recipients with 3-month and 3-year survival [28]. Our studies also showed an association between GH levels and 6-month survival in pediatric liver recipients [30].

THE ROLE OF GH/IGF-1 IN REGULATION OF IMMUNE RESPONSE

The role of the GH/IGF-1 system in the regulation of immune response has been the topic of many studies in recent decades [6, 31]. It has been shown that mutual regulation of the neuroendocrine and immune systems is ensured by the presence of common ligands and receptors, as a result of which neuroendocrine hormones have immunoregulatory functions, and cytokines affect neuronal functions. In addition, cells of the immune system can synthesize and secrete neuroendocrine hormones such as adrenocorticotropin, GH, prolactin, thyrotropin and others, and a wide range of cytokines can be produced by microglia cells in the central nervous system [32].

Cells of the immune system contain GH receptors, which has a direct effect on all major immune cell types, thereby influencing the immune response. In turn, cytokines produced by cells of the immune system specifically affect GH secretion by the pituitary gland. It has been shown that interleukins (IL-2, IL-6, IL-11, IL-1) and ciliary neurotrophic factor stimulate GH secretion, whereas transforming growth factor beta (TGF-b) and tumor necrosis factor alpha (TNF-α) can inhibit its secretion [33].

GH is necessary for immune system development and maintenance of cell-mediated and humoral responses. It affects hematopoiesis by stimulating neutrophil differentiation, increases erythropoiesis and bone marrow cell proliferation, and enhances thymocyte proliferation and export [34]. GH stimulates the production of cytokines – IL-1, IL-2, IL-6, interferon-c, TGF-b, and TNF-α [35].

In addition, GH prevents lymphocyte apoptosis by increasing NO production, reducing the synthesis of caspases involved in apoptosis, and promoting tubulin

polymerization, which stabilizes the microtubule network [36]. Some experimental studies have shown that GH protects immune cells against the immunosuppressive effect of glucocorticoids. Injection of GH into rats after dexamethasone administration or surgical stress improved the immune response [31].

The effects of IGF-1 on the immune system are manifold and are associated with the regulation of cell proliferation, differentiation, and metabolism. It has been established that the functional activity of IGF-1 and IGF-1 receptors on T cells is enhanced during T cell activation, proliferation, chemotaxis, and apoptosis [37]. IGF-1 also stimulates natural killer (NK) activity [38]. On one hand, IGF-1 exhibits the properties of a nonspecific immunomodulator by stimulating lymphopoiesis, immunoglobulin synthesis, and T cell differentiation; on the other hand, it has a selective inhibitory effect on IL-2-dependent lymphocyte growth, and also causes proliferation of regulatory T cells, preventing autoimmune diseases in mice [5, 39].

The presence of the IGF-1 receptor and binding protein in myeloid cells suggests the influence of IGF-1 on hematopoiesis and inflammation. IGF-1 can act as a proinflammatory factor by stimulating proinflammatory cytokines and chemokines, such as TNF-a and IL-8, and can also have an anti-inflammatory effect by stimulating IL-10 secretion and inhibiting Th1-mediated cellular immune responses in activated T cells [6, 40].

IGF-1 can affect the pathogenesis of immune diseases by regulating the activity of immune cells through endocrine, paracrine, and autocrine mechanisms. Experimental and clinical studies have shown that IGF-1 reduces immune response in autoimmune diseases [5]. In autoimmune diseases such as Graves' disease, rheumatoid arthritis, some inflammatory bowel diseases, and type 1 diabetes, the IGF-1 levels are decreased, which is accompanied by immunosuppression [41]. Elevated IGF-1 levels occur in some cancer types in which tumor cells express the hormone and its receptors, thus increasing immunosuppression and tumor growth [42, 43].

Some effects of IGF-1 and tacrolimus have been found to be realized via common calcineurin-dependent cellular pathways [44, 45]. In experimental studies, it has been shown that intravenous and oral administration of tacrolimus in rats leads to increased IGF-1 levels and also enhances biliary excretion, which is regulated by both factors separately or together [46]. Our studies have shown that IGF-1 levels directly correlate with the tacrolimus dose administered in paediatric patients one year after LTx. This allows us to consider it as a potential biomarker of immunosuppression efficiency [47]. However, the mechanisms of this relationship are not clear and further research is needed to understand them.

CONCLUSION

GH and IGF-1 levels not only depend on liver function but also largely determine its condition and can be considered as indicators of liver function in patients with hepatobiliary diseases. Changes in these hormone levels after LTx can serve as an objective indicator of the degree of normalization of the synthetic function of graft and recovery of neurohumoral regulation in paediatric liver recipients.

Further study on interrelations between the GH/IGF-1 hormonal system and other factors influencing the liver graft function will allow to estimate more precisely the possibilities of using GH and IGF-1 both to verify graft condition and to improve therapy in pediatric liver transplant recipients.

The authors declare no conflict of interest.

REFERENCES

1. *Wu YL, Ye J, Zhang S, Zhong J, Xi RP*. Clinical significance of serum IGF-I, IGF-II and IGFBP-3 in liver cirrhosis. *World J Gastroenterol.* 2004; 10 (18): 2740–2743.
2. *Menshikov V.* Encyclopedia of clinical laboratory tests. M.: 1997; 960.
3. *Leung KC, Ho KK*. Measurement of growth hormone, insulin-like growth factor I and their binding proteins: the clinical aspects. *Clin Chim Acta.* 2001; 313 (1–2): 119–123.
4. *Takahashi Y*. The Role of Growth Hormone and Insulin-Like Growth Factor-I in the Liver. *Int J Mol Sci.* 2017; 18 (7): 1447. doi: 10.3390/ijms18071447.
5. *Bilbao D, Luciani L, Johannesson B, Piszczek A, Rosenthal N*. Insulin-like growth factor-1 stimulates regulatory T cells and suppresses autoimmune disease. *EMBO Mol Med.* 2014; 6 (11): 1423–1435. doi: 10.15252/emmm.201303376.
6. *Weigent DA*. Lymphocyte GH-axis hormones in immunity. *Cell Immunol.* 2013; 285 (1–2): 118–132. doi: 10.1016/j.cellimm.2013.10.003.
7. *Conover CA, Oxvig C*. PAPP-A: a promising therapeutic target for healthy longevity. *Aging Cell.* 2017; 16 (2): 205–209.
8. *Cignarelli A, Genchi VA, Le Grazie G, Caruso I, Marrano N, Biondi G et al*. Mini Review: Effect of GLP-1 Receptor Agonists and SGLT-2 Inhibitors on the Growth Hormone/IGF Axis. *Front Endocrinol.* 2022; 13 (846903). doi: 10.3389/fendo.2022.846903.
9. *De Palo EF, Bassanello M, Lancerin F, Spinella P, Gatti R, D'Amico D et al*. GH/IGF system, cirrhosis and liver transplantation. *Clin Chim Acta.* 2001; 310 (1): 31–37.
10. *Liu Z, Cordoba-Chacon J, Kineman RD, Cronstein BN, Muzumdar R, Gong Z et al*. Growth Hormone Control of Hepatic Lipid Metabolism. *Diabetes.* 2016; 65 (12): 3598–3609. doi: 10.2337/db16-0649.
11. *Cao LH, Lu FM, Lu XJ, Zhu LY*. Study on the relationship between insulin growth factor 1 and liver fibrosis in patients with chronic hepatitis C with type 2 diabetes

mellitus. *J Cell Biochem.* 2018; 119 (11): 9513–9518. doi: 10.1002/jcb.27267.
12. *Gariani K, Toso C, Philippe J, Orci LA*. Effects of liver transplantation on endocrine function: A systematic review. *Liver Int.* 2016; 10 (10): 13158. doi: 1111/liv.
13. *Chishima S, Kogiso T, Matsushita N, Hashimoto E, Tokushige K*. The Relationship between the Growth Hormone/Insulin-like Growth Factor System and the Histological Features of Nonalcoholic Fatty Liver Disease. *Intern Med.* 2017; 56 (5): 473–480. doi: 10.2169/internalmedicine.56.7626.
14. *Bonefeld K, Moller S*. Insulin-like growth factor-I and the liver. *Liver Int.* 2011; 31 (7): 911–919. doi: 10.1111/j.1478-3231.2010.02428.x.
15. *Castro GR, Coelho JC, Parolin MB, Matias JE, de Freitas AC*. Insulin-like growth factor I correlates with MELD and returns to normal level after liver transplantation. *Ann Transplant.* 2013; 18: 57–62. doi: 10.12659/AOT.883819.
16. *Dichtel LE, Cordoba-Chacon J, Kineman RD*. Growth hormone and insulin-like growth factor I regulation of nonalcoholic fatty liver disease. *J Clin Endocrinol Metab.* 2022; 16 (10). doi: 1210/clinem/dgac088.
17. *Sobrevals L, Rodriguez C, Romero-Trevejo JL, Gondi G, Monreal I, Paneda A et al*. Insulin-like growth factor I gene transfer to cirrhotic liver induces fibrolysis and reduces fibrogenesis leading to cirrhosis reversion in rats. *Hepatology.* 2010; 51 (3): 912–921. doi: 10.1002/hep.23412.
18. *de la Garza RG, Morales-Garza LA, Martin-Estal I, Castilla-Cortazar I*. Insulin-Like Growth Factor-1 Deficiency and Cirrhosis Establishment. *J Clin Med Res.* 2017; 9 (4): 233–247. doi: 10.14740/jocmr2761w.
19. *Kawai M, Harada N, Takeyama H, Okajima K*. Neutrophil elastase contributes to the development of ischemia/reperfusion-induced liver injury by decreasing the production of insulin-like growth factor-I in rats. *Transl Res.* 2010; 155 (6): 294–304. doi: 10.1016/j.trsl.2010.02.003.
20. *Meng F, Zhang Z, Chen C, Liu Y, Yuan D, Hei Z et al*. PI3K/AKT activation attenuates acute kidney injury following liver transplantation by inducing FoxO3a nuclear export and deacetylation. *Life Sci.* 2021; 272 (119119): 26. doi: 10.1016/j.lfs.2021.119119.
21. *Conchillo M, de Knegt RJ, Payeras M, Quiroga J, Sangro B, Herrero JI et al*. Insulin-like growth factor I (IGF-I) replacement therapy increases albumin concentration in liver cirrhosis: results of a pilot randomized controlled clinical trial. *J Hepatol.* 2005; 43 (4): 630–636. doi: 10.1016/j.jhep.2005.03.025.
22. *Shevchenko OP, Tsirulnikova OM, Tsirulnikova IE, Kurabekova RM, Olefirenko GA, Stepanova OI et al.* Dynamics of insulin-like growth factor-1 (IGF-1) in children after AB0-incompatible liver transplantation. *Vestnik transplantologii i iskusstvennykh organov*. 2014; XVI (2): 46–51.
23. *Stefano JT, Correa-Giannella ML, Ribeiro CM, Alves VA, Massarollo PC, Machado MC et al*. Increased hepatic expression of insulin-like growth factor-I receptor in chronic hepatitis C. *World J Gastroenterol.* 2006; 12 (24): 3821–3828.
24. *Nishizawa H, Iguchi G, Fukuoka H, Takahashi M, Suda K, Bando H et al*. IGF-I induces senescence of hepatic stellate cells and limits fibrosis in a p53-dependent manner. *Sci Rep.* 2016; 6 (34605). doi: 10.1038/srep34605.
25. *Choi JS, Park YJ, Kim SW*. Three-dimensional Differentiated Human Mesenchymal Stem Cells Exhibit Robust Antifibrotic Potential and Ameliorates Mouse Liver Fibrosis. *Cell Transplant.* 2021; 30 (963689720987525): 0963689720987525. doi: 10.1177/.
26. *Lee SJ, Kim KH, Park KK*. Mechanisms of fibrogenesis in liver cirrhosis: The molecular aspects of epithelial-mesenchymal transition. *World J Hepatol.* 2014; 6 (4): 207–216. doi: 10.4254/wjh.v6.i4.207.
27. *Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C et al*. Senescence of activated stellate cells limits liver fibrosis. *Cell.* 2008; 134 (4): 657–667. doi: 10.1016/j.cell.2008.06.049.
28. *Nicolini D, Mocchegiani F, Palmonella G, Coletta M, Brugia M, Montalti R et al*. Postoperative Insulin-Like Growth Factor 1 Levels Reflect the Graft's Function and Predict Survival after Liver Transplantation. *PLoS One.* 2015; 10 (7). doi: 10.1371/journal.pone.0133153.
29. *Abdel-Wahab R, Hassan MM, George B, Carmagnani Pestana R, Xiao L, Lacin S et al*. Impact of Integrating Insulin-Like Growth Factor 1 Levels into Model for End-Stage Liver Disease Score for Survival Prediction in Hepatocellular Carcinoma Patients. *Oncology.* 2020; 98 (12): 836–846. doi: 10.1159/000502482.
30. *Kurabekova RM, Tsirulnikova OM, Pashkova IE, Makarova LV, Mozheiko NP, Monakhov AR, Shevchenko OP.* Association of growth hormone and insulin-like growth factor 1 (IGF-1) levels with liver function and short-term survival in liver transplant recipient children. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2020; 30 (4): 44–51. doi: 10.22416/1382-4376-2020-30-4-44-51.
31. *Kelley KW, Weigent DA, Kooijman R*. Protein hormones and immunity. *Brain Behav Immun.* 2007; 21 (4): 384–392. doi: 10.1016/j.bbi.2006.11.010.
32. *Gong FY, Deng JY, Shi YF*. Stimulatory effect of interleukin-1beta on growth hormone gene expression and growth hormone release from rat GH3 cells. *Neuroendocrinology.* 2005; 81 (4): 217–228. doi: 10.1159/000087160.
33. *Derfalvi B, Szalai C, Mandi Y, Kiraly A, Falus A*. Growth hormone receptor gene expression on human lymphocytic and monocytic cell lines. *Cell Biol Int.* 1998; 22 (11–12): 849–853. doi: 10.1006/cbir.1998.0324.
34. *Dardenne M, Smaniotto S, de Mello-Coelho V, Villa-Verde DM, Savino W*. Growth hormone modulates migration of developing T cells. *Ann N Y Acad Sci.* 2009. doi: 10.1111/j.1749-6632.2008.03977.x.
35. *Farmer JT, Weigent DA*. TGF-beta1 expression in EL4 lymphoma cells overexpressing growth hormone. *Cell Immunol.* 2006; 240 (1): 22–30. doi: 10.1016/j.cellimm.2006.06.003.
36. *Wang K, Wang M, Gannon M, Holterman A*. Growth Hormone Mediates Its Protective Effect in Hepatic

Apoptosis through Hnf6. *PLoS One.* 2016; 11 (12). doi: 10.1371/journal.pone.0167085.

37. *Walsh PT, Smith LM, O'Connor R*. Insulin-like growth factor-1 activates Akt and Jun N-terminal kinases (JNKs) in promoting the survival of T lymphocytes. *Immunology.* 2002; 107 (4): 461–471.
38. *Clark R, Strasser J, McCabe S, Robbins K, Jardieu P*. Insulin-like growth factor-1 stimulation of lymphopoiesis. *J Clin Invest.* 1993; 92 (2): 540–548.
39. *Xu J, Wang X, Chen J, Chen S, Li Z, Liu H et al*. Embryonic stem cell-derived mesenchymal stem cells promote colon epithelial integrity and regeneration by elevating circulating IGF-1 in colitis mice. *Theranostics*. 2020; 10 (26): 12204–12222. doi: 10.7150/thno.47683.
40. *Keshvari S, Caruso M, Teakle N, Batoon L, Sehgal A, Patkar OL et al*. CSF1R-dependent macrophages control postnatal somatic growth and organ maturation. *PLoS Genet.* 2021; 17 (6). doi: 10.1371/journal.pgen.1009605.
41. *Dehghani SM, Karamifar H, Hamzavi SS, Haghighat M, Malek-Hosseini SA*. Serum insulinlike growth factor-1 and its binding protein-3 levels in children with cirrhosis waiting for a liver transplant. *Exp Clin Transplant.* 2012; 10 (3): 252–257.
42. *Samani AA, Yakar S, LeRoith D, Brodt P*. The role of the IGF system in cancer growth and metastasis: overview and recent insights. *Endocr Rev.* 2007; 28 (1): 20–47.
43. *Qiao C, Huang W, Chen J, Feng W, Zhang T, Wang Y et al*. IGF1-mediated HOXA13 overexpression promotes colorectal cancer metastasis through upregulating ACLY and IGF1R. *Cell Death Dis.* 2021; 12 (6): 021-03833. doi: 10.1038/s41419-2.
44. *González-Juanatey JR, Piñeiro R, Iglesias MJ, Gualillo O, Kelly PA, Diéguez C et al*. GH prevents apoptosis in cardiomyocytes cultured in vitro through a calcineurin-dependent mechanism. *J Endocrinol.* 2004; 180 (2): 325–335. doi: 10.1677/joe.0.1800325.
45. *Li SY, Fang CX, Aberle NS, 2nd, Ren BH, Ceylan-Isik AF, Ren J*. Inhibition of PI-3 kinase/Akt/mTOR, but not calcineurin signaling, reverses insulin-like growth factor I-induced protection against glucose toxicity in cardiomyocyte contractile function. *J Endocrinol.* 2005; 186 (3): 491–503. doi: 10.1677/joe.1.06168.
46. *Kawamura I, Takeshita S, Fushimi M, Mabuchi M, Seki J, Goto T*. Induction of choleresis by immunosuppressant FK506 through stimulation of insulin-like growth factor-I production in the liver of rats. *Eur J Pharmacol.* 2001; 419 (1): 99–105. doi: 10.1016/s0014-2999(01)00961-x.
47. *Kurabekova RM, Tsirulnikova OM, Gichkun OE, Olefirenko GA, Pashkova IE, Belchenkov AA et al.* Relationship between insulin-like growth factor 1 levels and tacrolimus dose in liver transplant recipient children. *Bulletin of Transplantology and Artificial Organs*. 2021; 23 (2): 13–20. doi: 10.15825/1995-1191-2021-2-13-20.

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