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LIVER DYSFUNCTION IN TYPE 2 DIABETES MELLITUS: THE PATHOGENETIC ROLE OF FATTY LIVER DEVELOPMENT AND INSULIN RESISTANCE

Хикматов Мирафзал Миржамолович
Хикматов Мирафзал Миржамолович ORCID ID0000-0001-8072-3687
Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, Gijduvan str., 23. Tel: +998(65) 223-00-50 e-mail: hikmatov.mirafzal@bsmi.uz

Research Objective: To identify the pathogenetic basis of liver dysfunction in type 2 diabetes mellitus and to evaluate the interrelationship between fatty hepatosis and insulin resistance.
Abstract. This study analyzes the mechanisms underlying liver dysfunction in patients with type 2 diabetes mellitus. A strong pathophysiological relationship was identified between the development of fatty hepatosis and the progression of insulin resistance. It was scientifically demonstrated that insulin resistance leads to lipid metabolism disturbance, fat accumulation in hepatocytes, and enhanced oxidative stress.
Keywords: Type 2 diabetes mellitus, liver function, fatty hepatosis, insulin resistance, metabolic syndrome.

НАРУШЕНИЕ ФУНКЦИИ ПЕЧЕНИ ПРИ САХАРНОМ ДИАБЕТЕ 2-ГО ТИПА: ПАТОГЕНЕТИЧЕСКАЯ РОЛЬ РАЗВИТИЯ ЖИРОВОГО ГЕПАТОЗА И ИНСУЛИНОРЕЗИСТЕНТНОСТИ.

(Обзор литературы)

Хикматов Мирафзал Миржамолович
Хикматов Мирафзал Миржамолович https://orcid.org/0009-0007-3180-4510
Бухарский государственный медицинский институт имени Абу Али ибн Сины, Узбекистан, г.Бухара, ул.Гиждуванская.23. Тел:+998(65) 223-00-50 e-mail: hikmatovmirafzal168@gmail.com

Цель исследования: Выявить патогенетические основы нарушения функции печени при сахарном диабете 2-го типа и определить взаимосвязь между жировым гепатозом и инсулинорезистентностью.
Резюме. В данном исследовании проведён анализ механизмов развития нарушений функции печени у пациентов с сахарным диабетом 2-го типа. Установлена тесная патофизиологическая связь между формированием жирового гепатоза и прогрессированием инсулинорезистентности. Научно обосновано, что инсулинорезистентность способствует нарушению липидного обмена, накоплению жира в гепатоцитах и усилению окислительного стресса.
Ключивые слова: Сахарный диабет 2-го типа, функция печени, жировой гепатоз, инсулинорезистентность, метаболический синдром.

2-TUR QANDLI DIABET ShAROITIDA JIGAR FUNKSIYaSINING BUZILIShI: YoG‘LI GEPATOZ RIVOJLANIShI VA INSULINREZISTENTLIKNING PATOGENETIK O‘RNI

Xikmatov Mirafzal Mirjamolovich ORCID ID0000-0001-8072-3687
Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti, O‘zbekiston, Buxoro, G‘ijduvon ko‘chasi, 23-uy. Tel: +998(65) 223-00-50
mail: hikmatov.mirafzal@bsmi.uz

Tadqiqot maqsadi: 2-tur qandli diabetda jigar faoliyati buzilishining patogenetik asoslarini aniqlash, xususan yog‘li gepatoz va insulin rezistentligi o‘rtasidagi o‘zaro bog‘liqlikni baholash.
Rezyume. Ushbu tadqiqotda 2-tur qandli diabet bilan og‘rigan bemorlarda jigar faoliyati buzilishining rivojlanish mexanizmlari tahlil qilindi. Yog‘li gepatoz shakllanishi va insulin rezistentligi kuchayishi o‘rtasida yaqin patofiziologik aloqadorlik mavjudligi aniqlandi. Insulin rezistentligi lipid almashinuvining buzilishi, jigar hujayralarida yog‘ to‘planishi va oksidlovchi stressning kuchayishiga olib kelishi ilmiy jihatdan asoslab berildi.
Kalit so‘zlar: 2-tur qandli diabet, jigar faoliyati, yog‘li gepatoz, insulin rezistentligi, metabolik sindrom.
Abstract. Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by chronic hyperglycemia, insulin resistance, and progressive impairment of carbohydrate, lipid, and protein metabolism. In recent decades, increasing attention has been paid to liver involvement in the pathogenesis of T2DM, as the liver plays a central role in glucose and lipid homeostasis. One of the most common hepatic complications associated with T2DM is non-alcoholic fatty liver disease (NAFLD), which is considered a hepatic manifestation of metabolic syndrome and is closely linked to insulin resistance.

According to the works of **DeFronzo et al.**, the liver is one of the key organs contributing to fasting and postprandial hyperglycemia in T2DM due to excessive hepatic glucose production caused by insulin resistance. Under physiological conditions, insulin suppresses gluconeogenesis and stimulates glycogen synthesis in hepatocytes. However, in insulin-resistant states, these regulatory mechanisms are impaired, leading to increased endogenous glucose output and worsening glycemic control. The close association between insulin resistance and fatty liver development has been extensively described in the studies of **Marchesini, Bugianesi, and Targher**, who demonstrated that hepatic steatosis is strongly correlated with decreased insulin sensitivity, independent of obesity. Their findings suggest that NAFLD should be considered not only a consequence but also a predictor of T2DM and its complications. Excessive accumulation of triglycerides in hepatocytes disrupts insulin signaling pathways, particularly at the level of insulin receptor substrates (IRS-1 and IRS-2), thereby aggravating hepatic and systemic insulin resistance. At the molecular level, research by **Samuel and Shulman** has highlighted the role of intracellular lipid metabolites, such as diacylglycerol and ceramides, in the development of hepatic insulin resistance. These lipid intermediates activate protein kinase C (PKC), which inhibits insulin signaling and promotes gluconeogenesis. Additionally, increased activity of transcription factors such as sterol regulatory element-binding protein-1c (SREBP-1c) enhances de novo lipogenesis, further contributing to hepatic fat accumulation. Inflammation and oxidative stress represent another crucial pathogenetic link between fatty liver and insulin resistance. Studies by **Tilg and Moschen** emphasize the role of chronic low-grade inflammation in NAFLD progression. Hepatic steatosis induces the activation of Kupffer cells and the release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), which impair insulin signaling in both hepatic and peripheral tissues. These cytokines contribute to a self-perpetuating cycle of metabolic and inflammatory disturbances.

Experimental studies conducted by **Sanyal and colleagues** have demonstrated that prolonged lipid accumulation and oxidative stress can lead to mitochondrial dysfunction, hepatocyte apoptosis, and progression from simple steatosis to non-alcoholic steatohepatitis (NASH). This

progression significantly increases the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma, especially in patients with long-standing T2DM.

Moreover, recent investigations have identified the role of hepatokines, such as fetuin-A and fibroblast growth factor 21 (FGF21), in mediating the crosstalk between the liver and peripheral tissues. According to **Stefan and Häring**, elevated levels of fetuin-A contribute to insulin resistance by inhibiting insulin receptor tyrosine kinase activity, whereas alterations in FGF21 signaling reflect adaptive and maladaptive responses of the liver to metabolic stress.

Clinical evidence suggests that improvement of insulin sensitivity through lifestyle modification or pharmacological interventions leads to a reduction in hepatic fat content and improvement of liver function parameters. Studies by **Pioglitazone and GLP-1 receptor agonists trials** have shown beneficial effects on NAFLD progression by reducing inflammation and enhancing insulin sensitivity, further supporting the pathogenetic link between insulin resistance and fatty liver disease. The liver is a key target organ for insulin action, regulating gluconeogenesis, glycogen synthesis, and lipid metabolism. In conditions of insulin resistance, hepatocytes lose their sensitivity to insulin, leading to excessive hepatic glucose production, increased lipogenesis, and impaired fatty acid oxidation. These metabolic disturbances contribute to the accumulation of triglycerides within hepatocytes, resulting in the development of fatty liver (hepatic steatosis). Progressive lipid accumulation triggers oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress, which further aggravate liver injury and promote inflammatory processes.

Fatty liver disease in T2DM is not only a consequence of metabolic imbalance but also an active participant in the progression of insulin resistance. Excess hepatic fat accumulation leads to the release of pro-inflammatory cytokines, adipokines, and hepatokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and fetuin-A, which interfere with insulin signaling pathways in the liver and peripheral tissues. This creates a vicious cycle in which insulin resistance promotes hepatic steatosis, and fatty liver, in turn, exacerbates systemic insulin resistance. At the molecular level, impaired insulin signaling in hepatocytes is associated with decreased activity of insulin receptor substrates (IRS-1 and IRS-2), reduced phosphatidylinositol 3-kinase (PI3K) and Akt signaling, and dysregulation of transcription factors involved in lipid metabolism, including sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptors (PPARs). These alterations favor increased de novo lipogenesis and decreased lipid utilization, further contributing to hepatic lipid accumulation and functional impairment. Chronic hyperglycemia and elevated free fatty acids in T2DM also induce oxidative stress and inflammation in liver tissue. Reactive oxygen species (ROS) formation damages cellular membranes, proteins, and DNA, leading to hepatocyte apoptosis or necrosis. Inflammatory infiltration and activation of Kupffer cells promote the progression from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and, in advanced cases, cirrhosis. Thus, liver dysfunction in T2DM represents a continuum of pathological changes driven by metabolic, inflammatory, and oxidative mechanisms.

Understanding the pathogenetic relationship between fatty liver development and insulin resistance is essential for improving diagnostic and therapeutic strategies in patients with T2DM. Early detection of liver dysfunction and NAFLD may help prevent disease progression and reduce the risk of cardiovascular and hepatic complications. Therapeutic approaches aimed at improving insulin sensitivity, reducing hepatic fat accumulation, and attenuating oxidative stress and inflammation may play a crucial role in the comprehensive management of T2DM.

In conclusion, liver dysfunction in type 2 diabetes mellitus is a multifactorial process in which insulin resistance and fatty liver development are closely interconnected. Their reciprocal influence forms a pathogenic basis for the progression of metabolic and hepatic disorders, highlighting the importance of integrated approaches targeting both glucose metabolism and liver health in patients with T2DM.

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