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THE SIGNIFICANCE OF CLINICAL-LABORATORY AND MOLECULAR-GENETIC MARKERS IN THE DIAGNOSIS OF NON-ALCOHOLIC FATTY LIVER DISEASE

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INTRODUCTION

Today, non-alcoholic fatty liver disease (NAFLD) is one of the urgent problems of medicine in the field of hepatology. Indeed, In modern hepatology, NASH is the most common diffuse liver disease after the age of 40. The urgency of NASH, progressive growth, and widespread prevalence (20-45%), It is observed among the working-age population, is characterized by the ineffectiveness of specific treatment due to the nonspecificity of clinical signs in the initial stage, and the appearance of pronounced clinical signs in the late stages of the disease. NASH progresses to inflammatory changes, necrosis and fibrosis, cirrhosis and hepatocellular carcinoma. Its form, which is not prone to the noted developments - hepatic steatosis, occurs in 40-78% of patients. It is noteworthy that "... With a chronic course of the disease, 12-40% of patients develop nonalcoholic steatohepatitis after 8-13 years, 15% of them develop cirrhosis of the liver and liver failure, 7% develop cirrhosis of the liver, and after 10 years, hepatocellular carcinoma ..." .[1]

The results of research conducted in the world over the past decade have shown that genetic factors play a significant role in the progressive development of NAFLD. Today, a number of scientific studies are being conducted in the world to study its genetic basis, improve early diagnosis of the disease and prevent its complications through the improvement of treatment methods. Scientific studies and analysis of the studied literature show that genetic testing is necessary for accurate diagnosis of the development and course of NAFLD. One of the candidate genes for the accumulation of lipid fractions in the liver tissues in this disease, the development of more dangerous, aggressive forms of the disease, is GCKR and its polymorphism E P446L (rs1260326) and MBOAT7 (rs641738). Therefore, conducting research aimed at identifying these genes and their polymorphisms, alleles, and genotypes, the accumulation of lipid fractions in the liver, and the origin

[1] Tacuma, Y. Nonalcoholic steatohepatitis associated hepatocellular carcinoma: our case series and literature review / Y. Tacuma, K. Nouso / Wld. J. Gastroenterol. – 2010. – No. 16(12). - R. 1436-1441.

and genetic correlation of dangerous forms of NAFLD is one of the urgent problems of hepatology.

Targeted measures are being taken in Uzbekistan to develop the medical sector to world standards and improve the quality of high-quality medical services to the population. [2]The following tasks have been set: "...Prevention, early diagnosis, treatment and control of non-communicable diseases and their risk factors, prevention of premature mortality and morbidity of the population...". The implementation of these tasks will allow for the prevention and diagnosis of various diseases, improving the quality of medical services, diagnosing diseases of the liver and biliary tract, reducing the level of various somatic diseases among the population, and increasing life expectancy. Taking into account the above, early diagnosis of diseases in institutions providing primary medical and sanitary assistance to the population, alternating treatment will lead to a decrease in complications from NCDs.

This research work To a certain extent, it serves to implement the tasks set out in the Decree of the President of the Republic of Uzbekistan No. PF-60 dated January 28, 2022 “On the Development Strategy of the New Uzbekistan for 2022-2026”, Resolutions No. PP-5130 dated May 27, 2021 and No. PP-215 dated April 25, 2022 “On additional measures to bring primary medical and sanitary assistance closer to the population and increase the efficiency of medical services”, as well as other regulatory and legal documents related to this activity.

[2] Decrees of the President of the Republic of Uzbekistan No. PF-5590 dated December 7, 2018 "On comprehensive measures to radically improve the healthcare system of the Republic of Uzbekistan", Resolutions No. PP-4063 dated December 18, 2018 "On measures to prevent non-communicable diseases, support a healthy lifestyle and increase the level of physical activity of the population"

CHAPTER I. LITERATURE REVIEW. CLINICAL-LABORATORY AND MOLECULAR-GENETIC MARKERS OF THE DEVELOPMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

§ 1.1. Non-alcoholic fatty liver disease epidemiology

Nonalcoholic fatty liver disease (NAFLD) is a chronic disease characterized by the accumulation of fat in liver cells, independent of alcohol consumption, and is an important gastrointestinal disease [3 , 48, 54, 82, 150, 253].

NAFLD is a chronic multifactorial progressive liver disease complicated by steatosis (fat accumulation in the liver, fatty degeneration of hepatocytes), steatohepatitis (inflammatory infiltrate formation in liver cells around the focus of necrosis), nonalcoholic fibrosis (cirrhosis, liver architecture deterioration, and connective tissue growth), and is a group of diseases that has been the main focus of attention of domestic and foreign hepatologists in recent years [48,52,254]. With a chronic course of the disease, 12–40% of patients progress to nonalcoholic steatohepatitis after 8–13 years, 15% develop cirrhosis and liver failure, and 7% develop cirrhosis with an increased risk of hepatocellular carcinoma after 10 years [35,54,274]. The results of studies conducted over the past decade confirm the increase in the number of patients with NAFLD [1,257]. The prevalence of NAFLD in the general population has not been studied, but some authors who have conducted studies on this topic have found that the disease occurs in Italy and the USA in 3–58% [34,48, 258]. In 2007, 30 thousand outpatients were examined in the Russian Federation under the leadership of V.T. Ivashkin of the Russian Academy of Medical Sciences, and NAFLD was noted in 27% of them. Of these, 80.3% were diagnosed with non-alcoholic steatosis, 16.8% with steatohepatitis, and 2.9% with liver cirrhosis [52, 53, 54].

The increasing incidence of NAFLD is explained by the tendency of the population to be obese [9, 58, 71] . However, as the degree of obesity increases, the severity of the disease also increases [58] . NAFLD occurs in 30–100% of

people with excess body weight. In this case, fatty liver disease is detected by ultrasound examination of the patient [18, 19, 21, 26] . Also, according to data from scientific studies, NAFLD is detected in 70% of patients with type 2 diabetes [54, 76, 273].

Thus, the epidemiology of non-alcoholic fatty liver disease is considered one of the urgent problems of clinical medicine due to the fact that the progressive growth and spread of the disease is observed when the population is still functional, and obvious clinical signs are detected in the late stages of the disease.

1.1.1. Liver non-alcoholic oil of the disease danger factors and pathogenesis

Hepatic steatosis is usually polyetiological in origin, with primary steatosis occurring mainly on the basis of obesity, hyperlipidemia, and type II diabetes mellitus [75 , 77, 79, 85] . The development of secondary fatty hepatosis is caused by taking a certain group of drugs (steroid hormones, hormone replacement therapy, antiarrhythmic and antibacterial drugs, cytostatics, nonsteroidal anti-inflammatory drugs), chronic inflammatory diseases of the gastrointestinal system, a sudden sharp decrease in body mass, parenteral nutrition, pregnancy, hypoxia-causing diseases, Wilson Konovalova disease, abetalipoproteinemia, familial hepatic steatosis, glycogen accumulation, can cause galactosemia [22,36, 37, 39, 45, 52, 73, 75, 106]. Based on the entry of free fatty acids (FFAs) into the liver, triglycerides accumulate in the liver, the rate of β oxidation of FFAs in liver mitochondria decreases, and the synthesis of fatty acids increases. As a result, the synthesis of very low-density lipoproteins decreases and triglycerides are excreted from the liver [20,104, 109].

Accumulation of triglycerides in the liver is formed as a result of obesity and insulin resistance according to the "double hit" theory. Insulin resistance can develop as a result of mutation of genes related to β-oxidation of free fatty acids, O'NO-α activation of tumor cell necrosis. O'NO-α type 1 phosphorylated insulin receptors decrease insulin receptor sensitivity and glucose transport. Insulin resistance is formed on the basis of compensatory hyperinsulinemia, which, in turn, increases lipogenesis and gluconeogenesis in the liver, decreases lipolysis, and accumulates

fat in cells. Due to increased lipolysis, free fatty acids are released from visceral fat. An increase in EIOK decreases the binding of insulin receptors in hepatocytes, insulin resistance is formed in the liver. Fatty dystrophy can lead to impaired carbohydrate metabolism, subsequent glucose tolerance, and the development of type 2 diabetes [34,37, 111]. Insulin-resistant glucose is the main energy source. Activation of lipolysis and the formation of large amounts of EGF have a toxic effect, leading to changes in metabolism in 32-40 organs and tissues. Compensatory insulin secretion increases in pancreatic β cells. Glucose tolerance develops and diabetes mellitus occurs. At this time, a large amount of atherogenic very low density lipoproteins are produced [7, 37,127] . The liver, as a target organ, develops steatosis as a result of the release of fat reserves in obesity (3, 54, 107). Numerous studies have shown that insulin resistance and dyslipidemia are more pronounced in young men than in women [37,127]. The “first blow” in the formation of steatosis is the accumulation of EFA in hepatocytes, inhibition of their oxidation and inhibition of triglyceride elimination. In response to the oxidant stress molecule (aldehyde), various degrees of inflammation and fibrinogenesis are observed. Oxidative stress products induce the expression of matrix-associated genes. Oxidative stress, associated with the immune response, triggers fibrinogenesis. As a result of the accumulation of lipids and EFA in hepatocytes, functional insufficiency in mitochondria increases and steatosis is formed. The progressive development of steatosis creates the basis for steatohepatitis. Additional oxidative stress, peroxidized lipids lead to disruption of the cell defense mechanism, inflammation and necrosis. The main enzyme of the enzyme is cytochrome P450 (CYP) 2E1. CYP2E1 promotes the formation of free radicals from endogenous ketones, dietary nitrosamines, and aldehydes. Ketones and fatty acids may be cytochrome mediators [108,136,259].

Inflammatory processes can lead to the development of endotoxinemia in intestinal dysbiosis. Lipopolysaccharide, gram-negative bacteria enter the portal vein, activate type 4 immune responses, Toll-like receptors, and inflammation and fibrosis develop [109,110,111,113,114, 222] . In NSCLC, endotoxemia increases

the expression of pro-inflammatory cytokines (IL-α), interleukin-6, and 8, and the receptors for these cytokines [61,107,108,109,110,111,126,133,260].

Recent studies have shown that adipose tissue, specifically visceral fat, changes the endocrine composition, produces adipokine hormones, which affect lipid metabolism and the function of other organs and systems [59,82, 84] . Leptin, adiponectin, and resistin are adipokines. In steatosis, local obesity reduces the amount of adipokines, adiponectin, and increases leptin. Changes in the amount of adipokines increase tissue infiltration of monocytes and macrophages, and induce cytokines that lead to inflammation. Long-term steatosis and local inflammation can cause fibrosis and subsequent tumor formation. Over time, NAFLD leads to cirrhosis and hepatocellular carcinoma, which increases the risk of liver resection and transplantation [42,47,48,49,221]. In obesity, the high concentration of leptin in the blood stimulates the secretion of other neuropeptides - melanocyte-stimulating hormone, propiomelanocorcin, neuropeptide, corticotropin, corticotropin-releasing factor. All of the above -mentioned peptides cause dysfunction of the sympathetic nervous system, activate lipolysis in fat reserves, and accelerate the entry of EOK into the liver. EYoK stimulates glycogenesis in the liver, inhibits insulin secretion, develops insulin resistance. On the basis of hyperleptinemia, hyperglycemia, metabolic syndrome (MS) determined against the background of visceral obesity, patients often develop persistent hypertension, severe UIK, obstructive apnea syndrome [1,2,8, 26,32,34]. The literature highlights the high mortality rate and prevalence of cardiovascular disease in MS [26,31,34,101,102]. Gastrointestinal changes in metabolic syndrome have been poorly studied.

The diagnostic parameters of MS were approved at the 2005 Congress of Diabetologists (Berlin). According to it, abdominal obesity is the main diagnostic criterion for MS, and the following are considered: waist circumference in men - less than 94 cm, in women - 80 cm; high-density lipoproteins in men - more than 0.9 mmol/l, in women - more than 1.1 mmol/l; fasting blood glucose level in the blood serum - 5.6 mmol/l.

Currently, the following are considered typical criteria for MS:

– insulin resistance with relative hyperinsulinemia;

– violation of carbohydrate metabolism (violation of carbohydrate tolerance, insulin-dependent diabetes);

- abdominal visceral obesity;

- arterial hypertension;

- atherogenic dyslipidemia (decreased apoprotein V);

- microproteinuria;

- reduction of fibrinolytic activity of blood serum;

– decreased factor VII in blood serum;

– hyperuricemia and/or gout;

- night obstructive apnea;

– ovarian polycystosis;

– SIN.

In 2001, experts from the US National Institutes of Health introduced the MS criteria in the ICD. In recent years, a distinction has been made between typical MS and incomplete MS (when 2–3 of the above criteria are observed) [8, 26, 31, 34, 182].

Exogenous and endogenous mechanisms play an important role in the development of fatty liver. The result of the absorption of exogenous fatty acids in the intestines - glycerol, glucose, galactose, fructose, is an increase in peripheral lipolysis, a decrease in the consumption of fatty acids by liver cells, an increase in the synthesis of fats, protein deficiency in liver cells, a decrease in the activity of liver enzymes, an increase in the synthesis of very low density lipoproteins and their excretion by hepatocytes [65,78,109,115,116,224,241] . Dyslipoproteinemia (DLP) is characterized by a change in the homeostatic constant, a violation of the functioning of the systems. V.S. Savelyev combined dyslipoproteinemia with lipid distress syndrome (LDS) [46,109] . LDS can injure several target organs: brain, brain, lower limbs, circulatory disorders in the digestive system, pancreatic and liver steatosis, gallbladder cholesterol [12,13,16,44, 56, 58, 69, 80,82, 85,87,93,226,242].

As a target organ, LDS can damage the liver and form atherosclerosis in parallel vessels.

Some researchers emphasize that in dyslipidemia, as a result of damage to the hepatocyte membrane, there are disturbances in the process of bile formation and secretion. Other authors emphasize the need to eliminate the etiological factor of "safe condition" of DLP in liver steatosis [20,22,23,24]. These considerations are complicated, because in liver steatosis, mitochondria and lysosomes of liver cells are damaged, erythrocytes are not consumed, cholestasis and hyperlipidemia can develop.

In NAFLD, liver cell function is impaired, a large amount of cholesterol and a small amount of phospholipids and bile acids accumulate in the bile ducts, bile becomes lithogenic, and gallstone disease develops [14,29, 31,50,51,58], resulting in secondary metabolism disorders [50,228,229]. NAFLD is 5 times more common in patients than in the general population. Gallstones are observed in 18.2% and 31.1% of patients with nonalcoholic steatosis and steatohepatitis, respectively. In this case, cholelithiasis of the liver is detected in 41.7% of patients [29,57].

In recent decades, research has focused on the effects of endocrine and gastrointestinal hormones on the functioning of the digestive system. The relationship between hormonal homeostasis and digestive diseases is of great importance. Currently, hormonal control of bile production and secretion is being studied. Scientific research is being conducted on the functional activity of the adrenal cortex and the relationship of cortisol to the pathological process. Hyperinsulinemia is a key link in the development of IR - GI - obesity - IR. Today, an increase in reserves in adipose tissue due to high-calorie nutrition increases insulin sensitivity. Lack of physical activity leads to insulin resistance in adipose tissue, and hyperinsulinemia is formed as a result of a decrease in tissue sensitivity to insulin [10,33, 49, 51,52].

In hyperinsulinemia, first, carbohydrate metabolism is disturbed. In IR, the compensatory GI of the pancreas increases to a certain limit, then in the state of decompensation, glucose tolerance or non-insulin-dependent type II diabetes

(NIDID) develops. Secondly, as a result of intense lipolysis in fat reserves, tissues are supplied with energy in the form of fatty acids, and lipoproteins are formed in the liver. As a result of increased glucose and insulin levels in the liver, triglycerides are formed in greater quantities than glucose, and the amount of LDL increases, and the amount of HDL decreases. An increase in the amount of insulin in the liver also increases the amount of HDL. The elimination of HDL depends on the amount of insulin. IR develops resistance to lipoprotein lipase and the elimination of HDL decreases. Increased formation of HDL and decreased elimination of HDL lead to an increase in the amount of triglycerides (HDL) in the blood plasma [72,82,84,209,210]. The decrease in the amount of ZULP is associated with the breakdown of ZULP, which is precisely what causes hyperinsulinemia. Thus, an increase in the amount of IR and insulin is characterized by dyslipidemia, that is, a decrease in the amount of ZULP in the blood plasma and an increase in the amount of ZULP. The developing dyslipoproteinemia has an atherogenic nature. Thirdly, IR and compensatory GI increase sodium reabsorption in the distal tubules of the kidneys and circulating blood volume, water retention, as a result of which arterial hypertension is formed. GI also increases the activity of the compensatory sympathetic nervous system. Fourthly, the fibrinolytic activity of the blood changes, as a result of GI, the amount of fat in the reserve increases, synthesis in the fat reserve increases, plasminogen activity is inhibited, fibrinolysis decreases, and cell aggregation increases. The above factors are a hallmark of the metabolic syndrome, which is currently characterized by metabolic alterations. In the scientific literature, insulin resistance is considered one of the risk factors for NAFLD [63,103,125,127,131,132,133,134, 233].

The role of thyroid hormones in protein and lipid exchange has been widely studied in the literature. Acceleration of protein synthesis and reduction of degradation, increase in the amount of methionine, cysteine was determined after introduction of thyroxine hormone. Triiodothyronine stimulates lysosomal autophagy and accelerates protein metabolism. The participation of triiodothyronine in glycogen synthesis in the liver is shown in scientific literature. Thyroid hormones

are involved in fat metabolism. After thyroidectomy, the amount of phosphatidylethanolamine, phosphatidylinositol, and cholesterol in the liver increases, while the amount of phosphatidylcholine decreases. In scientific studies, it has been confirmed that the increase in the amount of thyroid hormones increases the increase in bile secretion, and the formation of cholestasis when the amount decreases. On the other hand, cholelithiasis has been observed to develop more frequently in patients with thyrotoxicosis [73,100,108].

The effect of gastrin on trophic, motility and secretion of the gastrointestinal tract has been widely studied. Gastrin also improves liver cell metabolism and blood circulation. Some authors associate the increase in gastrin levels in chronic hepatitis with hypochlorhydria of gastric juice. Pentagastrin improves motor-evacuator function by reducing the level of cAMP and acting on receptors of the gallbladder muscles. Gastrin chloride enhances the production of secretin, bile formation and secretion by increasing the production of acid and pepsin [52].

The scientific literature confirms that the hormones cholecystokinin (CCK-P3) and gastrin play an important role in the digestive process. Some researchers believe that cholecystokinin is important in improving the contractile function of the gallbladder. CCK-P3 hormones belong to the peptide structural family and act in one direction. Some authors have found a decrease in the amount of gastrin, CCK-P3 and secretin in asymptomatic cholelithiasis and duodenal ulcer disease accompanied by gallbladder hypomotility [31,38, 50,51,58, 74, 75, 86, 92, 94, 96,137].

XK-P3 stimulates the production of bile, increases the concentration of bicarbonate and chlorides. XK-P3 increases the contraction volume of the gallbladder by 30–80% and simultaneously relaxes the sphincter of Oddi. Numerous studies have scientifically proven the importance of cholecystokinin and prostaglandin in biliary tract dysfunction.

Thus, based on the analysis of scientific data obtained as a result of various studies in recent years, it can be said that changes in the hormonal balance of insulin

and cortisol play an important role in the development of NAFLD and cause various liver diseases.

§ 1.2. Oily hepatosis clinical and diagnostic features of the disease

In most cases (48–100%) of cases, NAFLD is asymptomatic. The main clinical symptoms that can be detected include nausea, dull pain under the right rib, dyspepsia, and hepatomegaly. However, NAFLD is often detected incidentally during examination in patients presenting with cardiovascular, digestive, endocrine, and tumor diseases, or other liver diseases [76,90, 93,117, 119:, 127,132,265].

As mentioned above, GD is a polyetiological disease. Therefore, the clinical manifestations may vary depending on the main inducing factor or the presence of the disease. For example, secondary GD resulting from polycystic ovary syndrome (PCOS), hypothyroidism, hypogonadism, and somatotropin deficiency may have similar clinical features [73,100].

The prevalence of NAFLD is almost equal in women and men. The disease is most common in people over 40–50 years of age, but it can also occur in children and adolescents. Also, as mentioned above, NAFLD is often associated with pathological conditions such as arterial hypertension, abdominal obesity, metabolic syndrome, and insulin resistance [77,106,140].

Biochemical analysis of blood may reveal hyperlipidemia, hyperglycemia, hyperinsulinemia, urobilinogenuria, hypertriglyceremia, and signs of insulin resistance, depending on the degree of the disease . ALT activity may be significantly increased by 1.5–2 times the normal range. Obesity, hyperlipidemia in type II diabetes, thymol test, and increased α 2 and gamma globulin levels are observed [70,95,128,129,130].

Alcohol anamnesis is denied in NAFLD. Transferrin, most often, sialic acid and mitochondrial isoenzyme AST are sensitive and specific, but is rarely used. Because a complete history is an important diagnostic tool in general practice, the use of the AST/ALT ratio may nevertheless have prognostic significance in NAFLD. This is because an AST/ALT ratio greater than 1 in NAFLD often indicates the

development of cirrhosis [30,52, 68,70, 141, 237]. Plasma concentrations of the gamma-glutamyl transpeptidase enzyme may be increased in NAFLD patients, but this change is not absolute. That is, AST, ALT, and GGTP enzymes may sometimes remain unchanged even in the most advanced stage of NAFLD. This is due to the fact that as a result of fatty degeneration-induced alterations in hepatocytes, apoptosis is more often observed in them and lysis of hepatocytes is relatively less observed, which leads to an increase in the concentration of AST, ALT, GGTP and other enzymes [52,66, 68, 70,95,121, 141,142,148, 151] . An increase in plasma ferritin concentration may indicate nonalcoholic steatosis and steatohepatitis, but it is extremely difficult to differentiate nonalcoholic steatosis from nonalcoholic steatohepatitis using other biochemical indicators. Also, although instrumental diagnostic methods such as ultrasound, CT, and MRI can accurately analyze fatty infiltration and the area of liver damage with high probability, it is impossible to distinguish the stages of steatosis and steatohepatitis [2, 5, 30, 43,97, 105,143,146,243,244,266] .

The UTT method helps to identify pathologies of the hepatobiliary system. When examining the liver with the help of UTT, it is possible to diagnose fatty dystrophy, with a sensitivity of 85% and a specificity of 94%. Sonography allows you to detect the following signs in hepatic steatosis : hepatomegaly, lower edge of the liver, homogeneous structure, increased echogenicity, decreased sound conductivity, and smoothing of the vascular image. It is difficult to assess the intensity and spread of the pathological process with the interpretation of subjective data analysis.

A new non-invasive method that provides fairly accurate information about liver fibrosis is ultrasound elastography, which was first reported 20 years ago. This method is currently widely used in MRI in radiological diagnostics. According to the data of a large number of literature studies, ultrasound elastography can provide accurate information about diffuse and focal pathologies in the liver [5,27, 30,335,143, 146] . In elastography, by studying the properties of the tissue, the transmitted waves allow us to identify diagnostic changes in the early stages of the

disease. In it, the transmitted waves, unlike conventional ultrasound, allow us to assess the elastic properties of the tissue. In point elastography, information about the damaged area can be obtained using transmitted waves. Point elastography is named after the company that produces the curved waves: ARFI - elastography (Siemens-Germany) or ElastPQ (Philips, Netherlands). However, this does not prevent the comparison of high-level data between healthy patients and chronic liver diseases (chronic hepatitis, cirrhosis) [5,30,60, 97,98,105] . However, to date, histological examination is the most effective method for diagnosing NAFLD, along with the stage of NAFLD. It is known that, based on histological characteristics, NAFLD stages are divided into five: steatosis, steatohepatitis (a stage with combined necrosis and inflammation), ballooning dystrophy stage, Mallory-Denk hyalinosis stage, and fibrosis. In particular, the histological appearance of nonalcoholic steatosis is often macrovesicular (gallbladder of large and small fat droplets), with the lipid vacuole displacing the hepatocyte nucleus and occupying almost the entire cell, resembling a lipocyte [35,62,81] . In medium-vesicular steatosis, the hepatocyte cell consists of a large number of small fatty vesicles. In steatosis, hepatocytes in the pericentral part are mainly affected, but depending on the degree of the disease, fatty degeneration can also be detected throughout the acinus [5,6,30,97,105,143,146, 267] .

On the other hand, in contrast to nonalcoholic steatosis, the prognosis of nonalcoholic steatohepatitis and the later stages of NASH is poor and may lead to death due to liver failure [3,41,192,194,195] . In the steatohepatitis stage, hepatocyte damage is severe, and hepatocyte necrosis and apoptosis are observed against the background of the inflammatory process. In addition to the histological features observed in steatosis, the detection of lobular inflammation and liver cell radiation or ballooning dystrophy is one of the most important differential diagnostic features for steatohepatitis [149] .

It is known that lobular inflammation consists of several foci formed by small immune cells, the main part of which is lymphocytes and macrophages. Neutrophil

proliferation and aggregation may be reduced in the presence of Mallory-Denk bodies (eosinophilic inclusions detected in hepatocytes) [61,78, 91,38,163] .

Histological examination is also very effective in grading steatosis and steatohepatitis. In particular, nonalcoholic steatosis is graded according to a four-point grading system (S0 to S3). In a normal liver, the number of hepatocytes with fat droplets in the field of view does not exceed 5% (S0 according to the grading system). The detection of hepatocytes with fat droplets in the amount of 5–33% of the total number of hepatocytes in several fields of view is S1; up to 66% is S2; and the detection of changes in more than 66% corresponds to S3 according to the grading system [35, 62,81,143] . On the other hand, the histological grading of nonalcoholic steatohepatitis is relatively complex and requires taking into account several factors. In particular, the above- mentioned grading system (S0–S3) is used to classify steatosis, and in addition, the activity (A0–A3) and the degree of fibrosis (F0–F3) are taken into account. The activity index is used to assess the degree of inflammation in the tissue and is the sum of the degrees of lobular inflammation (0–2) and ballooning dystrophy of hepatocytes (0–2). Also, the degree of fibrosis of the liver tissue (F0–F3) is taken into account, and in stage 1 - fibrosis is limited to the perivenular and perisinusoidal parts of the acinus itself; in stage 2 - the portal and central parts of the acinus are fibrosed; in stage 3 - developed and interconnected foci of fibrosis are detected; In the 4th stage - cirrhosis is detected [143,213,240,262] .

§ 1.3. The role of pro-inflammatory and anti-inflammatory cytokines in the development of non-alcoholic fatty liver disease

Cytokines are low molecular weight, ion-structured proteins, molecules that are secreted by various cells and play an important role in normal and pathological processes occurring in cells, in particular, in pathological processes such as normal

growth and differentiation, migration, apoptosis of cells, in particular, in inflammation, regeneration and repair, carcinogenesis, obesity, hemostasis [78,91,138,163, 196, 197] .

Cytokines are secreted by various immune and non-immune cells and are divided into groups according to the producing cell, effector cell and biological effect: lymphokines, monokines, chemokines, interleukins, interferons, colony stimulating factor and growth factors. All the mentioned factors cause various biochemical changes in the target cell by changing the expression of certain genes by triggering the specific receptor. A complex biological effect occurs as a result of the production of different groups of cytokines from different cells and their synergistic effect, as well as the expression of different groups of receptors in target cells [91,138,163,215,218] . Due to the existence of complex autocrine paracrine and sometimes endocrine effects of cytokines, their aberrant expression plays an important role in the pathogenesis of various diseases, in particular, atherosclerosis, rheumatoid arthritis, psoriasis and NAFLD [91,199,200,201,202] .

Before discussing the role of cytokines in the pathogenesis of NCDs, it is necessary to recall some general concepts of immunology. It is known that a foreign antigen entering an organ undergoes several processes, and antigen-presenting cells inform other adaptive immune cells about this antigen. At this stage, antigen-presenting cells present information about the antigen to CD4+ or T-helper lymphocytes (Th) through MHC II (major histocompatibility complex II). In this way, activated Th cells stimulate B-lymphocytes that can produce affinity immunoglobulins for this antigen. As a result, B-lymphocytes are transformed into plasma cells, produce antibodies corresponding to the antigen, and the antigen is eliminated [78,91,138,163, 174,175,176,178,179,180, 197] .

Th cells are divided into different groups based on their functional capacity and the cytokines they produce. Of these, T-helper 1 (Th1) and T-helper 2 (Th2) have been studied in detail. Th1 lymphocytes mainly produce pro-inflammatory cytokines (IFN-γ, IL-2, IL- α , IL- β), while Th2 lymphocytes mainly produce anti-inflammatory cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13) [156] .

The function of Th1 lymphocytes is aimed at the elimination of intracellular antigens, mainly activating macrophages (M1) with phagocytic ability and transforming B lymphocytes into plasma cells, providing them with the production of immunoglobulins that participate in opsonization. Therefore, Th1 lymphocytes are involved in the initial stage of the inflammatory process [45,47, 91, 126,156] (Fig. 1.4.1). Th2 lymphocytes, on the other hand, activate macrophages (M2) that express growth and repair factors and cytokines by producing cytokines such as IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. They also stimulate the differentiation of B lymphocytes that produce the antibody IgE. Therefore, Tx2 is mainly responsible for the elimination of extracellular antigens, particularly parasites. During inflammation, Tx2 cells are mainly activated to replace cells that have undergone necrosis and apoptosis as a result of alterations in the late stage of inflammation, and provide the production of growth factors from M2 cells [126] (see Figure 1.4.1).

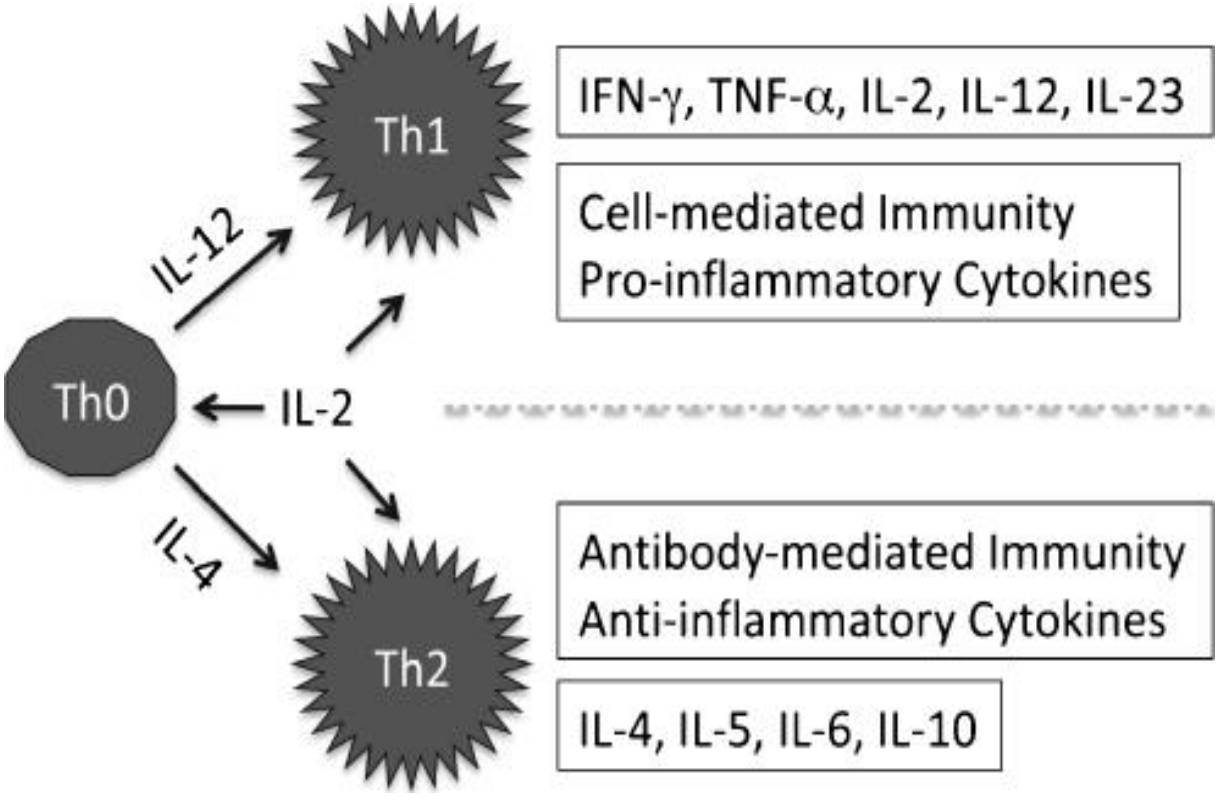

Figure 1.4.1. Th1 and Th2 lymphocytes differentiate under the influence of IL-12 and IL-4 cytokines, respectively, and produce their own group of cytokines.

The amount of Tx1/Tx2 lymphocytes and the pro-inflammatory and anti-inflammatory cytokines they produce must always be in balance. Otherwise , an

increase in this ratio can lead to the death of normal tissue and cells and other autoimmune diseases as a result of inducing hyperergic inflammatory process, while a decrease in this ratio can cause the development of allergies and other atopic diseases [45,47,91,126,156,88,234] .

The concentration of pro-inflammatory cytokines in JNAYoX has been shown to be higher than normal by several studies [156,227,234] .

Disturbance of Tx1/Tx2 balance is caused by imbalance of pro-inflammatory and anti-inflammatory cytokines. As mentioned above, the exact mechanism of this is due to abdominal obesity, in which a high amount of fat accumulates in adipocytes. As a result of lipocyte stress induced by excess fat accumulation, they chronically produce small amounts of pro-inflammatory cytokines. Chronically high levels of pro-inflammatory cytokines lead to insulin resistance. This causes an increase in the concentration of free triglyceride acids and an increase in glycogenesis in hepatocytes, thereby creating conditions for fat accumulation in liver cells [91] (Fig. 1.4.2).

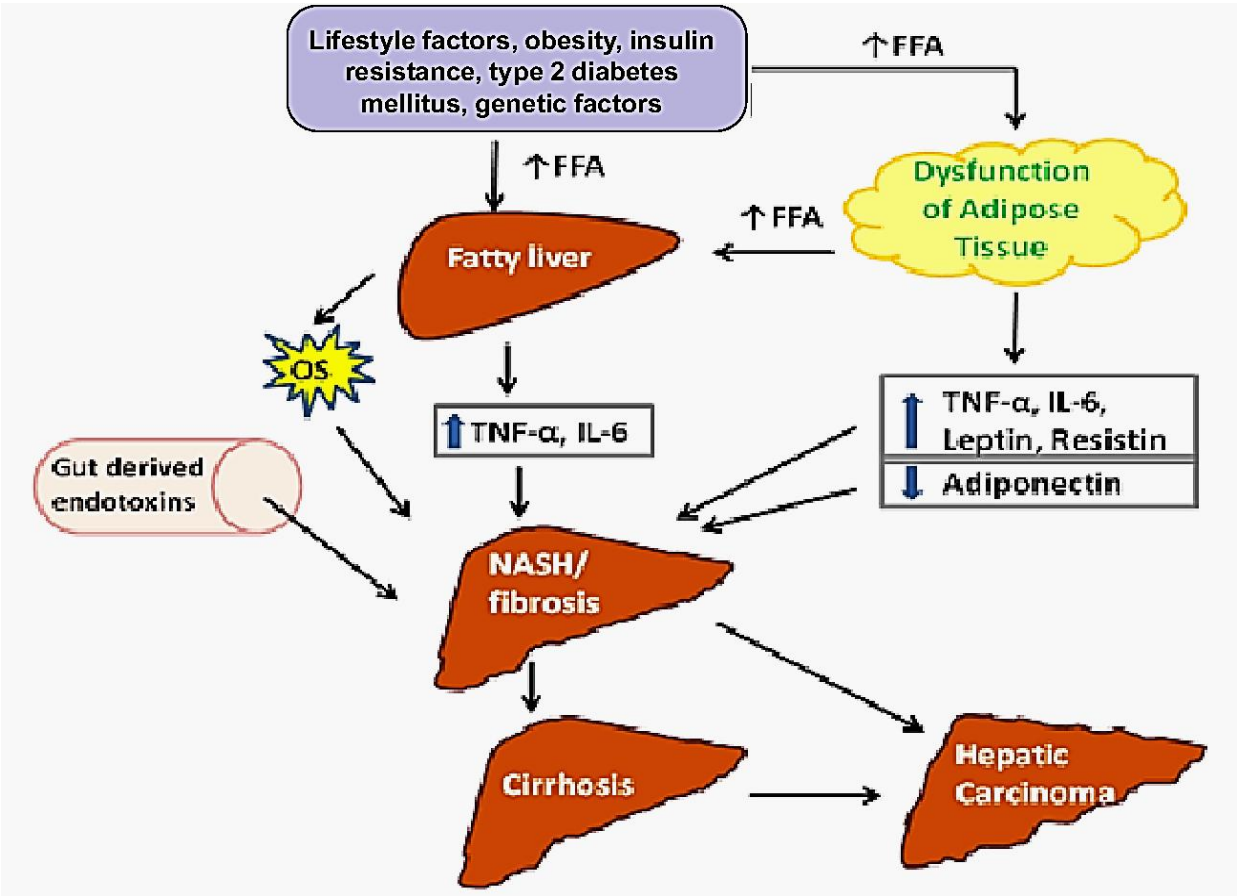

Figure 1.4.2. The importance of pro-inflammatory cytokines in the pathogenesis of NAFLD

The molecular mechanism of this occurs as follows: an increase in the amount of pro-inflammatory cytokines, in particular, IL-6 and IL-12, inhibits lipogenesis in adipocytes and enhances lipolysis by increasing the expression of stress-related kinases - c-jun N-terminal kinase (JNK) and inhibitor of kappa beta kinase beta subunit (IKK-β). This leads to an increase in the amount of free triglycerides and their accumulation in hepatocytes. JNK also inhibits the expression of peroxisome proliferator-activated receptor-γ (PPARγ), which increases the insulin resistance of cells. Insulin resistance induced by pro-inflammatory cytokines leads to fat accumulation in hepatocytes and mitochondrial dysfunction. As a result, dysfunctional mitochondria release many radicals that damage the cell and cause its death [47,91,126,156,227,234] .

to this condition leads to the development of chronic inflammation and fibrosis (nonalcoholic steatohepatitis) in the liver, as proinflammatory cytokines induce extensive necrosis and apoptosis of hepatocytes. That is, proinflammatory cytokines are not only involved in the development of nonalcoholic steatosis, but also play an important role in its progression and progression to the next stages [126,156,227,234]. On the other hand, cytokines with anti-inflammatory functions, the production of which is induced by Th2 cells, in particular IL-10, have an important protective role in NAFLD [91,126,156,227]. According to the results of other studies, inhibition of IL-10 leads to an increase in the expression of pro-inflammatory cytokines, in particular, IL-α, IL-6, IL-1β [227:88-95-b;230; 234;269;275;276]. This in turn leads to a decrease in the amount of IL-10, which shifts the balance of pro-inflammatory and anti-inflammatory cytokines towards the former, and thus, through the above mechanism, causes the development of NAFLD.

1.4 . Non-alcoholic fatty liver disease genetic markers in development importance

NAFLD is a polyetiological disease, and the list of genes that can influence the development of this disease is growing every year. This is because, although obesity and insulin resistance are considered the main trigger factors in the development of NAFLD, not all patients with this disease develop NAFLD. On the other hand, not all patients with NAFLD show signs of obesity and insulin resistance. This allows us to put forward ideas about the innate predisposition to the development of NAFLD in some patients, that is, the presence of defects in various genes.

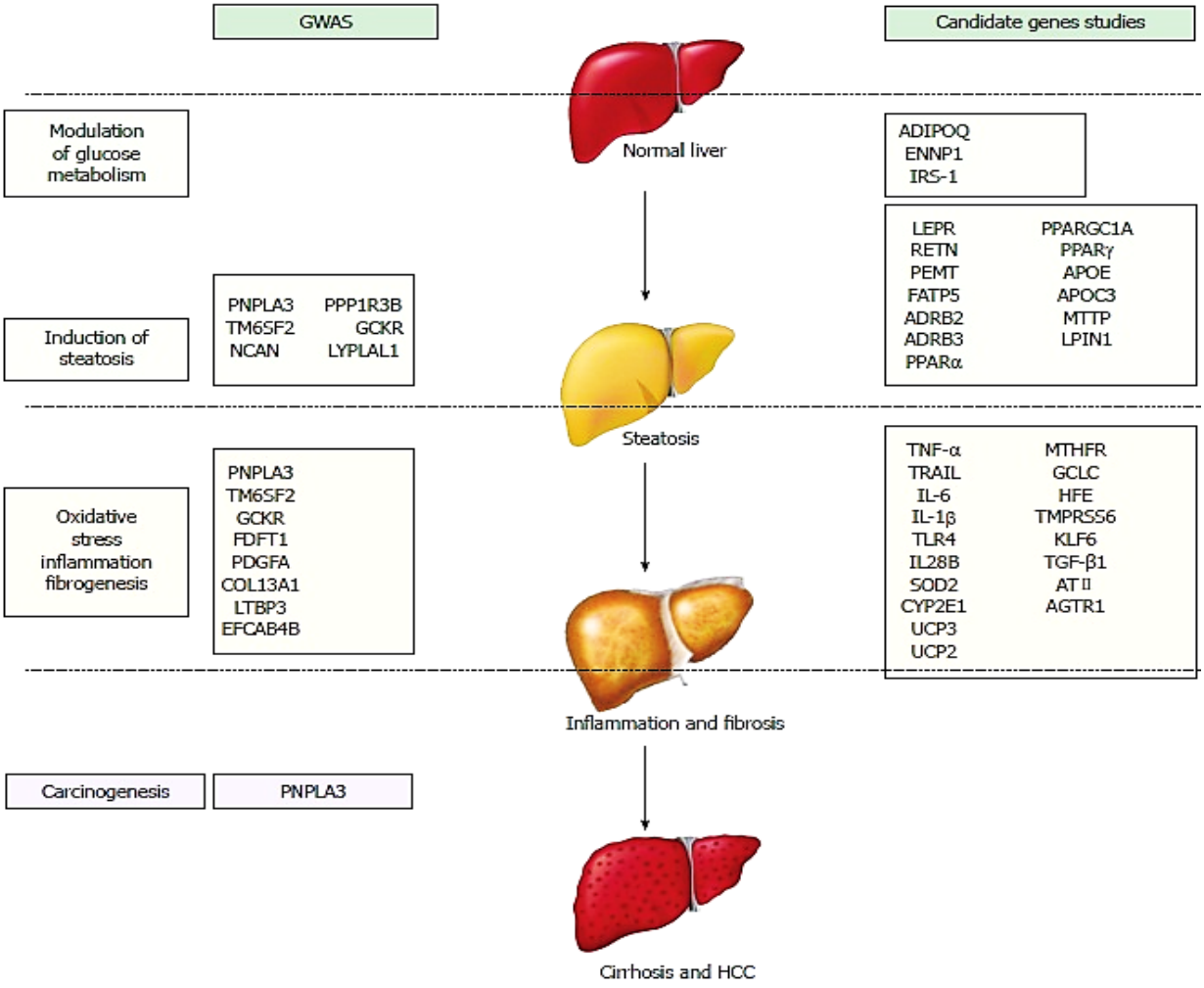

Figure 1.4.1. Some gene groups that induce the development of NAFLD through different pathogenetic mechanisms based on the results obtained from the GWA study

Numerous studies, including GWA (Genome Wide Analysis), have identified dozens of candidate genes associated with the development of NAFLD, and their number is increasing every year. Of these, minor alleles of polymorphisms of PNPLA3, TM6SF2, GCKR, MBOAT7, HSD17B13, SOX9, CCL20, CXCL1, CD24, CHST4, TR1B1, APOE, PNPLA3, *PPP1R3B, NCAN, LYPLAL1 and* other genes have been proven to have pathogenetic significance, increasing the likelihood of developing NAFLD [11,40,55,59,107,122,177,181,184, 186, 187, 189, 191, 193, 195, 206, 207, 208, 211, 212, 214, 216,217, 219, 220, 223, 235, 236,238, 246, 248, 249, 250, 251, 252,270,271]. In order to understand the relationship between the minor alleles of the listed genes and the development of JNAYoX , these genes can be divided into different groups based on their pathogenetic importance.

Although minor alleles of specific polymorphisms in the genes listed in the table may participate as risk factors in the development of NAFLD through their own complex pathogenetic mechanisms, they can be grouped together as a set of genes that generally lead to fat accumulation in hepatocytes as a result of impaired glucose or lipid metabolism [28,64,99,107,122, 177, 181,184].

Table 1.4.1

List of various gene polymorphisms that may induce the development of nonalcoholic steatosis, which is more likely to cause fat accumulation in hepatocytes by inducing impaired glucose or lipid metabolism

Gene name	Function	SNP locus
ENPP1 *(* ectonucleotide pyrophosphatase/phosphodiesterase1 or PC-1)	Reduces the activity of insulin by interacting with its receptor	rs1044498
IRS-1 *(* insulin receptor substrate 1)	It participates in the intracellular insulin pathway messenger and participates in the transmission of information to the nucleus	rs1801278
ADIPOQ , (adiponectin)	Adipocytokine is involved in the regulation of carbohydrate and lipid balance in the cell	rs2241766 rs1501299
LEPR , (leptin receptor)	Being a receptor for leptin hormone produced by adipocytes, it is involved in the normal functioning of insulin, thermoregulation and modulation of the immune system.	rs62589000 rs6700986 rs1137100 rs1137101 rs8179183

RETN (Resistin)	Adipocytokine is involved in lipid metabolism, fibrogenesis and inflammatory processes	rs3745367
PEMT (phosphatidylethanolamine N-methyltransferase)	Participates in the resynthesis of phosphatidylcholine in the liver	rs7946
FATP5 (Fatty Acid Transport Protein 5)	Participates in the transport of fatty acids in hepatocytes	rs56225452
ADRB2 and ***ADRB3 (*** β - adrenergic receptor 2 and 3)	b - adrenoreceptor , participates in maintaining the normal balance of lipids by inducing the process of lipolysis	rs4994 rs1042714 rs2053044 rs1116800 rs1195947 rs1042711
PPAR α (peroxisome proliferative activated receptor α)	It participates in the regulation of the biological effect of insulin	rs1800206
PPARGC1A (peroxisome proliferator-activated receptor γ coactivator 1- α)	It participates in the processes of gluconeogenesis and lipogenesis by regulating the function of mitochondria	rs8192678 rs2290602
PPAR γ (peroxisome proliferative activated receptor γ)	It participates in the regulation of the biological effect of insulin	rs1801282
APOE (apolipoprotein E)	ZPLP is an existing protein, which is involved in its binding to a specific receptor and thereby carrying out its biological function	N/A
APOC3 (apolipoprotein C-III)	ZYuLP, ZJPLP and the structural component of chylomicrons participate in the clearance of triglycerides	rs2854116 rs2854117
MTTP (microsomal triglyceride transfer protein)	Transport is a protein that participates in the synthesis of ApoV-lipoprotein	rs1800591 rs1800804 rs1057613 rs3805335
LPIN1 (lipin 1)	Phosphatase involved in metabolic interaction of adipocytes and liver	rs13412852
GCKR (Glucokinase) regulatory protein)	participates in its regulation by inhibiting the enzyme glucokinase in hepatocytes	rs1260326

On the other hand, the minor alleles of polymorphisms of the genes listed in Table 1.6.2 generally increase the susceptibility to the development of JNAYoX by inducing the inflammatory process. The mutation of the mentioned genes not only ensures the development of insulin resistance by inducing the inflammatory process, but also by causing the inflammation-induced lysis of liver cells, it can cause the

development of non-alcoholic steatohepatitis in comparison [152,153,154,155,159,160,161,162,191,193,195, 206, 207, 208, 211, 212, 214, 216, 217, 219, 220, 223, 204,205] (Table 1.4.2).

There are a large number of genes that cause NCDs, but in the course of this study, minor alleles of two gene polymorphisms (MBOAT7 gene rs641738 polymorphism and GCKR gene rs1260326 polymorphism) were selected from among them and their possible mechanisms of causing the development of NCDs were studied.

Table 1.4.2

List of different gene polymorphisms that may cause more non-alcoholic steatohepatitis by inducing insulin resistance and liver damage by inducing inflammation

Gene name	**Function**	**SNP locus**
O'NO- a (tumor necrosis factor -a)	Induces pro-inflammatory cytokines, inflammatory process and cell apoptosis causes insulin resistance	rs1800629 rs361525 rs1799964 rs1800630
IL-6 (interleukin-6)	Pro-inflammatory cytokines are produced by adipocytes, hepatocytes, immunocytes, and other cells and are involved in insulin resistance.	rs1800795
IL-1β (interleukin-1β)	Pro-inflammatory cytokines are mainly produced by adipocytes	rs16944
MTHFR (methylenetetrahydrofolate reductase)	Participating in the folate cycle, it participates in the transformation of homocysteine back into methionine	rs1801133 rs1801131
TMPRSS6 (trans-membrane protease serine 6)	Participates in the formation of hepcidin from the liver	rs855791
TGF- β1 (transforming growth factor β1)	Enhances fibrinogenesis	rs1800471
SOD2 (superoxide dismutase) dismutase 2)	It participates in the neutralization of superoxide radicals released from mitochondria	rs4880
MBOAT7 (Membrane Bound O-Acyltransferase Domain Containing 7)	Within the cell, arachidonic acid participates in maintaining the normal balance	rs641738

The MBOAT7 (Membrane -bound protein 7 O-acetyltransferase domain) gene is located at locus 19q13.42 and expresses the enzyme lysophosphatidylinositol

acyltransferase, and its main function is to regenerate the acyl moiety of phospholipids, an important component of cell membranes, using the substrates lysophosphatidylinositol, acetyl-CoA, and arachidonoyl-CoA , thereby controlling the concentration of free arachidonic acid in the cell (Land's cycle. Figure 1.4.2). Since arachidonic acid is a pro-inflammatory metabolite (from arachidonic acid various pro-inflammatory factors, in particular, prostaglandin and leukotrienes are synthesized by lipoxygenase and cyclooxygenase enzymes), an increase in its concentration creates conditions for the formation of many inflammatory mediators and thereby inflammation, therefore, its concentration is controlled inside the cell is extremely important [55,59, 107, 139,144, 145, 147,148, 164, 165, 166,167, 168, 171,187, 189,191,247,255].

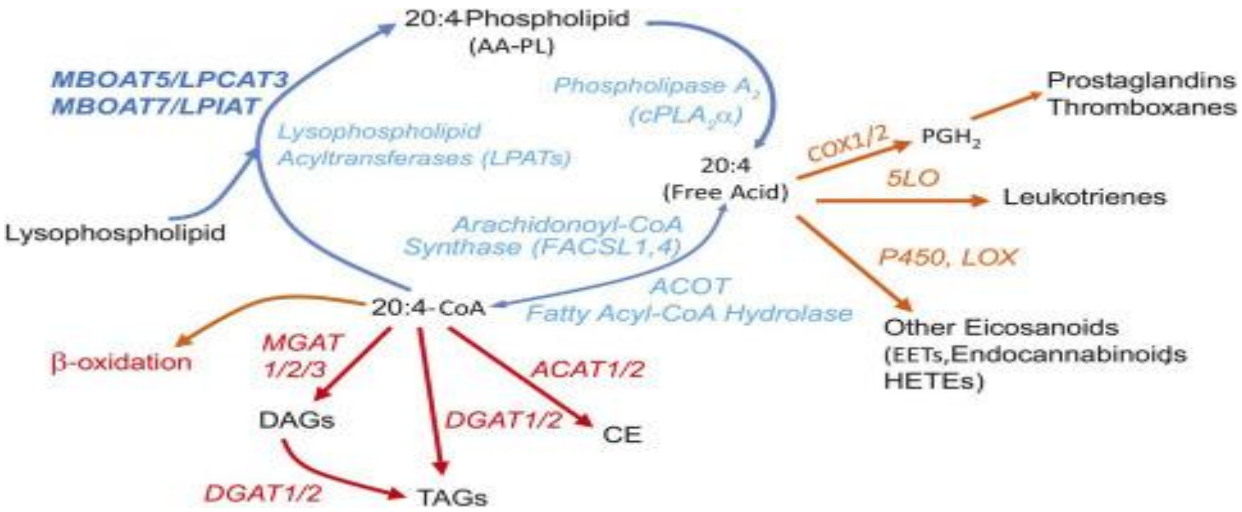

Figure 1.4.2. Arachidonic acid is transformed into complex phospholipid esters, which are components of cell membranes, by the lysophosphatidyl acyltransferase enzymes (MBOAT7 and MBOAT5). On the other hand, free arachidonic acid is a substrate for various prostaglandins and leukotrienes.

According to the literature, the T minor allele of the rs641738 C>T polymorphism of the MBOAT7 gene causes a Gly17Glu amino acid change in the protein expressed by it, resulting in a decrease in MBOAT7 expression in the cell compared to the wild-type allele [59,107,122, 177, 181, 184, 186, 187, 189, 190, 191, 193, 195, 206,256] . As a result, the concentration of free arachidonic acid and inflammatory markers synthesized from it (prostaglandins and leukotrienes)

increases inside the cell [107, 122,177,268] . This, in the case of the liver, causes inflammation and creates conditions for the development of steatohepatitis.

A meta-analysis of the GCKR gene rs1260326 polymorphism has shown an association between the polymorphism and NAFLD. In particular, a study conducted among Chinese subjects found a positive association between the GCKR gene rs1260326 polymorphism and NAFLD, with higher plasma triglycerides than controls. Another study reported a similar positive association among Asian subjects [107,122, 123,124] . According to data from another study conducted by Chinese scientists, no association was found between the GCKR gene rs1260326 polymorphism and the development of NSCLC, and only an association was observed between the polymorphism and TBI, plasma glucose, and triglyceride levels [184, 186, 187, 189, 191, 193, 195, 206, 207, 208, 211, 212, 249, 250, 251, 252] .

The GCKR gene is located at locus 2p23 and encodes a 686-amino acid protein with a molecular weight of 68 kDa and 19 exons [244,251,260,273] . The main function of the GCKR gene is to inhibit the glucokinase enzyme in hepatocytes by noncovalent binding. The glucokinase enzyme phosphorylates glucose in hepatocytes, which leads to its intracellular accumulation and glycogen synthesis. GCKR is an allosteric competitor of the glucokinase enzyme with glucose. Thus, in the absence of glucose, GCKR binds to and inhibits glucokinase, resulting in the inhibition of glycogenesis. On the other hand, if the concentration of glucose increases, glucokinase is reactivated, thereby increasing glycolysis and glycogenesis processes [184, 186, 187, 189, 191, 193, 195, 206, 207, 208, 211, 212, 214, 216, 217, 219, 220, 223, 235, 236,238] .

According to the literature, the GCKR gene rs1260326 polymorphism changes the nucleotide C to T, which in turn changes the 446th amino acid in the coding protein to proline leucine. This weakens the normal activity of GCKR, and glucokinase retains its activity even in relatively low glucose levels, ensuring the abundant transfer of glucose into hepatocytes, increasing the concentration of glucose and malonyl-CoA inside the cell. This leads to an increase in the processes

of glycogenesis and lipogenesis in hepatocytes, which, as a result, increases the susceptibility to the development of fatty hepatosis [172, 216, 235, 183, 185] .

In some populations, a positive association has been found between the GCKR gene rs1260326 polymorphism and the development of NAFLD, as well as triglyceride levels and TVI. In addition, some studies have shown that the T minor allele of the GCKR gene rs1260326 polymorphism also affects β cells, which changes the protein conformation expressed as a result of the change in expression. As a result, the regulation of GCK by GCKR in β cells is disrupted, increasing the concentration of glucose inside the cell, which can cause insulin hypersecretion. The chronic course of this condition leads to the development of insulin resistance and metabolic syndrome [172, 216, 235] .

CHAPTER II . RESULTS OF SPECIAL EXAMINATIONS. ASSESSMENT OF THE CLINICAL STATE OF THE SYSTEM IN THE STAGE OF NON-ALCOHOLIC FATTY LIVER DISEASE, STEATOSE AND STEATOHEPATITIS

§ 2.1 . Clinical description of patients

The ratio of women to men during the study was 1.25:1. The table shows that steatosis was more common in middle-aged patients (43.3%), while steatohepatitis was more common in elderly patients (45.2%). In addition, the lowest incidence of steatosis and steatohepatitis was in young patients (20.9% and 19.4%).

Table 2.1

Prevalence of steatosis and steatohepatitis stage in NASH by age, n (%)

Age of patients	ЖС n= 67	SG n=31
25-44 years old	14 (20.9 %)	6 (19.4 %)
45-59 years old	29 (43.3%)	11 (35.4 %)
60–75 years old	24 (35.8%)	14 (45.2 %)
Total	67	31

The analysis of demographic and anthropometric parameters of patients showed that the SG stage of the disease is more severe in patients (Table 2.2). 74 (76.5%) of the patients had disordered eating, eating a lot of fatty and fried foods.

In the observation group, 29 patients (43%) in the JS; 8 patients (26%) in the SG had an increase in body weight according to the Ketley index up to 30. Obesity level I (Ketley index 30–34.9) was detected in 17 patients (25%) in the JS, and in 14 patients (45%) in the SG; level II (Ketley index 35–39.9) in the JS – 15 patients (22.3%) in the SG – 5 patients (16%); level III (TVI 40 and above) in the JS – 6 patients (9%) in the SG – 4 patients (12.9%).

2. Table 2

Comparative analysis of demographic, anthropometric parameters in the main and control groups

Index	NG (n=70)	JS (n=67) 1	SG n=31 2	P 1-2
age	36.4±2.30	40.2±2.2	48.2±4.2	>0.2 , <0.05
Body weight, kg	63.0±1.03	82.0±3.2	82.0±4.22	0.001
Height, cm	170±4.2	165 ±4.33	167 ±3.25	>0.2 , >0.5
BVI, kg/m ^{2} (25-30)	22.0±0.37	26.2±1.6	28.1±1.8	<0.05, <0.01
BVI, kg/m ^{2} (30-34.9)	23.0±0.25	31.4±1.5	32.4±2.5	<0.001
BVI, kg/m ^{2} (35-39.9)	24.0±0.2	36.4±1.4	37.4±2.5	<0.001
BVI, kg/m ^{2} 40 <	24.0±0.5	38.2±2.4	40.2±2.6	<0.001

Note: n is the number of observations. P 1 – P 2 is the significant difference compared to the control group.

It is difficult to determine the duration of the appearance of symptoms of liver pathology in some patients, because they did not have complaints from the hepatobiliary system, and changes in the liver were discovered accidentally during the examination.

In patients with steatosis and steatohepatitis, up to 2–4 additional diseases of the digestive system were detected. Most often, pathologies of the gallbladder and pancreas, duodenum, gastroesophageal reflux disease were noted, which is directly explained by the anatomical and morphological features of the hepatopancreatoduodenal area. Such a location can lead to the development of damage and pathological changes in the listed organs. Additional diseases detected in patients were in remission.

In order to assess the nature of clinical manifestations, the range of leading symptoms of NAFLD, which constitute the essence of the disease, was initially determined. Each clinical sign was then analyzed.

The following are the main clinical signs characteristic of NAFLD: heaviness and discomfort under the right rib, belching, nausea, belching, flatulence,

constipation, diarrhea, fatigue, weakness. Figure 2.2 shows that clinical signs are more frequent in the steatohepatitis stage than in hepatic steatosis. Then, discomfort and heaviness under the right rib were 58.06%, and belching was 67.7%. In hepatic steatosis, belching was observed in 47.7% of cases. Thus, the frequency of manifestations of NAFLD symptoms is different and highly correlated with the stage of the disease. Among all clinical signs of NAFLD, belching was consistently observed. Regardless of the stage of the disease, this sign prevailed in the spectrum of clinical manifestations of NAFLD and constituted 61.2% in SG and 52.2% in liver steatosis. Constipation, another clinical symptom of NAFLD, was found in 54.8% in SG and 31.3% in HS.

Thus, the manifestation of clinical signs in JNAYoX is somewhat important and noteworthy, and throbbing pains, unpleasant sensations under the right rib, stuttering, hot flashes, rapid fatigue, and general weakness are more common in steatohepatitis than in steatosis .

I II. ASSESSMENT OF THE FUNCTIONAL STATE OF THE LIVER BASED ON ANALYSIS OF LABORATORY-BIOCHEMICAL AND HORMONEAL TESTS IN NON-ALCOHOLIC FATTY LIVER DISEASE

3.1 -§. Biochemical inspections based on functional state of the liver assessment

Lipid metabolism was examined to study the functional state of the liver in the CKD. Total cholesterol (TC) levels were assessed according to the European Atherosclerosis Society classification [13]: up to 5.2 mmol/l – normal; 5.3–6.5 mmol/l – mild hypercholesterolemia (MHC); 6.6–7.8 mmol/l – moderate, significant; more than 7.8 mmol/l – high. An extended lipid profile was also analyzed: triglycerides (TG), cholesterol (HDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The content of very low-density lipoproteins (VLDL) was calculated. According to the Russian recommendations for the diagnosis and correction of lipid metabolism for the prevention and treatment of atherosclerosis [13] (V revision), the norm was considered to be TG up to 1.7 mmol/l, LDL cholesterol - 2.6 mmol/l, and HDL cholesterol - more than 1.15 mmol/l. Lipid metabolism indicators are presented in Table 4.1.

Lipid metabolism disorders in NAFLD are one of the leading indicators of the disease [7,13, 15]. In this study, GHD (above 6 mmol/l) was observed. Dyslipidemia in NAFLD was characterized by TG above 1.9 mmol/l, and HDL <1 mmol/l. Such disorders were more pronounced in cases of profound lipid metabolism disorders. In the stage of steatosis and hepatic steatohepatitis, cholesterol (p=0.005), LDL cholesterol (p=0.001), LDL cholesterol (p=0.001), TG (p=0.001), AC (p=0.03), and LDL cholesterol (p = 0.001) were assessed. The results obtained showed the presence of atherogenic dyslipidemia in the steatosis and steatohepatitis stages of NAFLD. Atherogenicity is the ratio of good and bad fats. For testing, blood was taken from a vein, and the indicator coefficient was calculated using the colorimetric photometric method [8]. The atherogenicity coefficient was considered normal when

it was from 2.2 to 3.5. The atherogenicity coefficient was calculated using a simple formula:

3.1 - table

Indicators of lipid metabolism in the examined group of patients

Index	NG (n=70)	JS (n=67) 1	SG (n=31) 2	P $_{1-2}$
Cholesterol (mmol /l)	5.12±0.04	6.35±0.85	7.3±0.18	>0.1, <0.001
Cholesterol LDH (mmol /L)	0.37±0.06	0.66±0.21	0.92±0.12	>0.1, <0.001
Cholesterol LDL mmol /l)	3.26±0.07	3.95±0.41	4.62±0.12	>0.1, <0.001
Cholesterol LDH (mmol /L)	1.32±0.04	0.95±0.05	0.82±0.08	<0.001
Triglycerides (g/l)	0.93±0.02	1.76±0.21	1.97±0.18	<0.001
Atherogenicity coefficient (AK)	2.72 ±0.04	5.6 ±0.82	7.79±0.83	<0.001

Note: n is the number of observations. P $_1$ – P $_2$ is the significant difference compared to the control group.

Atherogenic coefficient (atherogenicity index) = (total cholesterol – ZYuLP)/ZYuLP

The results obtained in the course of the research showed that AK was higher than 6 mmol/l. The atherogenic index was significantly higher than the established index in all examined patients. In order to assess the functional state of the liver in the stage of steatosis and steatohepatitis, the parameters of pigment metabolism, cytolysis and cholestasis were studied. (Table 3.2).

Biochemical tests included α-laninaminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (GGTP), alkaline phosphatase (IF), total bilirubin and its fractions. The obtained results showed that the level of β ilirubin in the main group was significantly higher than that of the control group. In JS, cytolysis indicators were equal to AST – 20.9 , ALT – 27.6, in steatohepatitis, ALT – 88.6, AST – 48.2, which is 6–8 and 3–4 times higher than steatosis indicators, respectively. Alkaline phosphatase in JS It was 132.9 TB /l and corresponded to

normative values (Table 3.2.2) . Alkaline phosphatase was 1.5–2.5 times higher in steatohepatitis.

Table 3.2.

Indicators of transaminases in the examined groups

Indicators	NG (n=70)	SP (n=67) *1*	SG (n=31) *2*	P 1-2
Total protein (g/l)	65.2 2 ± 0.2 1	75.2±3.2	78.2±3.8	<0.01
Albumin g/l	53.2±1.0	45.2±2.2	44.2±2.2	<0.01, <0.001
Total bilirubin μmol/l	10.6±0.2	13.6±6.2	19.2±5.2	>0.5, >0.1
Bound bilirubin μmol/l	3.5±0.5	3.8±0.8	4.1±1.6	>0.5
ALT (TB/L)	17.6±0.96	27.6±8.7	88.6±31.7	>0.2, <0.05
AST (TB/L)	20.9±1.1	20.9±7.7	48.2±23.7	>0.5, >0.2
FFA (TB/L)	121.9±5.9	132.9±21.9	150.0±28.8	>0.5, >0.2
γ-GTP (TB)	24.9±1.1	34.9±12.7	71.9±41.7	>0.2
Glucose (mmol / l)	4.3±0.8	5.9±0.9	6.45±0.65	>0.1, <0.05

Note: n is the number of observations. P 1 – P 2 is the significant difference compared to the control group.

Thus, in this study, the main comparative characteristics of steatosis and steatohepatitis were assessed based on sufficient clinical practice, a clear biochemical level of cytolysis. Alkaline phosphatase and gamma-glutamyl transpeptidase (GGTP) activity (increased in isolation) were found to be moderately increased in SG. Dyslipidemia (hypertriglyceridemia, decreased LDL cholesterol, increased LDL cholesterol) was observed in 65–85% of patients. Basal insulin levels were significantly higher in patients with NAFLD. Correlation analysis of the results of this study showed that NAFLD is negatively correlated with steatosis, steatohepatitis, and total cholesterol, LDL cholesterol, and LDL cholesterol .

3 . § 1. Hormone testing

In the last decade, much attention has been paid to the study of the effects of endocrine and gastrointestinal hormones on the functioning of the digestive system. The connection of hormonal homeostasis changes with digestive diseases is of great importance. Hyperinsulinemia is a key link in the development of IR - GI - obesity - IR [49,93]. Today, an increase in reserves in adipose tissue due to high-calorie nutrition increases insulin sensitivity. Lack of physical activity leads to insulin resistance in adipose tissue, and hyperinsulinemia is formed as a result of a decrease in tissue sensitivity to insulin [125,127,170].

In hyperinsulinemia, carbohydrate metabolism is first disrupted. Then, as a result of intense lipolysis from fat reserves, tissues are supplied with energy in the form of fatty acids, and lipoproteins are formed in the liver. As a result of increased glucose and insulin levels in the liver, triglycerides are formed in greater quantities than glucose, and the amount of LDL increases and the amount of HDL decreases. An increase in the amount of insulin in the liver also increases the amount of HDL. The elimination of HDL depends on the amount of insulin. Resistance to IR lipoprotein lipase is formed and the elimination of HDL decreases. Increased production of HDL and decreased elimination of HDL lead to an increase in the amount of triglycerides (HDL) in the blood plasma. A decrease in HDL is associated with the breakdown of HDL, which is the cause of hyperinsulinemia [93,127,170]. Thus, an increase in IR and insulin levels is characterized by dyslipidemia, that is, a decrease in the amount of LDL and an increase in the amount of HDL in the blood plasma. Developing dyslipoproteinemia acquires an atherogenic nature. In the scientific literature, insulin resistance is considered one of the risk factors for the development of NAFLD . To determine the level of increased compensatory insulin levels in patients with steatosis and steatohepatitis stages of NAFLD, the HOMA-IR index was established. The HOMA-IR index is a homeostasis assessment model for insulin resistance. Normally, the HOMA-IR index does not exceed 2.7, this indicator is the same for men and women and does not depend on age. During adolescence, the HOMA indices increase slightly due to the physiological resistance of insulin at this age. Insulin resistance is a decrease in the sensitivity of insulin-

sensitive tissues to the effects of insulin when its concentration in the blood is sufficient. Insulin resistance has no specific symptoms and can occur in obese and non-diabetic individuals, occurring in approximately 25% of cases. This index was calculated using the following formula: [insulin at mealtime (mIU/mL) × glucose at mealtime (mmol/L)] / 22.5. A normal index is less than 2 [125,127]. HOMA-IR was significantly higher in the patients included in the study than in the control group (p=0.01) (Table 3.3).

Table 3.3.

Indicators of serum hormones in NAFLD

Hormone	NG (n=70)	JS (n=67) . 1	SG (n=31). 2	P $_{1-2}$
Insulin MTU/ml	11.53±1.46	15.12±1.42	18.2 2 ±1.6 1	>0.05, <0.01
Cortisol (nmol /l)	3 55 , 62 ± 3 2,3	401.2±31.21	519.2±22.31	>0.2, <0.001
HOMA-IR	2.2±0.56	5.58 ±0.9	7.68 ±1.1	<0.01, <0.001

Note: n is the number of observations. P $_1$ – P $_2$ is the significant difference compared to the control group.

The results of this study showed that basal insulin levels were significantly higher in patients with NAFLD (n=0.001).

Thus, the level of hypercortisolemia showed a negative correlation with the indicators of LDL and HDL. It was noted that there was a correlation between hypercortisolemia and hyperinsulinemia with atherogenic dyslipidemia, and glucose parameters with hyperinsulinemia. To determine the level of increased compensatory insulin levels in patients with steatosis and steatohepatitis stages of NAFLD, the HOMA-IR index was determined. In the patients included in this study, the HOMA-IR insulin resistance index was significantly higher than in the control group (n = 0.01).

CHAPTER IV . DETERMINATION OF CHANGES IN PRO-INFLAMMATORY (IL-A, IL-6) AND ANTI-INFLAMMATORY CYTOKINES (IL-10) AND ASSESSMENT OF LIVER FUNCTION IN THE STEATOSIS AND STEATOHEPATITIS STAGE OF NON-ALCOHOLIC FATTY LIVER DISEASE

4. § 1. Analysis of pro - inflammatory (IL-α, IL-6) and anti- **inflammatory cytokines** (IL-10)

Cytokines are molecules that are secreted by various cells and provide communication between cells and tissues. They play an important role in normal processes occurring in the body, in particular, normal growth and development of the body, obesity (fat accumulation), lactation, hematopoiesis, inflammation and hemostasis processes, and the pathogenesis of various diseases, such as atherosclerosis, rheumatoid arthritis, psoriasis, and NAFLD. [91,138,163,197] .

It is known that can have different pathomorphological manifestations depending on the histological state (from simple fat accumulation to a combination of inflammatory and fibrotic processes). To date, it has not been proven that they are different stages of a single disease or different diseases developing as a result of different etiopathogenetic mechanisms [78,91,138] .

Although there are several alternative classifications for this disease, to understand the role of cytokines, we used the classification proposed by Matteoni and colleagues in a simpler form. According to it, NAFLD F is divided into 4 types: type 1 - steatosis or simple fatty liver, type 2 - steatohepatitis (involvement of inflammation), type 3 - steatonecrosis (involvement of multiple necrosis of liver cells), and type 4 - steatonecrosis with Mallory hyaline or fibrosis [91,138,163,197] .

4 .2-§. Indicators of inflammatory cytokines in patients with fatty liver disease and their correlation with other biochemical indicators

In order to study the role of cytokines in the development of NAFLD, the levels of pro-inflammatory cytokines IL-6 and IL-1β in the serum of all patients (98) included in the study were measured. This test was also performed on healthy controls (70). When the results were compared and analyzed, a statistically significant difference was found between them ($p<0.001$) (Fig. 5.1). According to it, in the control group, TNF-α and IL-6 were 4.52±0.15 pg/ml and 4.16±0.15 pg/ml, respectively, while in the main group, TNF-α was 43.33±1.31 pg/ml, IL-6 was 33.8±1.17 pg/ml, which is 9.59 ($p<0.001$) and 8.12 ($p<0.001$) times higher than the control group, respectively (Fig. 5.1-a). Also, in all patients with NAFLD, the ONO-α index was significantly higher than the IL-6 index (43.33>33.8 pg/ml).

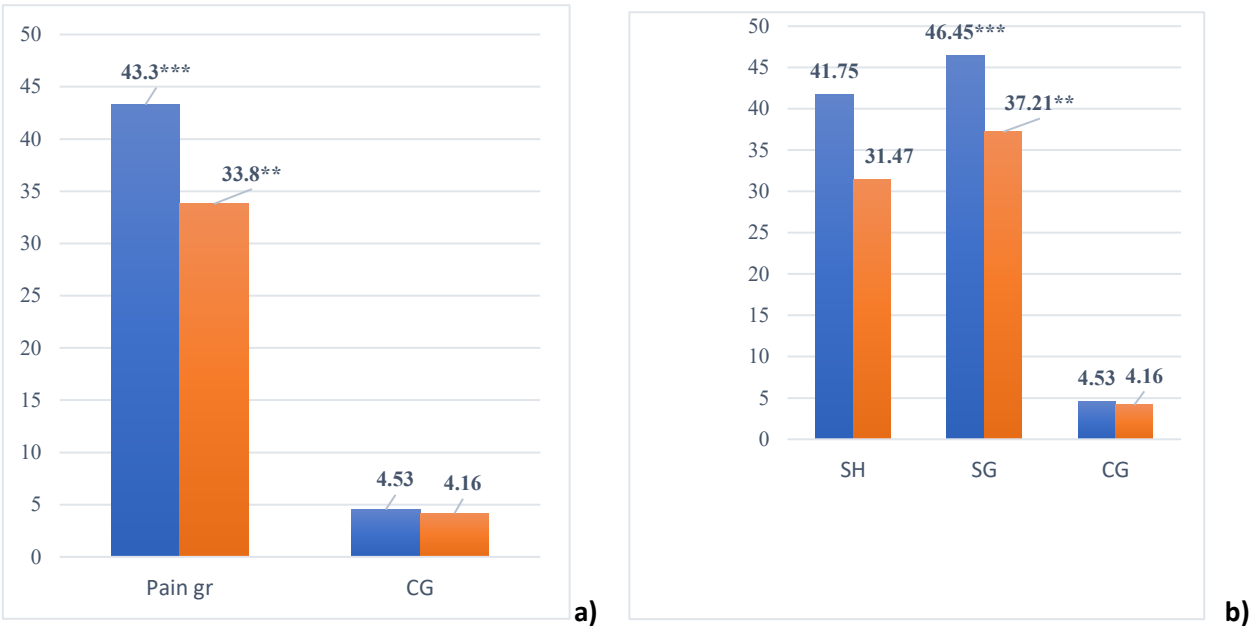

Figure 4.1-a: a) Indicators of TNF – α and IL – 6 cytokines in the main and control groups. T test>3.35; p<0.001; b) Indicators of TNF – α and IL – 6 cytokines in the steatosis, steatohepatitis and control groups. T test>2; p<0.05.

Note: differences are significant for steatosis and steatohepatitis (* - P<0.05, ** - P<0.01, *** - P<0.001)

Patients in the main group (98) were grouped using the classification developed by Matteoni et al., according to which 67 patients with steatosis were included in the first subgroup, and 31 patients with steatohepatitis were included in

the second subgroup. During the examination, no patients with steatonecrosis and fibrotic processes in the liver were identified.

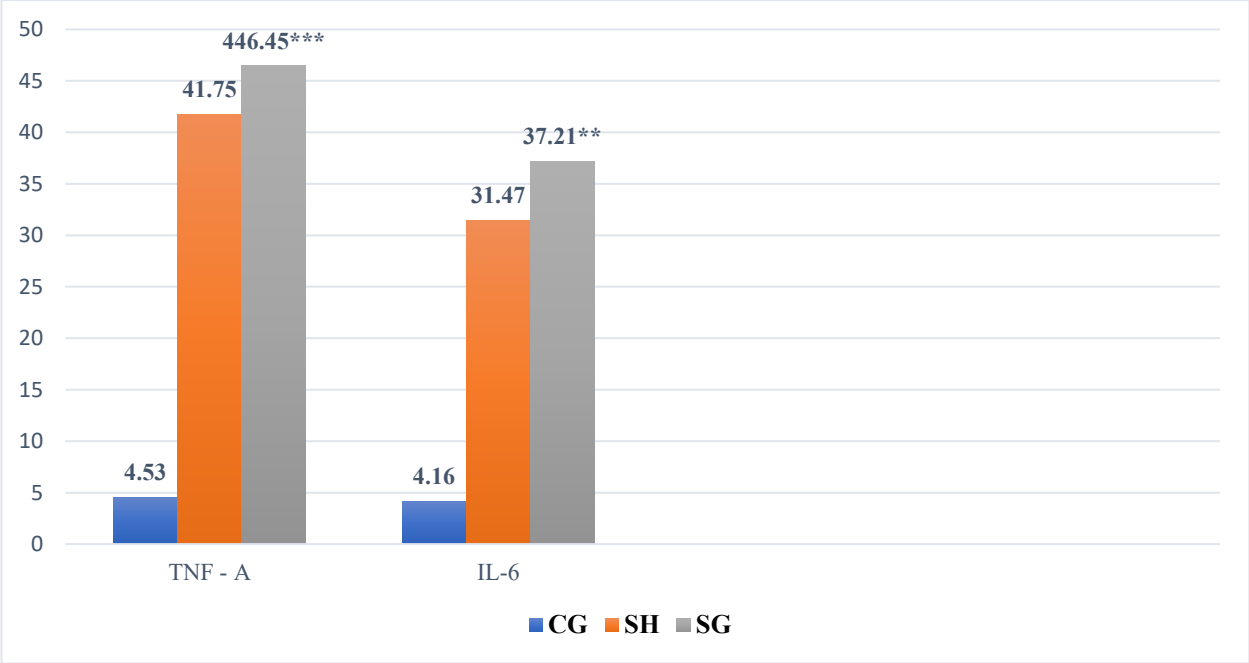

Fig. 4.1-b. Indicators of TNF – α, IL – 6 cytokines in the main and control groups. T-test>3.35; p<0.001 (a); TNF – α, IL – 6 cytokines in subgroups of patients with steatosis, steatohepatitis and the control group (b). T-test>2; p<0.05. Note: differences are significant for steatosis and steatohepatitis (* - P<0.05, ** - P<0.01, *** - P<0.001)

When comparing the data from the subgroups diagnosed with steatosis and steatohepatitis and the control group, a sharp difference was observed between the indicators of patients and healthy individuals, i.e., in the group of patients with steatosis, the cytokines TNF-α and IL-6 were 41.75±1.218 pg/ml and 31.47±1.83 pg/ml, respectively, which was statistically significantly higher than the indicators of the control group by 9.22 (p<0.001) and 7.56 (p<0.001) times (Fig. 4.1-b). In the group of patients with steatohepatitis, the results obtained for the above cytokines differed even more sharply from the control group : ONO-α - 46.45±3.07 pg/ml, IL-6 - 37.21±2.54 pg/ml, which is 10.28 (p<0.001) and 8.94 (p<0.001) times higher than the control group, respectively. Also, these indicators were 1.11 and 1.18 (p<0.05) times higher than the indicators obtained from patients with steatosis.

The differences were tested for validity and the statistical significance of the results was confirmed ($p<0.05$). Thus, it can be said that inflammatory processes in steatohepatitis are more intense than in steatosis.

According to the literature, the prevalence of NAFLD depends on gender, age, and race. Accordingly, in order to study the gender-dependent differences in cytokine hyperproduction in the pathogenesis of NAFLD, patients in small groups were further divided into subgroups by gender and the results were analyzed. In the group diagnosed with steatosis, 44.8% of patients were men and 55.2% were women.

Table 4.1

Sex-related levels of inflammatory cytokines in the serum of patients in all groups, M±m

Groups	ONO – α (pg/ml)		IL-6 (pg/ml)	
	Male	woman	man	Woman
Control group (n=70)	4.76 ± 0.24	4.31 ± 0.20	4.40 ± 0.19	3.94 ± 0.15
Steatosis (n=67)	41.17 ± 1.97 [a]	42.22 ± 1.14 [a]	36.19 ± 2.54 [a]	27.6 ± 1.84 [a, b]
Steatohepatitis (n=31)	52.01 ± 3.34 [a]	41.24 ± 2.79 [a, b]	40.64 ± 4.29 [a]	33.98 ± 2.75 [a, b]

Note: a – reliability of differences between the indicators of the control and patient groups, $p<0.05$; b – reliability of differences between the indicators of the intergroup male and female groups.

In the steatohepatitis group, men accounted for 48.4% and women for 51.6%, while in the control group, men accounted for 48.6% and women for 51.4%. Thus, it can be said that in this study, the risk of developing NAFLD was not confirmed by gender (the diagnosis of this disease was almost equal among men and women) (Table 4.1).

It can be seen from the table that there is no correlation between the level of cytokines in the blood serum of the control group and gender. The level of ONO-α in men was 4.76±0.24 pg/ml, in women - 4.31±0.20 pg/ml, the level of IL-6 in men and women was 4.40±0.19 and 3.94±0.31 pg/ml, respectively. The statistical

reliability of these results was not confirmed (T-test>2; p>0.05). There was no statistically significant difference in TNF-α indicators in both sexes with steatohepatosis, and the results obtained were 8.65 (p<0.001) and 9.8 (p<0.001) times higher than the control group, respectively, and when these indicators were compared by gender, it was found that this indicator was 1.13 times higher in women than in men. The serum IL-6 level in male patients diagnosed with steatohepatosis was 36.19±2.54 pg/ml, in women – 27.6±1.84 pg/ml, which is statistically significantly higher than the control group by 8.22 (p<0.001) and 7 (p<0.001) times. Also, the amount of IL-6 in men was 1.17 (p<0.05) times higher than in women. On the other hand, the results of the study of cytokines in the group of patients with steatosis showed significant differences between men and women: while the expression of TNF-α was mainly characteristic of women, a strong expression of IL-6 was often observed in men (in men – 36.19±2.53 pg/ml; in women – 27.6±1.84 pg/ml; p=0.0067).

In contrast, in the group of patients with steatohepatitis, the serum levels of ONO-α in men and women were 10.93 (p<0.001) times higher than in the control group and 1.26 (p<0.05) times higher than in the steatohepatitis group. In the group of women with steatohepatitis, the levels of this cytokine were 9.57 (p<0.001) times higher and did not differ from the levels in the steatohepatitis group. The levels of IL-6 cytokine were 9.24 (p<0.001) and 8.62 (p<0.001) times higher than in the control group in men and women. These levels were 1.12 and 1.23 (p<0.05) times higher than in the steatohepatitis group, respectively.

According to the literature, older people have higher concentrations of cytokines than younger people, which predisposes them to age-related chronic diseases such as cardiovascular and neurodegenerative diseases [198, 2 31]. Therefore, in this study, in order to confirm or deny that the results obtained on cytokines are also related to factors other than the investigated NCD, the age characteristics of the patients, which are one of the main factors affecting cytokine production, were also studied. The age classification of people developed by the WHO in 2015 was used. According to it, people aged 25–44 years are young, people

aged 44–60 years are middle-aged, 60–75 years are elderly, 75–90 years are elderly, and people over 90 years are long-lived [138,163,197] .

According to the results of the study, the levels of TNF-α and IL-6 cytokines in the blood serum increased with age in the control group. In particular, compared to the young group, the levels of TNF-α were 1.45 ($p<0.01$) and 1.66 ($p<0.01$) times higher in the middle-aged and elderly groups, and the levels of IL-6 were 1.21 ($p<0.05$) and 1.33 ($p<0.05$) times higher in the middle-aged group. While steatosis was mainly detected in the middle-aged group (43.3%), steatohepatitis was more common in the elderly group (45.2%). In addition, the lowest percentage of patients with this disease in the steatosis and steatohepatitis groups was in the young group (20.9% and 19.4%). In the group of patients diagnosed with steatosis, the serum levels of TNF-α in young, middle-aged and elderly patients were 10 ($p<0.001$), 7.52 ($p<0.001$), 6.26 ($p<0.001$) times higher than in the control group, and the strongest change was observed in young patients. The levels of IL-6 in these groups were 8.66 ($p<0.001$), 6.3 ($p<0.001$), 6.41 ($p<0.001$) times higher , and its sharp increase was observed in young patients (Table 4.2).

In the group of patients with steatohepatitis, the serum levels of ONO-α in young, middle-aged and elderly patients were statistically significantly higher than those in the control group by 12.46 ($p<0.001$), 7.07 ($p<0.001$), 7.57 ($p<0.001$), and the strongest change was observed in the young group. The levels of IL-6 were also 11.42 ($p<0.001$), 6.45 ($p<0.001$), and 7.56 ($p<0.001$) times higher in these groups, respectively, and a sharp increase in this indicator was noted in the young group.

Table 4.2

Age-related changes in the levels of inflammatory cytokines in the blood serum of controls, steatohepatitis, and steatohepatitis patients, M±m

Groups and their age	TNF – α (pg/ml)	IL-6 (pg/ml)
Control, n=70		
25 -44 (74.3%)	3, 9 6 ±0.14	3.93 ± 0.16
45-59 (14.3%)	5.76 ± 0.1 6 ^{p}	4.7 4 ± 0.24 ^{p}
60 and over (11.4%)	6 , 57 ±0, 2 3 ^{p}	5 , 2 1±0 ,2 9 ^{b}
Steatohepatosis, n=67		

25 -44 (20.9%)	39.56 ± 2.65 [a]	32.47 ± 3.12 [a]
45-59 (43.3%)	43.33 ± 1.81 [a]	29.87 ± 2.98 [a]
60 and over (35.8%)	41.12 ± 2.1 0 [a]	32.8 1± 3.26 [a]
Steatohepatitis, n=31		
25 -44 (19.4%)	49.35 ± 1.79 [a]	44.88 ± 2.0 2 [a]
45-59 (35.5%)	40.7 2± 2.8 1 [a]	30.5 3± 1.45 [a, b]
60 and over (45.2%)	49.72 ± 5.4 1 [a]	39.38 ± 3.83 [a]

Note : a – significance of differences between the indicators of the control and patient groups, p <0.05; b – significance of differences relative to the indicators of the youth group.

Along with the concentration of cytokines, obesity is considered one of the factors with a strong inducing effect on the origin of NAFLD [78, 91] .

Therefore, when studying the relationship between body mass index (BMI), steatosis, and inflammatory cytokines, it was found that all patients with NASH were overweight (BMI≥25). In the control group, BMI remained within normal limits. In particular, 43.3% of patients with nonalcoholic steatosis were overweight, 25.3% had grade I obesity, 22.4% had grade II obesity, and 9% had grade III obesity, while 25.8% of patients with nonalcoholic steatohepatitis were overweight, 45.2% had grade I obesity, 16.2% had grade II obesity, and 12.9% had grade III obesity (Table 5.3).

Table 4.3

serum levels of inflammatory cytokines in patients with steatohepatitis and steatohepatitis and

BMI, M±m

TVI	Steatosis (n=67)			Steatohepatitis (n=31)		
	n	TNF – α	IL-6	n	TNF – α	IL-6
Overweight	29	38.1 ± 0.89	20.0 ± 1.02	8	31.46 ± 0.85	26.5 ± 0.79
Obesity of the first degree	17	39.1 ± 1.12	28.4 ± 0.84 [a]	14	44.25 ± 1.4 [a]	31.1 ± 1.18 [a]
II degree obesity	15	44.7 ± 1.15 [ac]	45.1 ± 1.35 [ac]	5	50.86 ± 2.2 [ac]	51.52 ± 1.83 [ac]

III degree obesity	6	59.6 ± 0.98 acd	57.5 ± 0.88 acd	4	78.5 ± 1.51 acd	61.77 ± 1.1 acd

Note : a – relative to the overweight indicator, p < 0.05 ; b – relative to the overweight indicator, p >0.05; c – relative to the obesity index of grade I , p < 0.05 ; d – II Compared to the obesity index, p < 0.05.

It can be seen from the table that in patients with steatosis, with an increase in TVI, the amount of cytokines that cause inflammation also increased statistically significantly. In particular, the amount of TNF-α in the blood serum of patients with excess body weight and obesity of I, II, III degrees increased statistically significantly by 8.41 (p<0.001), 8.63 (p<0.001), 9.87 (p<0.001), 13.16 (p<0.001) times compared to the control group. When compared to the indicators of patients with excess body weight, a tendency to increase in indicators was observed in obesity of I degree , while in obesity of II and III degrees it was 1.17 (p<0.05), 1.54 (p<0.01) times statistically significantly higher. In patients with steatosis, overweight and obesity of I, II, III degrees, the level of IL-6 in the blood serum was 4.89 (p<0.001), 6.83 (p<0.001), 10.84 (p<0.001), 13.82 times higher than in the control group, respectively. Compared to the indicators of patients with excess body weight, it was 1.42 (p<0.01), 2.28 (p<0.001), 2.87 (p<0.001) times higher in obesity of I, II, III degrees.

In patients with steatohepatitis, the amount of cytokines that cause inflammation also increased statistically significantly with an increase in TVI. In particular, the amount of TNF-α in the serum of patients with excess body weight and obesity of I, II, III degrees was statistically significantly higher than that of the control group by 6.94 (p<0.001), 9.77 (p<0.001), 11.23 (p<0.001), 17.33 (p<0.001). If these indicators are taken for patients with excess body weight, then in obesity of I, II, III degrees it was statistically significantly higher by 1.41 (p<0.01), 1.62 (p<0.01), 2.5 (p<0.001). In patients with steatohepatitis who were overweight and had obesity of I, II, and III degrees, the level of IL-6 in the blood serum was statistically significantly higher than that of the control group by 6.37 (p<0.001), 7.48 (p<0.001), 12.38 (p<0.001), and 14.85 (p<0.001). If these indicators are taken

for overweight patients, then in obesity of I, II, and III degrees, they were statistically significantly higher by 1.17 ($p<0.05$), 1.94 ($p<0.001$), and 2.33 ($p<0.001$).

According to the literature, this is because the accumulation of fat in adipose tissue, particularly in adipocyte cells, causes a fat-induced stress state in the cells, which increases the secretion of cytokines that cause inflammation (see Figure 4.2). [63] .

such changes, the production of adiponectin, one of the anti-inflammatory factors, decreases. This leads to the development of systemic inflammatory syndrome.

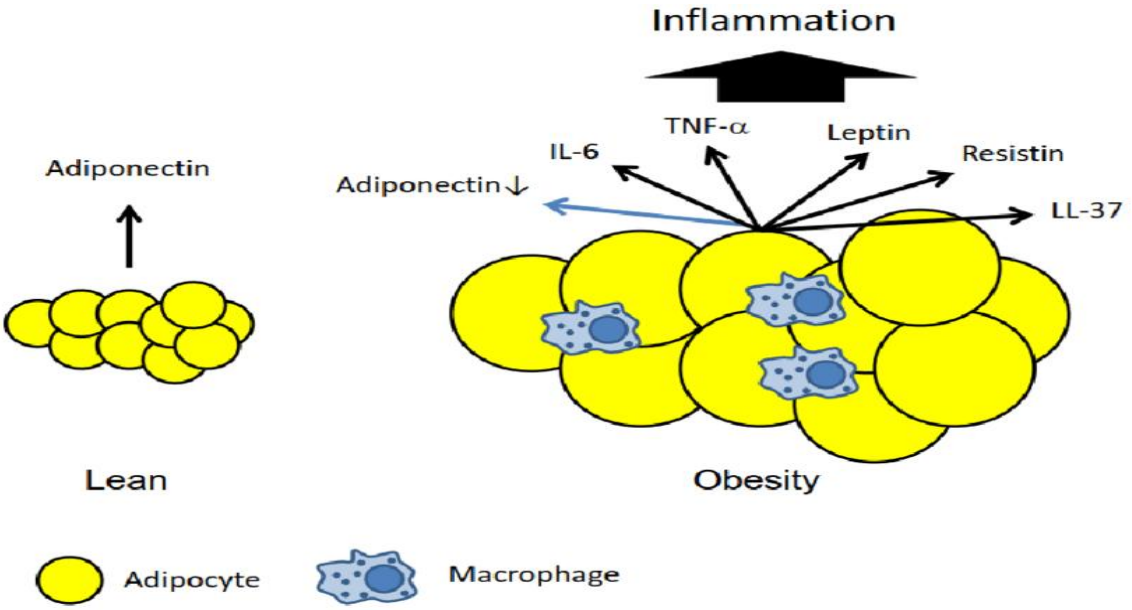

Figure 4.2. Mechanism of systemic inflammation in obesity [295] .

In addition, to determine the role of proinflammatory cytokines in predicting the severity of NAFLD, the results obtained on cytokines were correlated with other biochemical parameters. Thus, in the pathogenesis of NAFLD, the level of cytokines was examined, the severity of cytolytic processes in the liver (through the level of aminotransferase enzymes and total bilirubin), the degree of disruption of its synthetic function as a result of fatty liver (through the level of albumin, cholesterol, LDL and HDL), and the degree of metabolic disorders (through insulin, HOMA-IR index and triglycerides) and the level of cytokines were examined (Table 4.4).

It can be seen from the table that there were moderate positive correlations between the amount of TNF-α and the amount of ALT, AST and total bilirubin, and

a strong positive correlation between the amount of IL-6 and the listed indicators. Also, a moderate strong correlation was noted between the cytokines TNF-α and IL-6 and the indicators of triglycerides, insulin and HOMA-IR. In addition, a moderate and strong inverse (negative) correlation was observed between the amount of albumin and HDL, which indicate the synthetic function of the liver, with cytokines.

Table 4.4

Correlation of the level of pro-inflammatory cytokines with other biochemical parameters in patients with steatosis

Biochemical indicators	ONO – α		IL-6	
	r	p	r	P
ALT	0.54	<0.001	0.75	<0.001
AST	0.41	<0.001	0.75	<0.001
Total bilirubin	0.50	<0.001	0.81	<0.001
Conjugated bilirubin	0.48	<0.001	0.74	<0.001
Albumin	-0.45	<0.001	-0.74	<0.001
Cholesterol	0.35	<0.01	0.65	<0.001
LDL	0.49	<0.001	0.85	<0.001
HDL	-0.22	>0.05	-0.57	<0.001
Triacylglycerides	0.44	<0.001	0.54	<0.001
Insulin	0.39	<0.01	0.65	<0.001
HOMA-IR	0.33	<0.01	0.41	<0.001

Remember : r - correlation coefficient ; P is a reliable difference relative to the correlation coefficient.

Correlations between proinflammatory cytokines and various biochemical tests were also found in patients with steatohepatitis (Table 4.5).

It can be seen from the table that in patients with nonalcoholic steatohepatitis, the process of cytolysis in hepatocytes and the corresponding liver dysfunction were more rapid than in patients with steatosis. Also, a moderate positive correlation was observed between the listed cytokines, cholesterol, LDLP, insulin and HOMA-IR indicators, a strong direct -direct relationship was found between the amount of

TNF-α and triglycerides. On the other hand, when calculating the correlation between the listed biochemical indicators and IL-6, in most cases, results close to the observed indicators of TNF-α were obtained. In particular, a strong direct relationship was found between IL-6 and ALT, AST, total bilirubin and triglycerides; a strong inverse relationship was found between the listed interleukins and bound bilirubin, and albumin; a moderate direct relationship with LDLP, insulin indicators; a weak positive relationship with cholesterol and HOMA-IR indicators; A weak negative association with ZYULP was found.

Table 4.5

Correlation of inflammatory cytokine levels with other biochemical parameters in patients with steatohepatitis

Biochemical indicators	TNF – α		IL-6	
	r	P	r	P
ALT	0.66	<0.001	0.77	<0.001
AST	0.74	<0.001	0.76	<0.001
Total bilirubin	0.68	<0.001	0.77	<0.001
Conjugated bilirubin	-0.74	<0.001	-0.78	<0.001
Albumin	-0.68	<0.001	-0.71	<0.001
Cholesterol	0.37	<0.05	0.28	>0.1
ZPLP	0.63	<0.001	0.67	<0.001
ZULP	-0.17	>0.2	-0.16	>0.2
Triacylglycerides	0.73	<0.001	0.72	<0.001
Insulin	0.57	<0.01	0.57	<0.001
HOMA-IR	0.32	>0.05	0.27	>0.1

Remember : r - correlation coefficient ; P is a reliable difference relative to the correlation coefficient.

It can be said that the increase in cytokine concentrations indicates the degree of alteration induced by fatty dystrophy of liver cells , and in this case, the IL-6 cytokine in particular was confirmed to have a clearly informative value in both subgroups (with steatosis and steatohepatitis).

The reason for the positive correlation between the examined cytokines, triglycerides, insulin and HOMA-IR indicators was studied. According to the literature, insulin resistance plays an important role in the etiopathogenesis of non-alcoholic steatosis and steatohepatitis. That is, due to insulin resistance, triglycerides and other free fats accumulate in hepatocytes. This leads to the excessive production of inflammatory cytokines by hepatocytes (also adipocytes play an important role in this pathophysiological process) as a result of lipid peroxidation, an increase in free radicals and cellular stress induced by fat dystrophy [163,197] .

Cytokine hypersecretion reduces insulin resistance of cells by inhibiting insulin signal transduction in insulin-sensitive cells [78,91], resulting in a specific pathophysiological loop.

The presence of a negative relationship between inflammatory cytokines, albumin, and ZYuLP in both mentioned groups helps us to conclude that the normal synthetic activity of the liver is reduced. In addition, since there is a positive correlation between the amount of cholesterol and LDL and the mentioned inflammatory cytokines, first of all, if the amount of pro-inflammatory cytokines indicates the severity of hepatocyte alteration, in this case, the normal cholesterol excretion of the liver, the amount of cholesterol and LDLP in the blood increases. On the other hand, an increase in the amount of cholesterol in the blood causes its accumulation in the liver, which has an adverse effect on the mitochondria in hepatocytes and has a negative effect on biological oxidation processes, which causes an increase in free radicals inside the cell, thereby causing cell stress and cytokine hypersecretion [91,138] .

The positive correlation between cholesterol, LDL, and pro-inflammatory cytokines can also be viewed as a component of the pathophysiological loop between insulin resistance, fatty liver, and inflammatory cytokines mentioned above. That is, hypercholesterolemia results in the accumulation of cholesterol and triglycerides in hepatocytes and their injury, thereby leading to hypersecretion of pro-inflammatory cytokines from hepatocytes, which further aggravates insulin resistance. The repetition of these processes leads to the exacerbation of the disease.

Another noteworthy aspect of the results of the presented correlational study is that, while a positive association was found between inflammatory cytokines and conjugated bilirubin in the group of patients with nonalcoholic steatosis, a negative association was noted between these two factors in patients with nonalcoholic steatohepatitis. This can be explained by the fact that fatty liver due to nonalcoholic steatosis impedes the normal flow of bile in the intrahepatic bile ducts, thereby increasing the amount of all types of bilirubin in the blood [78,91,138,163,197] .

On the other hand, in nonalcoholic steatohepatitis, the condition is further aggravated by the swelling induced by the inflammatory process along with the accumulation of fat in the liver, and in the case of steatohepatitis, the excessive cytolysis of hepatocytes increases liver dysfunction and the function of conjugating unconjugated bilirubin with glucuronic acid to form conjugated bilirubin is weakened. It was observed that the more severe the steatohepatitis, the lower the amount of conjugated bilirubin. Therefore, determining the amount of conjugated bilirubin is important in the differential diagnosis of nonalcoholic steatosis and steatohepatitis.

It is known that numerous studies have proven that steatohepatitis can develop after a certain period of time in nonalcoholic steatosis [78,91,138]. According to the literature, in steatosis caused by various factors (genetic, endocrine, nutritional, toxic), when hepatocytes suffer from lipotoxic effects for a certain period of time, the synthesis and secretion of inflammatory cytokines increases in them, thereby activating a nonspecific immune response and inducing hepatocyte cytolysis. That is, chronic hyperexpression of inflammatory cytokines plays an important role as a risk factor in the progression of nonalcoholic steatohepatitis [91,138] . Therefore, based on the inducing role of inflammatory cytokines in the development of nonalcoholic steatohepatitis from a state of nonalcoholic steatosis, their relative risk (RR) and odds ratio (OR) (Table 4.6).

Table 4.6

The importance of inflammatory cytokines as a risk factor in the development of steatohepatitis from nonalcoholic steatosis

Cytokines	RR	95%CI	OR	95%CI	P
TNF – α	2.54	0.85-7.56	3.6	0.98-13.32	0.054
IL-6	6.4	1.63-25.1	10.4	2.29-47.2	<0.001

It can be seen from the table that, although TNF-α increased the risk of developing steatohepatitis from nonalcoholic steatosis by 2.54 times (95% CI: 0.85–7.56) and 3.6 times (95% CI: 0.98–13.32) in terms of odds ratio, the statistical significance of these results was not confirmed ($p>0.05$). IL-6, on the other hand, was found to increase the risk of developing steatohepatitis from nonalcoholic steatosis by 6.4 times (95% CI: 1.63–25.1) and 10.4 times (95% CI: 2.29–47.2) in terms of odds ratio, and the statistical significance of this result was confirmed. The results confirmed a statistically significant effect of the pro-inflammatory cytokine IL-6 on increasing the risk of developing nonalcoholic steatohepatitis.

Thus, a statistically significant difference was found between the main and control groups in terms of the amount of inflammatory cytokines, and this difference, as expected, was sharp between the non-alcoholic steatohepatitis and control groups. Also, when examining the amount of TNF - α and IL - 6 by gender, a predominance was noted mainly in the male group, but the statistical reliability of this result was not confirmed in some cases. On the other hand, changes in the amount of the listed cytokines depending on age were also not confirmed. However, in the main group, a statistically significant increase in their amount was observed with an increase in body weight. At the same time, the results obtained from the listed inflammatory cytokines and other biochemical analyzes, in particular, ALT, AST, total bilirubin, cholesterol, LDL, triglycerides and insulin, were found to have a positive correlation with the HOMA-IR index, and a negative correlation with albumin and HDL. Furthermore, the role of proinflammatory cytokines in the progression of liver disease from simple steatosis to steatohepatitis was investigated using relative risk and odds ratio (RR) analyses. The results demonstrated that IL-6 is a potent inducing factor that increases the risk of steatosis to steatohepatitis.

4 .3-§. Distinctive features of pro-inflammatory cytokine indices in patients with fatty liver disease and relatively healthy individuals

IL-10 is an anti-inflammatory cytokine that reduces inflammation and tissue damage by acting on immunocytes and inhibiting the production of pro-inflammatory cytokines [91]. Numerous studies, including those in primates , have shown that IL-10 prevents endotoxemia by reducing the production of pro-inflammatory cytokines [138]. IL-10 also suppresses the immune response by directly affecting immune cells themselves, in particular by inhibiting the differentiation of T-helper lymphocytes and reducing the expression of major histocompatibility complex II (MHC II) on cells [91,138].

In order to establish the role of anti-inflammatory cytokines in the pathogenesis of NCD, the level of IL-10 was measured in the serum of all (98) patients with NCD who were included in the study. This test was also performed on healthy controls. When comparing the data obtained, a statistically significant difference was noted between them (Fig. 4.3-a). In particular, in all patients with NCD (n=98), the IL-10 level was 50.21±1.29 pg/ml, while in the control group this indicator was only 5.28±0.24 pg/ml, which is 9.51 times higher, respectively ($p<0.001$). This indicator was 48.15±1.32 pg/ml in the group of patients with steatosis (n=67) (9.12 times higher than the control group, $p<0.001$), and 54.68±1.46 pg/ml in the group of patients with steatohepatitis (10.36 times higher than the control group, $p<0.001$). Thus, it can be concluded that in patients with NAFLD, a significant increase in the level of the anti-inflammatory cytokine IL-10 was observed in comparison with the control group, due to a compensatory mechanism, and this difference was especially pronounced in the subgroup with steatohepatitis.

Also, in order to compensate for the hypersecretion of pro-inflammatory cytokines observed during this study, the amount of IL-10 produced and secreted by sex was examined and the importance of the sex factor in the development of hyperergic inflammation in the patients included in the study was studied (Fig. 4.3-b). The results confirmed that the level of IL-10 cytokine in the control group was

not dependent on sex, its level in men and women was 5.37±0.37 and 5.37±0.37, respectively. It was 5.20±0.32 pg/ml.

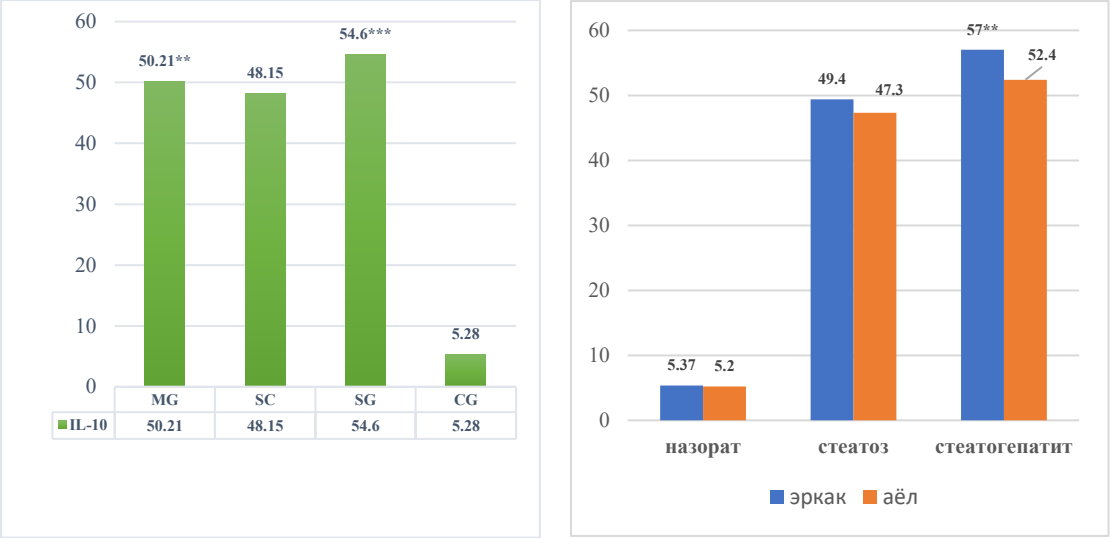

Figure 4.3. Changes in serum IL-10 levels in patients with steatosis and steatohepatitis (a) and their relationship to gender (b).

Remember: (* - P<0,05, ** - P<0,01, *** - P<0,001)

No gender-related changes in the serum IL-10 levels of patients with steatosis were detected; its levels were 9.2 ($p<0.001$) and 9.1 ($p<0.001$) times higher in men and women compared to the control group, amounting to 49.4±1.5 and 47.3±1.46 pg/ml, respectively. Similar changes were also observed in the group of patients with steatohepatitis: in men –57.1±1.81 pg/ml, in women –52.4±1.56 pg/ml, which is 10.61 ($p<0.001$) and 10.08 ($p<0.001$) times higher than the control group, respectively. Thus, there is no gender-related difference in the compensatory hypersecretion of IL-10 in reducing the inflammatory process. The age-related relationship of IL-10 cytokine was also examined (Table 4.7).

It can be seen from the table that in the control group, there was a tendency for IL-10 levels to increase with age, but the differences between them were not statistically significant. The level of IL-10 in the serum of patients with steatosis was 9.45 ($p<0.001$), 9.14 ($p<0.001$), 7.67 ($p<0.001$) times higher than in the control group in patients of young, middle-aged and elderly age groups. In patients with steatohepatitis, this indicator was 10.26 ($p<0.001$), 9.38 ($p<0.001$), 10.11 ($p<0.001$) times higher than in the control group . Thus, based on the results obtained, it can be

said that the change in IL-10 levels in patients with steatosis and steatohepatitis does not depend on age.

Table 4.7

Age-related changes in IL-10 levels in the control, nonalcoholic steatosis, and steatohepatitis groups, M ± m

Age	control	steatosis	steatohepatitis
25-44	5.15 ± 0.27	48.68 ± 2.54 *	52.82 ± 3.33 *
44-60	5.46 ± 0.34	49.91 ± 2.03 *	51.24 ± 2.3 2 *
60-75	5.69 ± 0.79	43.62 ± 1.55 **	57.5 0± 3.1 1 *

Note: a – significance of differences between the indicators of the control and patient groups, p <0.05; b – significance of differences relative to the indicators of the youth group.

Serum IL-10 levels were also analyzed according to body mass index (Table 5.8). As noted above, the body mass index in the control group was around 25. Serum IL-10 levels in patients with steatosis were 7.83 ($p<0.001$), 8.96 ($p<0.001$), 10.47 ($p<0.001$), 12.44 ($p<0.001$) times higher than in the control group in overweight, obesity of I, II, III degrees. Serum IL-10 levels in obesity of I, II, III degrees were 1.14, 1.34 ($p<0.05$) and 1.58 ($p<0.01$) times higher than in the overweight group. Serum IL-10 levels in patients with steatohepatitis were 8.16 ($p<0.001$), 9.98 ($p<0.001$), 8.68 ($p<0.001$), 16.93 ($p<0.001$) times higher than in the control group in overweight patients, I, II, III degree obesity. Serum IL-10 levels in patients with I, II, III degree obesity were 1.22 ($p<0.05$), 1.19 ($p<0.05$), 2.07 ($p<0.001$) times higher than in the overweight group. Thus, the data obtained confirm that changes in IL-10 levels in patients with steatosis and steatohepatitis are dependent on TVI.

The reason for this is that, as mentioned above, with an increase in TBI, anti-inflammatory interleukins also increase due to the increased secretion of inflammatory cytokines, that is, due to the maintenance of a balance between them, the concentration of IL-10 also increases.

Table 4.8

The relationship between IL-10 levels and body mass index in the control, nonalcoholic steatosis, and steatohepatitis groups, M ± m

TVI	Steatosis (n=67)		Steatohepatitis (n=31)	
	n	IL – 10 pg/ml	N	IL – 10 pg/ml
Overweight	29	41.35 ± 0.89	8	43.1 ± 1.5
Obesity of the first degree	17	47.3 ± 1.88 [a]	14	52.7 ± 2.0 [a]
II degree obesity	15	55.3 ± 1.9 [ab]	5	51.14 ± 2.38 [ac]
III degree obesity	6	65.7 ± 1.26 [abd]	4	89.4 ± 2.83 [abd]

Note: a – compared to the indicators of the overweight group, p <0.05; b – compared to the indicators of the group with grade I obesity, p <0.05; c – compared to the indicators of the group with grade II obesity, p >0.05; d – compared to the indicators of the group with grade III obesity, p <0.05. * – p>0.05; ** – p<0.05.

Correlation analysis was performed to determine the changes in other biochemical parameters in accordance with the varying IL-10 concentrations in patients. In particular, in patients with nonalcoholic steatosis, mainly as a result of cell cytolysis, a moderate positive correlation was found between ALT and AST enzymes, cholesterol, LDL, total and conjugated bilirubin in the blood serum, and a moderate negative correlation with albumin, which is a synthetic and toxic substance-neutralizing property of the liver, and LDL (Table 5.9). In addition, a moderate positive correlation was noted with IL-10 and parameters related to metabolic disorders, in particular, with insulin, and a weak direct correlation with the HOMA-IR index.

In patients with steatohepatitis, a moderately strong positive correlation was found between ALT, AST, total bilirubin, LDL, triglycerides, insulin, and HOMA-IR, a weak positive correlation with cholesterol, a strong inverse correlation with conjugated bilirubin and albumin, and a weak inverse correlation with LDL.

Table 4.9

Correlation between the amount of inflammatory cytokines and biochemical parameters in a group of patients with steatosis and steatohepatitis

Biochemical indicators	Steatosis group	Steatohepatitis group
ALT	0.69	0.56
AST	0.49	0.70
Total bilirubin	0.63	0.63
Conjugated bilirubin	0.60	-0.77
Albumin	-0.46	-0.69
Cholesterol	0.43	0.28
LDL	0.66	0.59
HDL	-0.33	-0.19
Triacylglycerides	0.54	0.57
Insulin	0.40	0.57
HOMA-IR	0.32	0.35

Note: reliable difference compared to the main group indicators.

Taking into account the importance of a nonspecific immune reaction in the development of steatohepatitis from steatosis, the significance of the difference in the concentration of cytokines in the subgroups was determined in the differential diagnosis of non-alcoholic steatosis and steatohepatitis (Table 5.10).

As can be seen from the table, high specificity (84%, 79% and 81%, respectively) was found for the cytokines TNF-α, IL-6 and IL-10, but their low sensitivity (30%, 26% and 35.5%, respectively) was also noted. The differences in the concentrations of TNF-α, IL-6, and IL-10 in patients with nonalcoholic steatosis or steatohepatitis were found to have good diagnostic accuracy for ONO-α and moderate for IL-6 and IL-10 in the differential diagnosis of these diseases (diagnostic accuracy was assessed as follows: 100–90% or 1.0–0.9 - excellent; 90–80% or 0.9–0.8 - very good; 80–70% or 0.8–0.7 - good ; 70–60 % or 0.7–0.6 - average; 60–50 % or 0.6–0.5 - unsatisfactory) [91,138,191,194,197].

Table 4.10

Significance of cytokine levels in the differential diagnosis of nonalcoholic steatosis and steatohepatitis

Cytokines	Sensitivity	Specialty	Diagnostic efficiency
ONO a	30%	84%	70%
IL-6	26%	79%	62.2%
IL-10	35.5%	81%	66%

Thus, the results of the study showed that the level of IL-10 in the group of patients with non-alcoholic steatosis and non-alcoholic steatohepatitis was significantly increased compared to the control group due to the compensatory mechanism of fat-induced lipotoxicity, this difference was especially pronounced in the subgroup with steatohepatitis. When examining the sex-related difference in the concentration of IL-10, no statistically significant difference was found between women and men. Also, age-related changes in the level of IL-10 were not confirmed. However, in the main group, a statistically significant increase in their level was observed with increasing body weight. Also, a positive or negative correlation was found between the results of the IL-10 cytokine and other biochemical analyzes in both subgroups.

Based on the results obtained, it can be said that in steatosis, especially in steatohepatitis, the levels of inflammatory cytokines IL-α and IL-6, which lead to inflammation, as well as IL-10, which suppresses inflammation, increase sharply due to the development of fatty inflammatory processes. An increase in the level of IL-10 in the serum of patients occurs due to compensatory processes and suppresses inflammatory processes. Such changes are directly related to gender (while IL-α expression was mainly characteristic of women, strong expression of IL-6 was observed more often in men), age (cytokine expression was strongest in patients aged 25–49 years) and TVI. The strongest correlations were observed with TVI, and with an increase in its index, the level of cytokines also increased. A moderate to strong positive correlation was observed between the levels of IL-α, IL-6 and IL-10 in steatosis, especially in steatohepatitis, and the biochemical parameters ALT, AST, total bilirubin, cholesterol, triglycerides, insulin and HOMA-IR, while moderate to

strong negative correlations were found with cholesterol in albumin and LDL. A strong positive correlation was noted between conjugated bilirubin and cytokines in steatosis, and a strong negative correlation was noted between them in steatohepatitis. Therefore, the determination of the amount of conjugated bilirubin may play an important role in the differential diagnosis of nonalcoholic steatosis and steatohepatitis. The results presented confirm that increased serum cytokine concentrations indicate alterations induced by fatty liver, in particular IL-6 cytokine, which is of great informative value. It was found that IL-6 cytokine has a statistically significant effect on the risk of developing nonalcoholic steatohepatitis.

Conclusion:

– In patients with NAFLD, an 8–16-fold increase in TNF-α, IL-6, and IL-10 was observed in the serum, and dramatic changes in steatohepatitis were noted;

– a sharp increase in serum levels of TNF-α, IL-6 and IL-10 was detected mainly in young and middle-aged patients. The development of hypercytokinemia was directly related to the body mass index of patients, and the most pronounced changes were observed in patients with grade III obesity;

– Different levels of correlations were noted with the amount of cytokines and other biochemical parameters: moderate and strong positive correlations were observed with the indicators of cytolysis and cholestasis syndromes, and moderate and strong negative correlations were observed with the indicators of liver synthetic function. In steatosis, a strong positive correlation of the amount of cytokines with the amount of conjugated bilirubin was found, in steatohepatitis - a strong negative correlation;

– Although TNF-α as a relative risk factor increased the risk of developing steatohepatitis from nonalcoholic steatosis by 2.54 times (95% CI: 0.85–7.56), and in terms of the odds ratio by 3.6 times (95% CI: 0.98–13.32), the statistical reliability of these results was not confirmed ($p>0.05$). IL-6 was found to increase by 6.4 times (95% CI: 1.63–25.1), and in terms of the odds ratio by 10.4 times (95% CI: 2.29–47.2), and the statistical reliability of this result was confirmed;

– In the differential diagnosis of steatosis and steatohepatitis stages of NAFLD, sensitivity was 26–36%, specificity 79–84%, and diagnostic efficiency was 62–70%, which was considered good for TNF-α and average for IL-6 and IL-10.

CHAPTER V. SIGNIFICANCE OF MBOAT7 GENE RS641738 POLYMORPHISM AND GCKR GENE RS1260326 POLYMORPHISM IN THE DEVELOPMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

5 .1- § . The significance of the MBOAT7 gene rs641738 polymorphism in the development of nonalcoholic fatty liver disease

Although numerous studies have been conducted to study the role of various gene polymorphisms in the development of NAFLD, the significance of the MBOAT7 gene rs641738 G>T polymorphism in the development of NAFLD in the Uzbek population has not been fully elucidated. Therefore, the significance of the MBOAT7 gene rs641738 polymorphism in the pathogenesis of NAFLD was examined in a group of 98 patients with NAFLD and 70 healthy controls.

The results of the study from 70 healthy individuals in the control group showed that the allele distribution of the MBOAT7 gene rs641738 polymorphism was 81.4% for the wild-type allele G and 18.6% for the minor allele T. Also, the genotype distribution of the MBOAT7 gene rs641738 polymorphism was 65.7% for the wild-type homozygous G/G genotype, 31.4% for the heterozygous G/T genotype, and 2.9% for the mutant homozygous T/T genotype. The results of this group for the MBOAT7 gene rs641738 polymorphism were close to those of East Asians [65].

In the main group of patients diagnosed with CKD (98 people), according to the distribution of alleles, the G wild-type allele was found in 64.8%, the T minor allele in 35.2%, which is 1.3 and 1.89 times higher than the control group, respectively. According to the distribution of genotypes in the MBOAT7 gene rs641738 polymorphism, in the main group, the wild-type homozygous G / G genotype was 41.8%, the G / T heterozygous genotype was 45.9%, and the T / T mutant homozygous genotype was 12.2%. The results showed that the main group indicators differed significantly from the control group , and these differences were manifested in the fact that the homozygous G/G genotype was 1.37 times less

common in the main group, the heterozygous G/T genotype was 1.45 times less common, and the mutant T/T genotype was 4.21 times more common (Figure 5.1.1).

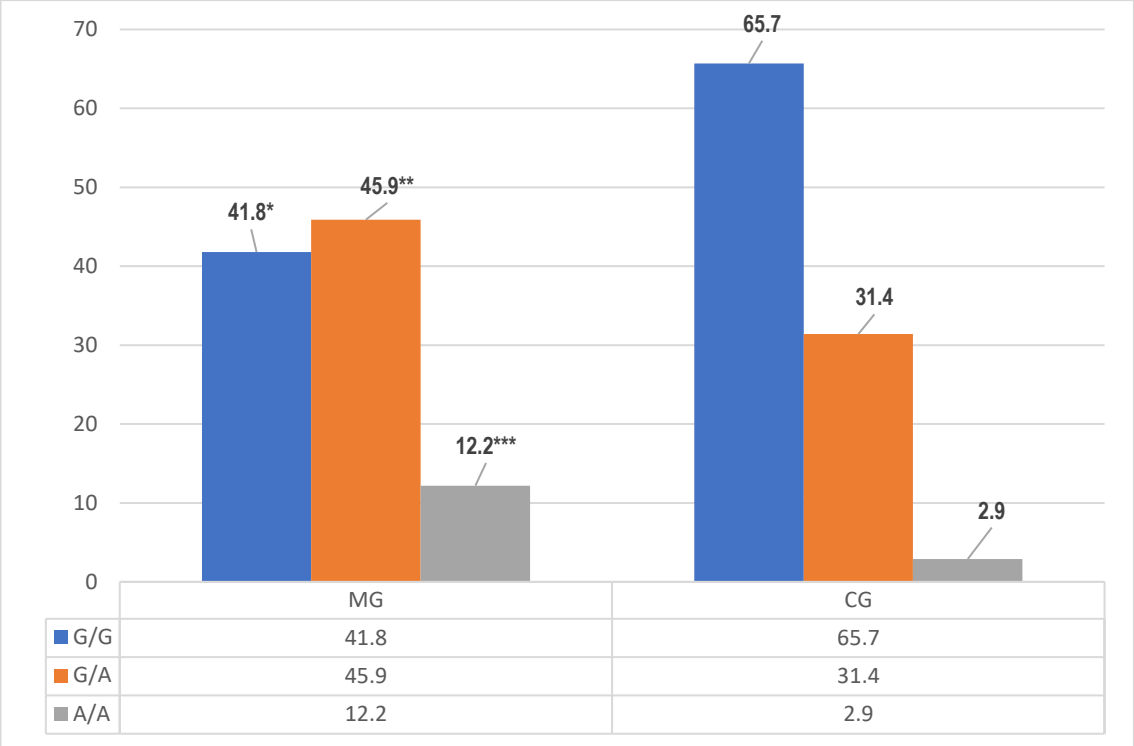

Figure 5.1.1. Distribution of the MBOAT7 gene rs641738 polymorphism in the main and control groups, %. (* - P<0,05, ** - P<0,01, *** - P<0,001)

The results obtained from the analysis of the MBOAT7 gene rs641738 polymorphism were tested according to the Hardy-Weinberg law and, although a weak deviation was observed, it was found to obey this law ($3.84 > \chi^2$; $0.05 < p$). The results of the empirical test for the normal homozygote - G/G and mutant homozygote genotypes T/T were slightly higher than the results expected according to the Hardy-Weinberg law (0.418; 0.122 and 0.4115; 0.1215, respectively), the heterozygote genotype prevailed with slight differences from the theoretically expected and empirically determined results (0.459 and 0.447, respectively) (Table 5.1.1). In addition, in the analysis of the MBOAT7 gene rs641738 polymorphism in the patients included in this study, when the result obtained from the heterozygous genotype was checked using the D-value (D=(Ho–He)/He), the heterozygous genotype showed a positive result (D= 0.028) (Table 5.1.3). It was found that the results obtained during the analysis corresponded to the Hardy-Weinberg law, and

the errors made during the selection of patients with NCDs in the Uzbek population were minimal.

Table 5.1.1

Compliance of the results obtained for the MBOAT7 gene rs641738 polymorphism in the main group with the Hardy-Weinberg law (df=1)

Main group HWE				
Alleles	Percentage distribution			
G	64.8%			
T	35.2%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype G / ***G***	0.418	0.4115	0.021	0.885
Genotype G ***/T***	0.459	0.447	0.021	0.886
Genotype ***T/T***	0.122	0.1215	0.000	1,000
Total	1.0	1.0	0.021	0.885

Also, when the results from the control group were tested according to the Hardy-Weinberg law, a weak deviation was detected, but when this was re-tested using the chi-square test, it was found to be insignificant ($\chi^2 < 3.84$; $p > 0.05$ at a significance level of 0.05). The results obtained for the normal homozygous genotype and the heterozygous genotype from the control group individuals included in this study were lower than the theoretically expected results (for the G/G genotype and the G/T genotype, respectively, 0.657 and 0.663; 0.314 and 0.303), while the observed result for the homozygous mutant genotype was slightly higher than the expected result (Table 5.1.2). The result obtained from the heterozygous genotype was verified using the D-quantity and a positive result similar to the main group was obtained (D=0.036) (Table 5.1.3).

Table 5.1.2

of the results obtained for the MBOAT7 gene rs641738 polymorphism in the control group with the Hardy-Weinberg law (df=1)

Control group HWE				
Alleles	Percentage distribution			
G	81.4 %			
T	18.6 %			
Genotypes	Observable	Expected	χ^2	P-value
Genotype G */ **G***	0 .657	0 .663	0.033	0.855
Genotype G */**T***	0.314	0.303	0.035	0.851
Genotype ***T/T***	0.029	0.034	0.208	0.649
Total	1.0	1.0	-	-

Table 5.1.3

The difference between the empirical and expected theoretical results obtained in the main and control groups according to the heterozygous genotype

Groups	Observable	Expected	D*
Main group	0.459	0.447	0.027
Control group	0.314	0.303	0.036

*Formula *: $D = (H_{obs} - H_{exp}) / H_{exp}$.*

Thus, the results of the study of the MBOAT7 gene rs641738 polymorphism in patients with NAFLD confirmed that the homozygous G / G and heterozygous G /T genotypes are less common, and the mutant T/T genotype is more common with statistical confidence.

The significance of the MBOAT7 gene rs641738 polymorphism in the development of NAFLD. The study of the relationship between the wild and mutant alleles of the MBOAT7 gene rs641738 polymorphism and the occurrence of NAFLD in the A -group and control groups showed that the wild G allele reduces the occurrence of the disease by 30% by exerting a protective effect on the occurrence of NAFLD (RR=0.7; 95% CI: 0.611–0.862), while the mutant allele

exerts an initiating effect on the occurrence of NAFLD, with a relative risk of 1.38 (95% CI: 1.16–1.64). The results obtained were tested using chi-square and p-value indicators and their significance and reliability in the development of CKD were confirmed (χ^2=11.1; p<0.001) (Table 5.1.4).

Also, when examining the role of the genotype distribution of the studied polymorphism in the main and control groups, it was found that the G/G wild homozygous genotype has a strong protective effect on the development of the disease (OR=0.375; 95% CI: 0.199–0.709) and the significance of the results obtained was confirmed (χ^2=7.8; p<0.01). On the other hand, it was found that the T/T mutant homozygous genotype has an initiating effect on the development of the disease (OR=4.74; 95% CI: 1.027 – 21.9) and increases the risk of the disease by 1.54 times (RR=1.54; 95% CI: 1.2 – 1.98), and the relationship between the mutant genotype and the development of the disease was proven to be significant (χ^2=4.7; p<0.05). Although the heterozygous genotype increased the risk of developing NCDs (RR=1.28; 95% CI: 0.997 – 1.643), this effect was confirmed to be insignificant in statistical analysis (χ^2>3.84; p>0.05) (Table 5.1.4).

Thus, in the pathogenesis of primary AKI in the Uzbek population, the T allele of the MBOAT7 gene rs641738 polymorphism (OR=2.38; 95 % CI: 1.42–3.99) and the T/T genotype (OR=4.74; 95% CI 1.027–21.9) were found to be significant risk factors. The homozygous G/G genotype, on the contrary, had a protective effect against the development of pathology (OR=0.67; 95% CI: 0.199–0.709) (Table 5.1.4) .

Table 5.1.4

Distribution of the MBOAT7 gene rs641738 polymorphism in the case and control groups

rs641738	Main group n=98	%	Comparison group n=70	%	χ^2	*P*	*(Relative risk) RR*		*(odds ratio) OR*	
							Value	95% CI	Value	95% CI
Alleles										
G	127	64.8	114	81 , 4	11.1	0.0 01	0.7	0.611-0.862	0.42	0.25-0.74
T	69	35.2	26	18 , 8			1.38	1.16-1.64	2.38	1.42-3.99
Genotypes										
G/G	41	41.8	46	65.7	7.8	0.006	0.67	0.514-0.872	0.375	0.199-0.709
G/ T	45	45.9	22	31.4	3.5	0.06	1.28	0.997-1.643	1.8	0.975-3.521
T/T	12	12.2	2	2.9	4.7	0.03	1.54	1.2-1.98	4.74	1.027-21.9

In addition, the main group of patients was divided into two subgroups according to the presence of steatohepatitis in addition to steatosis, which was determined based on the course of the disease and the results of instrumental examinations. In this grouping of patients, a simpler classification was used, developed by Matteoni et al. According to it, NAFLD is divided into 4 types: the first type is steatosis or simple fatty liver, the second type is steatohepatitis (inflammation is added to the process), the third type is steatonecrosis (multiple necrosis of liver cells is added to the process), and the fourth type is steatonecrosis with Mallory hyaline or fibrosis.

The aim of this study was to determine the differences in OR and other statistical indicators between groups by studying the prevalence of alleles and genotypes of the MBOAT7 gene rs641738 polymorphism in small groups. This also allows us to determine whether the studied gene polymorphism can induce

inflammation and other pathological processes in the liver in addition to hepatic hepatosis.

The first subgroup included 67 patients with nonalcoholic steatosis, and the second subgroup included 31 patients with steatohepatitis. Then, the prevalence of alleles and the distribution of genotypes in both groups were examined according to the Hardy-Weinberg law. According to it, the results obtained from the first subgroup corresponded to the Hardy-Weinberg law, since there was no significant difference between the empirical and theoretically expected results observed during the study (χ^2 =0.092, P= 0.95), i.e., the number of homozygous wild-type and mutant homozygous genotypes was found to be lower than the expected empirical results (G / *G* 0.433 and 0.441; T/T 0.130 and 0.133), which indicates that homozygous genotypes are relatively rare in the first group of patients, and the results obtained for the heterozygous genotype exceed the theoretically expected results (G/T 0.464 and 0.446) (Table 5.1.5).

It was also found that the results obtained from the group of patients with nonalcoholic steatohepatitis of the liver also corresponded to the Hardy-Weinberg law, confirming that in this subgroup, unlike the subgroup with nonalcoholic steatosis, the number of patients with heterozygous genotypes was lower than the expected theoretical result (G/T 0.452 and 0.474, respectively), and the result of homozygous genotypes exceeded it (G / *G , respectively).* 0.387 and 0.376; T/T 0.161 and 0.15) (Table 5.1.6).

Table 5.1.5

according to the Hardy-Weinberg law in the first subgroup (df=1)

NA steatosis HWE				
Alleles	Percentage distribution			
G	66.4%			
T	33.6%			
Genotypes	Observable	Expected	χ^2	P-value

Genotype G / ***G***	0, 433	0.441	0.066	0.798
Genotype G ***/T***	0.464	0.446	0.065	0.799
Genotype ***T/T***	0.103	0.113	0.161	0.688
Total	1.0	1.0	-	-

In the first subgroup, when examining the association between the MBOAT7 gene rs641738 polymorphism and nonalcoholic steatosis, the wild G allele was detected in 66.4% of patients, and the mutant T allele in 33.6%.

Table 5.1.6

the Hardy-Weinberg law test in the second subgroup

(df=1)

NA steatohepatitis HWE				
Alleles	Percentage distribution			
G	61.3%			
T	38.7%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype **G / G**	0.387	0.376	0.069	0.793
Genotype G ***/T***	0.452	0.474	0.065	0.799
Genotype ***T/T***	0.161	0.15	0.111	0.740
Total	1.0	1.0	-	-

Analysis of these results showed that the wild allele plays a protective role in the pathogenesis of the disease (odds ratio - 0.45 ; 95% CI: 0.258–0.787), while the mutant allele has an increasing effect on the risk of developing the disease (OR = 2.21; 95% CI: 2.21 1.27–3.869). The association between the alleles and the disease was statistically significant and reliable ($\chi^2 = 8$; P = 0.005) (Table 5.1.7).

In the first subgroup, when the distribution of the MBOAT7 gene rs641738 polymorphism by genotype was studied, the wild G/G genotype was significantly more common in the control group (65.7% and 43.3%). At the same time, the

protective role of the wild homozygous genotype in the pathogenesis of non-alcoholic steatosis was statistically significant (OR=0.4 95% CI: 0.2–0.79; $\chi^2 = 6.95$ p= 0.009). On the other hand, although the prevalence of homozygous mutant and heterozygous genotypes was found to be more common in the first subgroup than in the control group (10.3% and 46.4%, respectively, while in the control group these indicators were 2.9% and 31.4%), their disease-inducing effect was found (OR=1.88; 95% CI: 0.936–3.771 for heterozygous genotype, OR=3.97; 95% CI: 0.793–19.832), the statistical reliability of these results was not confirmed (χ^2 <3.84; P> 0.05) (Table 5.1.7).

On the other hand, when the distribution of wild and mutant alleles of the MBOAT7 gene rs641738 polymorphism was studied in the second subgroup, it was found that the prevalence of the mutant allele was twice as high in patients with nonalcoholic steatohepatitis compared to the control group (38.7% and 18.8%), while the prevalence of the wild allele was predominant in the control group with 81.4% (this figure was 61.3% in the nonalcoholic steatohepatitis group). Meanwhile, the pathogenetic significance of the alleles was examined and it was found that the mutant allele had an inducing effect, increasing the relative risk of developing the disease by 1.92 (95%CI: 1.29–2.861) times and the odds ratio by 2.78 (95%CI: 1.424–5.386) times, while the wild G allele had a strong protective role in the development of the disease (OR=0.36; 95% CI: 0.196–0.702). The statistical significance of the results was also confirmed ($\chi^2 = 9.4$ p= 0.003).

According to the genotype analysis, 38.7% of patients in the group with nonalcoholic steatohepatitis had the G/G genotype, 16.1% had the T/T genotype (these indicators were 65.7% and 2.9% in the control group, respectively). The results of the heterozygous genotype analysis were recorded in 31.4% of cases in the control group and 45.2% in the group with nonalcoholic steatohepatitis. It was confirmed that the G/G genotype significantly reduces the likelihood of developing the disease ($\chi^2 =6.4$ p= 0.012), that is, it has a protective effect (OR=0.33; 95%CI: 0.137–0.791).

Table 5.1.7

Distribution of the MBOAT7 gene rs641738 polymorphism in the subgroup with non-oncological steatosis and the control group

rs641738	NA steatosis group n=67	%	Comparison group n=70	%	χ^2	*P*	*(Relative risk) RR*		*(odds ratio) OR*	
							Value	95% CI	Value	95% CI
Alleles										
G	89	66.4	114	81,4	8.0	0.005	0.7	0.547-0.875	0.45	0.258-0.787
T	45	33.6	26	18,8			1.45	1.142-1.83	2.21	1.27-3.869
Genotypes										
G/G	29	43.3	46	65.7	6.95	0.009	0.63	0.446-0.893	0.4	0.2-0.79
G/ T	31	46.4	22	31.4	3.18	0.075	1.36	0.976-1.90	1.88	0.936-3.771
T/T	7	10,3	2	2.9	3.21	0.074	1.66	1,118-2,463	3.97	0.793-19.832

On the other hand, a direct (OR=6.54; 95%CI: 1.193–35.83) statistically significant (χ^2 =5.8 p= 0.016) association was found between the T/T genotype and the onset of the disease. Although the heterozygote prevalence was higher in the nonalcoholic steatohepatitis group, no significant association was found between this genotype and the development of the disease (χ^2 <3.84 p> 0.05) (Table 5.1.8).

Table 5.1.8

Distribution of MBOAT7 gene rs641738 polymorphism in nonalcoholic steatohepatitis subgroup and control group

rs641738	NA Steatohepatitis group n=31	%	Comparison group n=70	%	χ^2	*P*	*(Relative risk) RR*		*(odds ratio) OR*	
							Value	95% CI	Value	95% CI
For alleles										

G	38	61.3	114	81 , 4	9.4	0.003	0.52	0.35-0.776	0.36	0.186-0.702
T	24	38.7	26	18 , 8			1.92	1.29-2.861	2.78	1,424-5,386
For genotypes										
G/G	12	38.7	46	65.7	6.4	0.012	0.47	0.256-0.858	0.33	0.137-0.791
G/ T	14	45.2	22	31.4	1.76	0.18	1.48	0.834-2.65	1.8	0.754-4.284
T/T	5	16.1	2	2.9	5.8	0.016	2.58	1.45-4.572	6.54	1,193-35,83

Analysis of the results of the study allows us to conclude that there is a positive association between nonalcoholic fatty liver disease and the mutant T allele and homozygous mutant T/T genotype of the rs641738 polymorphism of the MBOAT7 gene. In addition, in patients with nonalcoholic fatty liver disease, divided into two subgroups according to the presence of an inflammatory process, there was a statistically significant direct positive association between the mutant allele and the mutant homozygous genotype of the rs641738 polymorphism of the MBOAT7 gene and patients with nonalcoholic steatohepatitis, on the other hand, there was no statistically significant association between patients with nonalcoholic fatty liver disease without inflammation and the tested gene polymorphism.

Numerous studies have shown a positive association between the MBOAT7 gene rs641738 polymorphism and NAFLD. In particular, Mancina et al. confirmed that the MBOAT7 gene rs641738 polymorphism increases the risk of NAFLD in the European population [181,186, 203,206,211]. In addition, the gene polymorphism presented by di Costanzo et al. in the Caucasian population and by Kawaguchi et al. in Asians was shown to increase the risk of NAFLD [186, 203,206,211]. A positive association between the MBOAT7 gene rs641738 polymorphism and steatohepatitis has also been confirmed in some studies [206,211].

The MBOAT7 (Membrane-bound protein 7 O-acetyltransferase domain) gene is located at locus 19q13.42 and expresses the enzyme lysophosphatidylinositol acyltransferase, the main function of which is to regenerate the acyl moiety of phospholipids, which are important components of the cell membrane, using the substrates lysophosphatidylinositol, acyl-CoA, and arachidonic-CoA , thereby controlling the concentration of free arachidonic acid in the cell (Land's cycle, Figure 6.1.2). Since arachidonic acid is a pro-inflammatory metabolite (various pro-inflammatory factors, in particular prostaglandins and leukotrienes, are synthesized from arachidonic acid by the enzymes lipoxygenase and cyclooxygenase), an increase in its concentration can create conditions for the formation of many inflammatory mediators, thereby causing inflammation. Therefore, it is very important to control its concentration inside the cell [181,186, 203,206,211].

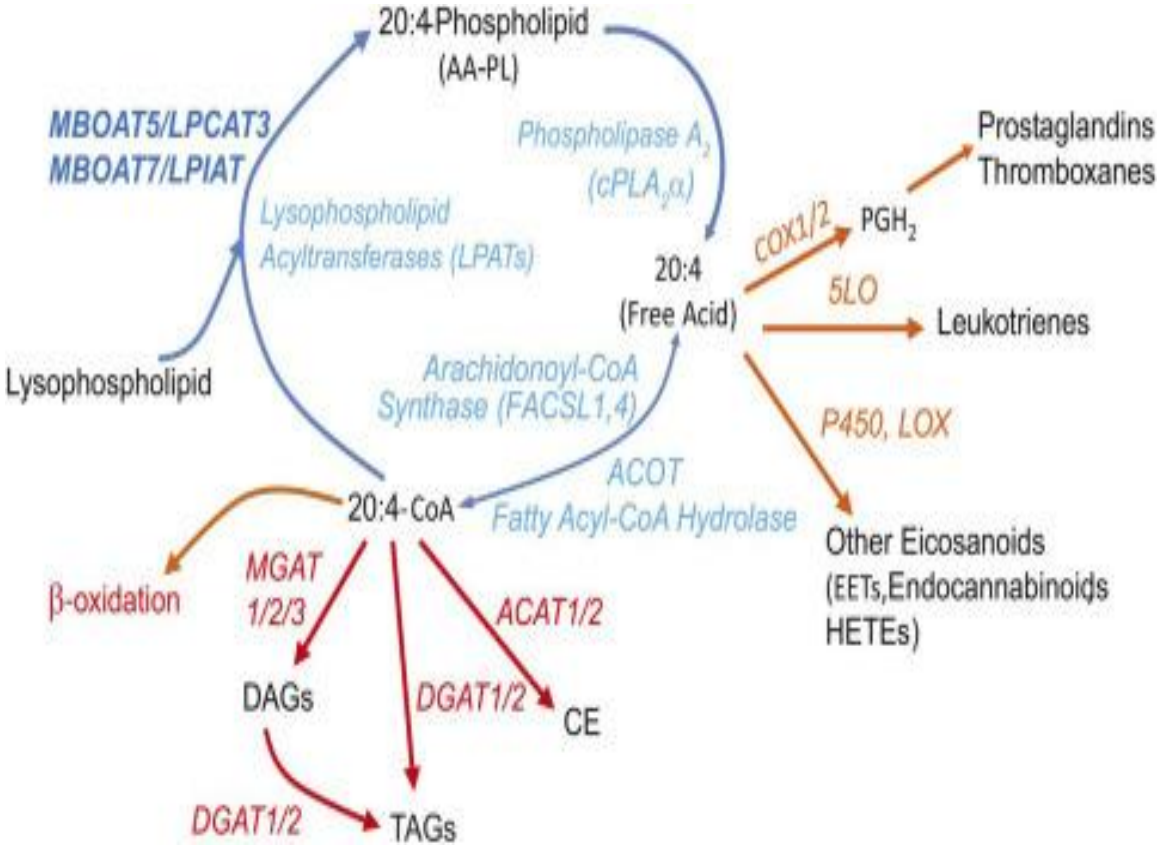

Figure 5.1.2. Arachidonic acid is converted to complex phospholipid esters, which are components of cell membranes, by lysophosphatidyl acyltransferase enzymes (MBOAT7 and MBOAT5). On the other hand, free arachidonic acid is a substrate for various prostaglandins and leukotrienes [203,206,211,235,245] .

According to the literature, the T minor allele of the rs641738 G>T polymorphism in the MBOAT7 gene causes a Gly17Glu amino acid change in the protein expressed from it, resulting in a decrease in MBOAT7 expression in the cell compared to the wild-type allele [203,206,211,235,245]. As a result, the concentration of free arachidonic acid and inflammatory markers synthesized from it (prostaglandins and leukotrienes) increases inside the cell [211,235,245]. This, in turn, causes inflammatory diseases in the liver, creating conditions for the development of steatohepatitis. This study showed a strong positive association between the mutant T/T genotype of the MBOAT7 gene rs641738 polymorphism and the occurrence of nonalcoholic steatohepatitis ($\chi^2 = 5.8$ p= 0.016).

Considering that the MBOAT7 gene rs641738 polymorphism can cause nonalcoholic steatohepatitis over time by inducing an inflammatory process in hepatocytes (according to some studies, steatosis can also turn into steatohepatitis after a certain time), markers of inflammation-induced cytolysis in liver cells were compared between patients with different genotypes in the main group and the control group (Table 5.1.9).

Table 5.1.9

Differences in the amount of cytolysis markers in different groups of patients according to the genotypes of the MBOAT7 gene rs641738 polymorphism, M±m

Indicators	A group of patients with steatosis (n = 67)			Control group (n=70)
	T/T genotype (n=7)	T/ G genotype (n=31)	G / G genotype (n=29)	
ALT (TB/L)	33.93±0.92 [ac]	30.64±1.28 [a]	24.91±0.7	17.6±0.06
AST (TB/L)	27.07±1.18 [ac]	23.07±0.92 [a]	19.45±0.80	20.9±0.09
IF (TB/L)	144.20±4.5 [units]	140.75±2.34 [a]	127.94±1.84	121.94±0.42
γ-GTP (TB/L)	47.73±2.38 [acre]	38.48±1.47 [a]	31.83±1.16	24.9±0.09
Indicators	A group of patients with steatohepatitis (n =31)			Control group (n=70)
	T/T genotype	T/C genotype	C/C genotype	

	(n=5)	(n=14)	(n=12)	
ALT (TB/L)	119.4±0.47 [ac]	94.72±2.4 [a]	67.89±2.74	17.6±0.06
AST (TB/L)	67.74±1.89 [acre]	50.7±2.92 [a]	40.86±2.16	20.9±0.09
IF (TB/L)	173.84±2.76 [acres]	149.73±3.43 [b]	142.28±2.17	121.94±0.42
γ-GTP (TB/L)	112.78±0.68 [ac]	67.76±3.6 [b]	65.07±3.98	24.9±0.09

Note : a – when compared to the G / G genotype, p <0.05; b – when compared to the G / G genotype, p>0.05; c – when compared to the G /T genotype, p <0.05; d – when compared to the G /T genotype, p>0.05.

It can be seen from the table that in the group of patients with steatosis (n=67) the levels of ALT, AST, IF and γ-GTP enzymes were significantly and statistically significantly higher in the mutant homozygous T/T and heterozygous groups than in the normal homozygous G/G group for these enzymes ($p<0.05$), while the T/T genotype had an advantage over the G/T genotype in terms of the results of ALT, AST and γ-GTP enzymes ($p<0.05$). On the other hand, in the group of patients with steatohepatitis, the difference in the results of these enzymes for different genotypes was even more pronounced, and while the results for ALT in the mutant T/T genotype were 2 times higher than the results obtained in patients with the G/G genotype ($p<0.05$), patients with the S/T genotype showed a result that was almost 1.5 times higher ($p<0.05$). Similarly, in the AST enzyme results, mutant homozygous - T/T and heterozygous patients had statistically significant superiority over normal homozygous patients, but the difference in the results obtained for the IF and γ-GTP enzymes was statistically significant only between homozygous mutant patients and homozygous normal patients ($p<0.05$).

Currently, although the role of arachidonic acid imbalance in the MBOAT7 gene rs641738 polymorphism in the development of NAFLD has not been scientifically explained, in our opinion, the imbalance in the amount of intracellular arachidonic acid induced by the MBOAT7 gene rs641738 polymorphism results in the excessive production of inflammatory factors and chronic hypersecretion of some proinflammatory cytokines by cells and tissues. According to the literature, chronic hypersecretion of proinflammatory cytokines, in particular, IL-6, causes insulin resistance [181,186, 203,206,211,235,245]. It is known that insulin

resistance plays an important role in the development of NAFLD [118, 158,163]. In addition, MBOAT7 deficiency causes liver cell damage. induces hepatocytes to insulin resistance by disrupting the normal metabolism of phosphatidylinositol (FI) and lysophosphatidylinositol (LFI). By doing so, liver cells are predisposed to non-alcohol-dependent fat accumulation [181].

To determine this, the relationship between genotype distribution and cytokine levels in different groups of patients was determined (Table 5.1.10).

Table 5.1.10

Differences in proinflammatory cytokines and insulin resistance test results in different groups of patients according to the genotypes of the MBOAT7 gene rs641738 polymorphism, M±m

Indicators	A group of patients with steatosis (n = 67)			Control group (n=70)
	T/T genotype (n=7)	T/ G genotype (n=31)	G / G genotype (n=29)	
ONO – α (pg/ml)	54.00±2.79 [a c]	42.11±1.05 [a]	39.02±1.1	4.58±0.1 5
IL- 6 (pg/ml)	42.61±3.51 [a]	37.24±1.36 [a]	24.03±1.47	4.16±0.14
HOMA - IR (pg/ml)	6.07±0.11 [ac]	5.59±0.13 [b]	5.52±0.077	2.29 ± 0.038
Indicators	A group of patients with steatohepatitis (n =31)			Control group (n =70)
	T/T genotype (n =5)	T/ G genotype (n =1 4)	G / G genotype (n=12)	
ONO – α (pg/ml)	66.0±5.59 [ac]	52.36±4.2 [a]	35.83±2.5	4.58±0.1 5
IL- 6 (pg/ml)	49.29±4.49 [a]	38.58±4.3 [a]	32.42±2.9	4.16±0.14
HOMA - IR (pg/ml)	8.50±0.13 [ac]	7.68±0.12 [b]	7.4±0.17	2.29 ± 0.038

Note : a – when compared to the C/C genotype, p<0.05; b – when compared to the C/C genotype, p>0.05; c – when compared to the C/T genotype, p<0.05; d – when compared to the C/T genotype, p>0.05.

It can be seen from the table that in both subgroups, the T/T mutant homozygous genotype had a statistically significant superiority in terms of proinflammatory cytokine levels and insulin resistance test (HOMA-IR) over the results obtained from patients with normal homozygous and heterozygous genotypes ($p<0.05$). On the other hand, such a significant superiority was found only in terms of cytokine levels when comparing heterozygous and homozygous normal G/G genotypes, while the difference in HOMA-IR test did not confirm the reliability between the two genotypes ($p>0.05$) (Table 5.1.10). Also, when comparing patients with T/T or T/G genotypes in the steatohepatitis and steatosis groups according to the presented indicators, a significant statistical difference was found in terms of ONO-α and HOMA-IR indicators ($p<0.05$), and representatives of the first subgroup prevailed. Interestingly, the results obtained from patients with steatohepatitis and steatosis with a normal homozygous genotype were dominated by the second group (UNO – α – $p<0.05$; IL – 6 – $p>0.05$; HOMA-IR – $p<0.05$). These results indicate that the MBOAT7 gene rs641738 polymorphism may increase the risk of developing NAFLD by increasing the secretion of inflammatory cytokines and causing insulin resistance.

Another initiating effect of MBOAT7 deficiency in the pathogenesis of fatty liver is the disruption of the normal balance of lipogenic and lipolytic gene expression. Various studies have shown that in hepatocytes with MBOAT7 deficiency, one of the lipogenic enzymes, stearoIL-CoA desaturase , is expressed more and other lipolytic enzymes are expressed less. This slows down the oxidation of free fatty acids and their accumulation in liver cells under the influence of lipogenic substances can lead to the development of fatty liver [203,206,207]. It is known that the slowing down of fat oxidation is manifested by obesity and increased blood triglyceride concentrations.

Table 5.1.11 presents the results of a study of the distribution of different genotypes of the MBOAT7 gene rs641738 polymorphism and the relationship between body mass index (BMI) and triglyceride levels in small groups of patients.

Table 5.1.11

Differences in TVI and triglyceride levels according to different genotypes of the MBOAT7 gene rs641738 polymorphism in a small group of patients, M±m

Indicators	A group of patients with steatosis (n = 67)			Control group (n=70)
	T/T genotype (n=7)	T/ G genotype (n=31)	G / G genotype (n=29)	
TVI	35.78 ± 1.45 units	34.31 ± 1.09 [a]	27.55 ± 0.52	20.9 ± 0.15
TG (g/l)	1.85 ± 0.04 units	1.81 ± 0.03 [b]	1.73 ± 0.02	0.93 ± 0.001
Indicators	A group of patients with steatohepatitis (n =31)			Control group (n =70)
	T/T genotype (n =5)	T/ G genotype (n =1 4)	G / G genotype (n=12)	
TVI	38.5 ± 1.12 [ac]	32.90 ± 0.71 [a]	29.22 ± 0.97	20.9 ± 0.15
TG (g/l)	2.09 ± .0.03 units	2.02 ± 0.04 [a]	1.91 ± 0.02	0.93 ± 0.001

Note : a – when compared to the G / G genotype, p <0.05; b – when compared to the G / G genotype, p>0.05; c – when compared to the G /T genotype, p <0.05; d – when compared to the G /T genotype, p>0.05.

As shown in the table, in both groups of patients with the MBOAT7 gene rs641738 polymorphism, patients with the T/T genotype had a superiority over patients with the G/G genotype in terms of TVI and TG concentration (p<0.05). On the other hand, a statistically significant difference in the results between heterozygous and normal G/G genotype patients was detected only in the

steatohepatitis group, while the steatosis group had a superiority over the G/G genotype in terms of TVI only ($p<0.05$).

Thus, the MBOAT7 gene rs641738 polymorphism can cause various metabolic disorders in homozygous mutant T/T cells, in particular, as a result of impaired synthesis of phospholipids that are part of the cell membrane from arachidonic acid, its intracellular proliferation and the formation of numerous inflammatory factors, prostaglandins and leukotrienes, which can induce inflammation, as well as the accumulation of fat in hepatocytes and inflammation as a result of decreased lipolytic processes and increased lipogenesis. The results of this study confirmed the existence of a positive statistically significant association between the MBOAT7 gene rs641738 polymorphism and NAFLD, and this association is especially pronounced in patients with nonalcoholic steatohepatitis.

5 .2- § . The significance of the GCKR gene rs1260326 polymorphism in the development of nonalcoholic fatty liver disease

Another gene that increases the susceptibility to the development of NAFLD is the GCKR (Glucokinase Regulatory protein gene) rs1260326 (P446L) polymorphism. In order to study the relationship between the GCKR gene rs1260326 polymorphism and NAFLD, this gene polymorphism was tested in all (98) patients included in the study. The same test was carried out in practically healthy individuals in the control group (70 people). According to the results obtained, in the control group, the GCKR gene rs1260326 polymorphism, according to the allele distribution, was the wild G allele - 83.6%, and the minor allele T - 16.4%. Also, according to the distribution of genotypes, the frequency of occurrence of the wild G/G homozygous genotype was 70.0%, T/G heterozygous genotype was 27.1%, and the homozygous mutant T/T genotype was 2.9% (Figure 5.2.1). The occurrence of the minor allele in 16.4% of cases in this study is close to the prevalence of the studied gene polymorphism in various populations in South Asians.

When analyzing the allele distribution of the GCKR gene rs1260326 polymorphism in blood cells of 98 patients with CLL (the main group), the wild G allele was detected in 74.5%, and the minor T allele in 25.5% (Fig. 5.2.1). This showed that the frequency of the G allele decreased by 1.12 times compared to the control group, and the frequency of the T allele increased by 1.55 times. Also, according to the distribution of genotypes, the frequency of the wild C/C homozygous genotype was 57.1%, the heterozygous T/C and homozygous mutant T/T genotypes were 24.7% and 8.2%, respectively. The obtained results slightly differed from the control group, that is, the occurrence of the S/S homozygous genotype decreased by 1.23 times, the occurrence of the T/S heterozygous genotype did not change much, and the occurrence of the mutant T/T genotype increased by 2.83 times.

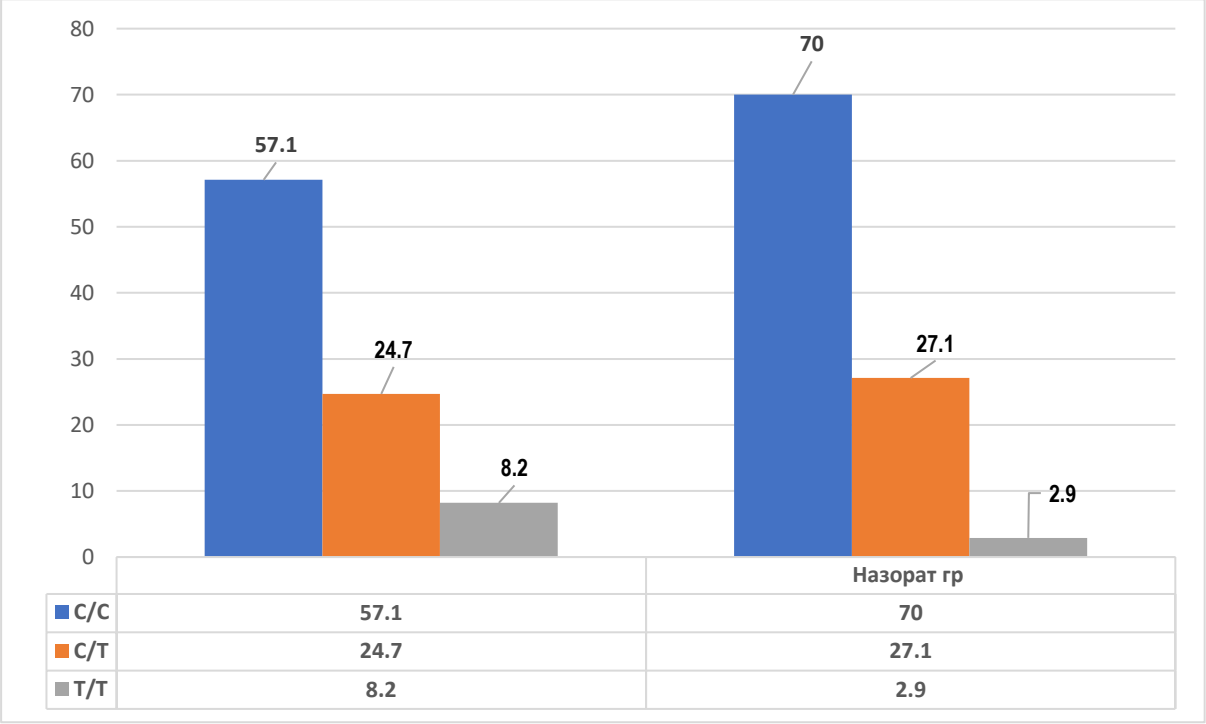

Figure 5.2.1. Distribution of different genotypes of the GCKR gene rs1260326 polymorphism in patients and controls

The results obtained during the study were checked according to the Hardy-Weinberg law. The results obtained showed that no statistically significant deviations from this law were detected ($\chi^2 < 3.84$ $p > 0.05$) and the compliance of the results obtained in this study with the Hardy-Weinberg law was confirmed. In particular, the results observed for homozygous genotypes in the main group

exceeded the results theoretically calculated for the corresponding genotypes according to the Hardy-Weinberg law (for the G/G genotype - 0.571 and 0.555; for the T/T genotype - 0.082 and 0.065) (Table 5.2.1). In addition, the observed heterozygous genotype indicator of the tested polymorphism had a negative coefficient of deviation from the expected result D = -0.086. This indicates a lack of patients with heterozygous genotypes in the tested group.

Table 5.2.1

Observed – empirical and expected – theoretical indicators in the main group for the GCKR gene rs1260326 polymorphism (df=1)

Main group HWE				
Alleles	Percentage distribution			
G	74.5%			
T	25.5%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype G / *G*	0.571	0.555	0.083	0.773
Genotype G / *T*	0.347	0.38	0.199	0.656
Genotype *T/T*	0.082	0.06 5	0.308	0.579
Total	1.0	1.0	-	-

The results from the control group also showed that the GCKR gene rs1260326 polymorphism obeyed the Hardy-Weinberg law. According to this, the theoretically expected homozygous wild-type and mutant genotypes (0.70 and 0.029, respectively) and the observed empirical homozygous genotypes (0.69 and 0.027, respectively) were also found to prevail in the control group (Table 5.2.2).

It was found that the observed results for heterozygous genotypes were less than the theoretical results expected – D=0–.015 (Table 5.2.3).

Table 5.2.2

Empirical and expected theoretical parameters of the GCKR gene rs1260326 polymorphism observed in the control group (df=1)

Control group HWE				
Alleles	Percentage distribution			
G	83.6%			
T	16.4%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype G */ **G***	0.70	0.698	0.000	1,000
Genotype G */**T***	0.271	0.275	0.000	1,000
Genotype ***T/T***	0.029	0.027	0.000	1,000
Total	1.0	1.0	-	-

.

Table 5.2.3

Difference between empirical and expected theoretical results of heterozygous genotype in main and control group

Groups	Observable	Expected	D*
Main group	0.347	0.38	0.086
Control group	0.271	0.275	-0.015

Formula: $D=(H_{obs}-H_{exp})/H_{exp}$.*

When studying the relationship between the indicators of the GCKR gene rs1260326 polymorphism obtained from the main and control groups and the occurrence of NCDs, it was found that the G wild-type gene allele plays a protective role in the occurrence of the disease, while the T allele has a relatively increased risk of developing NCDs in patients with a pro-inflammatory effect, and the probability of developing the disease in the main group was 1.23 times higher in relative risk (95%CI: 1.0–1.49), 1.74 times higher in odds ratio (95%CI: 1.0–3.02), while the presence of the wild-type allele reduced the risk of developing the disease by almost 20% (RR=0.8; 95% CI: 0.67–0.98), and almost two times higher in odds ratio (OR=0.57; 95% CI: 0.331–0.99). The statistical significance of these results,

determined for alleles in the studied gene polymorphism, was confirmed (χ^2 =3.9 p= 0.047) (Table 5.2.4).

Also, when studying the pathogenetic significance of the results obtained on the distribution of genotypes in NAFLD, it was found that the wild homozygous G/G genotype reduces the risk of developing the disease (RR=0.8; 95% CI: 0.623–1.027; OR=0.46; 95% CI: 0.244–0.871), while the heterozygous G/T and mutant homozygous T/T genotypes increase the risk of developing the disease (for G/T – RR=1.15; 95% CI: 0.890–1.49; OR=1.43; 95% CI: 0.729–2.79 and for T/T genotype – RR=1.4; 95% CI: 1.0=1.97; OR=3.0; 95% CI: 0.62–14.7), the studied gene polymorphism The correlation between genotypes and disease development was not found to be statistically significant and reliable (χ^2 <3.84; p> 0.05) (Table 6.2.4).

Table 5.2.4

Distribution of the GCKR gene rs1260326 polymorphism in the case and control groups and its association with the occurrence of NCDs

rs1260326	Main group n=98	%	Comparison group n=70	%	χ^2	*P*	*(Relative risk) RR*		*(odds ratio) OR*	
							Value	95% CI	Value	95% CI
For alleles										
G	146	74.5	117	83.6	3.9	0.047	0.81	0.67-0.98	0.57	0.331-0.99
T	50	25.5	23	16.4			1.23	1.0-1.49	1.74	1.0-3.02
For genotypes										
G/G	56	57.1	49	70	2.8	0.09	0.8	0.623-1.027	0.46	0.244-0.871
G/ T	34	34.7	19	27.1	1.1	0.3	1.15	0.890-1.49	1.43	0.729-2.79
T/T	8	8.2	2	2.9	2.0	0.15	1.4	1.0-1.97	3.0	0.62-14.7

As mentioned above, to study the relationship between the GCKR gene rs1260326 polymorphism and NAFLD , the main group of patients was divided into subgroups based on the NAFLD classification developed by Matteonni et al., and thus the relationship of the studied gene polymorphism with the occurrence of the

disease in different groups and the pathogenetic effect (steatosis or steatohepatitis) that may be responsible for the onset of the disease were examined.

The first subgroup included 67 patients with nonalcoholic steatosis. According to the allele distribution in this group, the wild allele was 73.1%, and the mutant allele was 16.4%. In addition, the prevalence of G/G, G/T, and T/T genotypes in the first subgroup was 55.2%; 35.8%, and 9%, respectively.

The obtained data were checked according to the Hardy-Weinberg law and it was found that the results determined in this study were not statistically significantly different from the expected theoretical results - obeying the Hardy-Weinber law (Table 5.2.5).

Table 5.2.5

Observed empirical and expected theoretical indicators in the first subgroup for the GCKR gene rs1260326 polymorphism (df=1)

Non-alcoholic steatosis group patients HWE				
Alleles	Percentage distribution			
G	73.1			
T	26.9			
Genotypes	Observable	Expected	χ^2	P-value
Genotype G / ***G***	0.552	0.534	0.030	0.862
Genotype G /***T***	0.358	0.393	0.128	0.721
Genotype ***T/T***	0.09	0.072	0.099	0.753
Total	1	1	-	-

When studying the pathogenetic significance of the introduced alleles, it was found that the wild C allele has a protective effect in the development of non-inflammatory NAFLD (OR=0.54; 95% CI: 0.297–0.963), while the minor T allele increases the risk of developing the disease (OR=1.87; 95% CI: 1.038–3.364).

The statistical reliability of these results was confirmed (χ^2 =4.4 p= 0.036). According to the distribution of genotypes in the first subgroup, the prevalence of the wild homozygous G/G genotype was lower than that found in the control group (70% and 55.2%, respectively). Also, the prevalence of the G/T and T/T genotypes

in patients in the first subgroup was higher than in the control group (G/T – 35.8% and 27.1%, T/T – 9% and 2.9%).

In the first subgroup, different genotypes of the studied gene polymorphism and their pathogenetic significance in causing the disease were analyzed. Although the relative risk and odds ratio showed that the C/C genotype was protective in the first subgroup of patients with nonalcoholic steatosis (RR=0.73; 95% CI: 0.523–1.022 and OR=0.53; 95% CI: 0.262–1.067), while the heterozygous and mutant homozygous genotypes had an increased risk of the disease (for the C/T genotype, RR=1.22; 95% CI: 0.864–1.723 and OR=1.5; 95% CI: 0.725–3.096 and for the T/T genotype, RR=1.58; 95% CI: 1.022–2.46 and OR=3.3; 95% CI: 0.65–17.2), these results were not statistically significant (χ^2 <3.84; p> 0.05) (Table 5.2.6).

The second subgroup included 31 patients with nonalcoholic steatohepatitis, and the relationship between the development of the disease and the GCKR gene rs1260326 polymorphism was examined . According to the distribution of alleles in this group of patients, the wild C allele was 77.4%, and the wild T allele was 22.6%. The results did not differ significantly from the control group (in the control group, these indicators were 82.9% and 17.1%, respectively). In addition, according to the distribution of genotypes, in the second subgroup, the G/G genotype was 61.3%, the G/T genotype was 32.3%, and the T/T genotype was 6.4% (in the control group, these indicators were 68.6%; 28.6% and 2.8%, respectively).

Table 5.2.6

Distribution of the GCKR gene rs1260326 polymorphism in the first subgroup and control groups and its significance in the etiology of nonalcoholic steatosis

rs1260326	First small group n=67	%	Comparative group n=70	%	χ2	P	(Relative danger) RR		(Probably ratio) OR	
							Value	95% CI	Value	95% CI
Alleles for										
G	98	73.1	117	83.6	4.4	0.036	0.75	0.581-0.96	0.54	0.297-0.96
T	36	26.9	23	16.4			1.34	1.0-1.72	1.87	1.03-3.36
Genotypes for										

G / G	37	55.2	49	70	2.7	0.1	0.73	0.523-1.02	0.53	0.262-1.067
G /T	24	35.8	19	27.1	1.2	0.27	1.22	0.864-1.72	1.5	0.725-3.096
T/T	6	9	2	2.9	2.3	0.13	1.58	1.022-2.46	3.3	0.65-17.2

In order to exclude the possibility of various errors in the results obtained, they were checked using the Hardy-Weinberg formula and found to comply with the given law ($\chi^2 < 3.84$; $p > 0.05$) (Table 6.2.7).

Table 5.2.7

Observed empirical and expected theoretical indicators of the GCKR gene rs1260326 polymorphism in the second subgroup (df=1)

non-alcoholic steatohepatitis group patients HWE				
Alleles	Percentage distribution			
G	77.4			
T	22.6			
Genotypes	Observable	Expected	χ^2	P-value
Genotype G / ***G***	0, 613	0.60	0.069	0.793
Genotype G ***/T***	0, 323	0.35	0.072	0.788
Genotype ***T/T***	0.0 64	0.05	0.350	0.554
Total	1	1	-	-

Although the relative risk and odds ratios for the presence of a protective effect of the wild-type allele on disease development and an inducing effect of the mutant allele were recognized, the statistical significance of the association between them was not confirmed. As shown in Table 5.2.8, no reliable correlation was found between different genotypes of the examined gene and the origin of the disease.

Table 5.2.8

Distribution of the GCKR gene rs1260326 polymorphism in the second subgroup and control groups and its significance in the etiology of nonalcoholic steatohepatitis

rs1260326	The second subgrou	%	Comparison group n=70	%	χ^2	***P***	***(Relative risk) RR***	***(odds ratio) OR***

	p n=31						Valu e	95% CI	Valu e	95% CI
For alleles										
G	48	77.4	117	83.6	0.83	0.36	0.77	0.477-1.24	0.67	0.32-1.42
T	14	22.6	23	16.4			1.3	0.807-2.09	1.48	0.705-3.12
For genotypes										
G/G	19	61.3	49	70	0.74	0.39	0.76	0.42-1.38	0.67	0.28-1.645
G/ T	10	32.3	19	27.1	0.27	0.6	1.18	0.638-2.19	1.27	0.51-3.20
T/T	2	6.4	2	2.9	0.73	0.39	1.6	0.599-4.67	2.3	0.315-17.5

Meta-analysis of the GCKR gene rs1260326 polymorphism revealed mixed results regarding the association between the polymorphism and NAFLD. In particular, a study conducted among Chinese subjects found a positive association between the GCKR gene rs1260326 polymorphism and NAFLD, and a higher plasma triglyceride level than controls [172], and a similar positive association was found among Asians [216,225]. Also, studies conducted by other Chinese scientists did not find an association between the GCKR gene rs1260326 polymorphism and the development of NAFLD, and only an association was noted between the levels of TVI, plasma glucose, and triglycerides with the polymorphism [172,225].

The GCKR gene is located at locus 2p23 and encodes a 686-amino acid protein with a molecular weight of 68 kDa and consists of 19 exons [10]. The main function of the GCKR gene is to inhibit the glucokinase enzyme in hepatocytes by noncovalent binding to it. The glucokinase enzyme phosphorylates glucose in hepatocytes, which leads to its intracellular accumulation and, thereby, glycogen synthesis. GCKR is an allosteric competitor of the glucokinase enzyme with glucose. Thus, in the absence of glucose, GCKR binds to glucokinase and inhibits it, resulting in the inhibition of glycogenesis. On the other hand, when glucose concentration increases, glucokinase is reactivated, thereby enhancing glycolysis and glycogenesis [216,225,227].

According to the literature, the rs1260326 polymorphism in the GCKR gene changes the nucleotide C to T and the 446th amino acid in the coding protein changes

proline to leucine. This weakens the normal activity of GCKR, and glucokinase retains its active state even in relatively low glucose concentrations, ensuring the abundant transfer of glucose into hepatocytes, increasing the concentration of glucose and malonyl-CoA inside the cell. This leads to an increase in the processes of glycogenesis and lipogenesis in hepatocytes, which, as a result, increases the susceptibility to the development of fatty hepatosis [216,225,227].

As mentioned above, several studies have found a positive association between the GCKR gene rs1260326 polymorphism and the development of NAFLD in some populations, as well as between triglyceride levels and TVI. In addition, some studies have shown that the conformational change of the protein expressed as a result of the T minor allele of the GCKR gene rs1260326 polymorphism also affects β cells. As a result, the regulation of GCK by GCKR in β cells may be disrupted, increasing the concentration of glucose inside the cell and, consequently, insulin hypersecretion. The chronic course of this condition leads to the development of insulin resistance and metabolic syndrome [227]. Therefore, differences in the distribution of the GCKR gene rs1260326 polymorphism G/G, G/T, and T/T genotypes, as well as some of their anthropometric and biochemical parameters, were compared in all patients in the main group (Table 5.2.9).

Table 5.2.9

of the GCKR gene rs1260326 polymorphism with biochemical and anthropometric parameters in patients with nonalcoholic fatty liver disease, M±m

Indicators	Main group (n=98)			Control group (n=70)
	T/T genotype (n=8)	T/ G genotype (n=34)	G / G genotype (n=56)	
TVI	34.89± 1 , 30 units	33.83±0.90 a	29.91±0.64	20.9 ± 0.15
TG (g/l)	1.90 ± 0.04 units	1,86 ± 0,029a	1.74 ± 0.016	0.93 ± 0.001
Glucose (mmol/l)	6.31 ± 0.15 units	6 , 33 ±0, 088 a	6.05 ± 0.055	4.44 ± 0.03

Insulin (McTB/ml)	16.64 ± 0.22 units	16 , 53 ± 0.29 b	16.01 ± 0.21	11.53 ± 0.09
HOMA-IR	6.50 ± 0.25 db	6.29 ± 0.14 b	6.22 ±0.14	2.29 ± 0.038
A LT (TB/l)	57.19 ± 7.4 bp	50.86 ± 3.95 b	47.46 ±3.1	17.6±0.06
A ST (TB/l)	35.85 ± 3.27 db	32.85 ± 2.96 b	28.30 ±2.06	20.9±0.09

Note: a – when compared to the G / G genotype, p <0.05; b – when compared to the G / G genotype, p>0.05; c – when compared to the G /T genotype, p <0.05; d – when compared to the G /T genotype, p>0.05.

It can be seen from the table that, according to the conducted study, patients with minor alleles (T/T and G/T) of the GCKR gene rs1260326 polymorphism had a statistically significant advantage over patients with homozygous normal genotypes in terms of TVI and plasma triglycerides. In addition, such a significant advantage was also confirmed for glucose indicators. In addition , it was found that among the different genotypes, only patients with homozygous mutant genotypes had an advantage over representatives of homozygous normal genotypes in terms of insulin levels ($p<0.05$), while the advantage shown by patients with heterozygous groups was not statistically significant ($p >0.05$). For the remaining parameters, no significant difference was found between patients with wild homozygous and minor alleles.

Thus, although the minor allele of the GCKR gene rs1260326 polymorphism was significantly more prevalent in the main group with a statistically significant difference, no statistically significant association was found between the distribution of genotypes in patients with the minor allele (G/T and T/T) and the development of NSCLC.

CHAPTER V *I.* CRITERIA FOR PREDICTING THE OUTCOMES OF NON-ALCOHOLIC FATTY LIVER DISEASE

6 . § 1. Clinical, laboratory and instrumental inspection methods comparative assessment based on disease consequences prophecy algorithm

According to the literature, the incidence of NCDs in outpatient visits to general practitioners is 27%. As is known, NCDs are an interdisciplinary pathology, and their diagnosis is carried out by the method of exclusion using a sequential algorithm.

The first phase of this study examined the prevalence of NASH by age. Then, the non-cirrhotic stages of NASH – nonalcoholic steatosis (NAS) and nonalcoholic steatohepatitis – were identified and assessed. During the first phase of the visit, basic patient information was collected.

Thus, the introduction of a new algorithm for the diagnosis of CKD allows for the diagnosis of a patient in an outpatient setting, reducing disability by 30%, predicting complications in advance, and ensuring high economic efficiency by reducing the cost of medical care and the working hours of medical personnel. Another notable practical achievement of this scientific research is that, based on the results obtained, it is possible to predict the type of complications of CKD and, on this basis, to eliminate various factors that cause them early.

CONCLUSION

Despite numerous studies, CJD remains one of the most pressing problems in modern gastroenterology. This is explained not only by the widespread prevalence of this disease, but also by the high mortality rate due to its dangerous complications (liver cirrhosis, hepatocarcinoma).

This research was conducted in the clinical base of the Bukhara State Medical Institute during 2019–2022 . To achieve the objectives of the research, 98 patients with NAFLD were recruited and selected based on the data from the proposed clinical classification of NAFLD [41:98–101]. 53 (54%) of the patients were female and 45 (46%) were male, and their age ranged from 20–75 (mean 49.2±4.2) years. Of the 98 patients with NAFLD included in the study, 67 (68.3%) had hepatic steatosis (HS) stage, Steatohepatitis (SH) stage was noted in 31 (31.6%) patients . The results of the examination were assessed using a clinical-information card (questionnaire). Consent was obtained from the members of the ethics committee established at the Bukhara Medical Institute for the study . To exclude alcoholic fatty liver disease, anamnesis (periodic abstinence from alcoholic beverages) was collected and selected using a special CAGE questionnaire [88,89].

To adequately assess the data obtained from the study, 70 practically healthy people aged 18–40 years (34.51±4.5) were selected for the control group (CG). Of these, 36 (51.4%) were women and 34 (48.5%) were men. All individuals in the CG had no complaints characteristic of liver diseases in the recent or long-term past, no history of chronic liver disease, and no disease was detected by instrumental methods used during the examination.

During the diagnosis of patients, anamnesis data were collected, laboratory and ultrasound examinations were performed. Ultrasound examination of the hepatobiliary system was performed in 500 patients with risk factors for NAFLD, such as obesity, dyslipidemia, impaired carbohydrate tolerance. Among them, 98 patients with NAFLD, diagnosed with steatosis and steatohepatitis, were identified. In accordance with the tasks set for the study, the main and control groups were divided into representative groups according to demographic (age, gender, etc.),

anthropometric (weight, body mass index or Quetelet index, etc.) indicators and other parameters. When dividing patients by age, the age classification of people developed by the WHO in 2015 was used. According to it, people aged 25-44 years were divided into the young group, people aged 44-60 years were divided into middle-aged people, people aged 60-75 years were divided into elderly people, people aged 75-90 years were divided into elderly people, and people over 90 years were divided into long-livers. During the studies, the ratio of women to men was 1.25:1. It can be seen from the table that steatosis was more common in middle-aged people (43.3%), while steatohepatitis was more common in elderly patients (45.2%). Also, in the steatosis and steatohepatitis groups, the lowest percentage of patients with the disease was in the young group (20.9% and 19.4%).

In the analysis of demographic and anthropometric indicators of patients, it was found that patients with steatohepatitis have a more severe course of the disease. When the patients were surveyed, 74% of them had disordered eating, eating a lot of fatty and fried foods. In order to evaluate the characteristics of clinical manifestations, it was first necessary to determine the range of leading symptoms of NAFLD, which constitute the essence of the disease. Therefore, the frequency and occurrence rate of each clinical sign was analyzed in detail, and the following were included among such clinical signs: heaviness and unpleasant sensation under the right rib, heartburn, nausea, belching, flatulence, constipation, flatulence, rapid fatigue, weakness. The analyzes showed that the clinical symptoms of the SG stage of NAFLD meet at a higher frequency compared to liver steatosis.

In order to study the functional state of the liver in NAFLD, its lipid metabolism was checked and analyzed. In it, lipid metabolism disorder is considered one of the leading indicators of the disease. GXS (above 6 mmol/l) was observed in this study. Dyslipidemia in NAFLD was described as TG higher than 1.9 mmol/l, XS HDL <1 mmol/l. Such disorders became more noticeable in deep disorders of lipid metabolism. The obtained results showed the presence of atherogenic dyslipidemia in the stage of steatosis and steatohepatitis in patients diagnosed with NAFLD. Thus, in this study, the main comparative description of steatosis and

steatohepatitis was assessed on the basis of adequate clinical practice, the level of obvious biochemical cytolysis. Alkaline phosphatase and gamma-glutamyltranspeptidase activity (GGTP) (separately increased) were found to increase moderately in SG. Dyslipidemia (hypertriglyceridemia, decreased LDL-C, increased LDL-C) was observed in 65–85% of patients. Basal insulin levels were significantly increased in patients with NAFLD. Correlation analyses conducted during the study showed that NAFLD is negatively correlated with steatosis, steatohepatitis, and total cholesterol, LDL-C, and LDL-C.

In the last decade, much attention has been paid to the study of the effects of hormones of the endocrine glands and gastrointestinal hormones on the functioning of the digestive system. The connection of changes in hormonal homeostasis with diseases of the digestive system is of great importance. Hyperinsulinemia is the main link in the development of IR - GI - obesity - IR [3 , 8 , 98 , 188]. Today, an increase in reserves in adipose tissue due to high-calorie nutrition increases insulin sensitivity. Lack of physical activity leads to insulin resistance in adipose tissue , and hyperinsulinemia is formed as a result of a decrease in tissue sensitivity to insulin [52,82].

The HOMA-IR index was determined to determine the level of compensatory insulin secretion in patients with steatosis and steatohepatitis stages of NAFLD . The HOMA-IR index is a homeostasis model assessment for insulin resistance. Normally, the HOMA-IR index does not exceed 2.7, this indicator is the same for men and women and does not depend on age. During adolescence, the HOMA indices increase slightly due to the physiological resistance of insulin at this age. Insulin resistance is a decrease in the sensitivity of insulin-sensitive tissues to the effects of insulin when its concentration in the blood is sufficient. Insulin resistance does not have specific symptoms, and it can also occur in obese and non-diabetic people, and this occurs in approximately 25% of cases. This indicator is calculated according to the following formula:

[meal insulin (mED/ml) × postprandial glucose (mmol/l)] / 22.5.

A normal value is less than 2 [127,133]. HOMA-IR insulin resistance index was significantly higher in the patients included in the study compared to the control group (p=0.01). In the patients included in this study, HOMA-IR insulin resistance index was significantly higher than in the control group (p=0.01). Hypercortisolemia levels showed a negative correlation with LDP and HDL indices. There was a correlation between hypercortisolemia and hyperinsulinemia with atherogenic dyslipidemia, and glucose parameters with hyperinsulinemia.

Cytokines are molecules that are secreted by various cells and provide communication between cells and tissues. They play an important role in the normal processes occurring in the body, in particular, the normal growth and development of the body, obesity (fat accumulation), lactation, blood formation, inflammation and hemostasis processes, and the pathogenesis of various diseases, such as atherosclerosis, rheumatoid arthritis, psoriasis, and NAFLD [118] .

In order to study the role of cytokines in the development of NAFLD, the levels of inflammatory cytokines IL-6 and IL-11 were measured in the serum of all patients (98) with NAFLD who were included in the study. This test was also performed in the control group. When comparing the data from the subgroups with steatosis and steatohepatitis and the control group, a significant difference was observed between the parameters of patients and healthy individuals, i.e., in the group of patients with steatosis, the levels of IL-11 and IL-6 cytokines were 41.75±1.218 pg/ml and 31.47±1.83 pg/ml, respectively, which was 9.22 ($p<0.001$) and 7.56 ($p<0.001$) times higher than the control group (Fig. 4.1-b). In the group of patients with steatohepatitis, the results obtained for the given cytokines were even more significant than in the control group: ONO – α – 46.45±3.07 pg/ml, IL – 6 – 37.21±2.54 pg/ml, which is 10.28 ($p<0.001$) and 8.94 ($p<0.001$) times higher than the control group, respectively. Also, these indicators were 1.11 and 1.18 ($p<0.05$) times higher than the indicators obtained from patients with steatosis. The given differences were checked according to the criterion of validity and the statistical reliability of the obtained results was confirmed ($p<0.05$). Thus, it can be said that inflammatory processes in steatohepatitis proceed more rapidly than in steatosis.

In patients with steatohepatitis, a statistically significant increase in the level of pro-inflammatory cytokines was also observed with an increase in TVI. According to the literature, this is due to the fact that with the accumulation of fat in adipose tissue, in particular, in adipocyte cells, the secretion of pro-inflammatory cytokines increases as a result of the fat-induced stress state in the cells. Due to such changes, the production of one of the anti-inflammatory factors, adiponectin, decreases. This predisposes to the development of systemic inflammatory syndrome . Also, the results obtained on cytokines were correlated with other biochemical parameters to determine the significance of pro-inflammatory cytokines in predicting the severity of NASH. Thus, in the pathogenesis of NAFLD, the correlation between the amount of cytokines, the severity of cytolytic processes in the liver (through the amount of aminotransferase enzymes and total bilirubin), the disruption of its synthetic function as a result of fatty liver (through the amount of albumin, cholesterol, LDL and HDL), and the degree of metabolic disorders (through the amount of insulin, HOMA-IR index and triglycerides) and the amount of cytokines was investigated.

At the same time, the results of the inflammatory cytokines and other biochemical analyzes, in particular, ALT, AST, total bilirubin, cholesterol, LDL, triglycerides and insulin, were found to be positively correlated with HOMA-IR, and negatively correlated with albumin and LDL. Also, the role of proinflammatory cytokines in the pathogenesis of NAFLD in the transition of the liver from simple steatosis to the stage of steatohepatitis development was examined using relative risk and odds ratio indicators. The results obtained proved that the cytokine IL-6 is a factor that induces the risk of developing steatosis from steatohepatitis.

IL-10 is an anti-inflammatory cytokine that reduces inflammation and tissue damage by acting on immunocytes and inhibiting inflammatory cytokines. Numerous studies, including those in primates, have shown that IL-10 prevents the development of endotoxemia by reducing the production of inflammatory cytokines . IL-10 also suppresses the immune response by directly affecting immune cells themselves, in particular by inhibiting the differentiation of T-helper lymphocytes

and reducing the expression of major histocompatibility complex II (MHC II) on cells.

In order to establish the role of anti-inflammatory cytokines in the pathogenesis of NCD, the level of IL-10 was measured in the serum of all (98) patients with NCD who were included in the study. This test was also performed on healthy controls. When comparing the data obtained, a statistically significant difference was noted between them (Fig. 4.3-a). In particular, in all patients with NCD (n=98), the IL-10 level was 50.21±1.29 pg/ml, while in the control group this indicator was only 5.28±0.24 pg/ml, which is 9.51 times higher, respectively ($p<0.001$). This indicator was 48.15±1.32 pg/ml in the group of patients with steatosis (n=67) (9.12 times higher than the control group, $p<0.001$), and 54.68±1.46 pg/ml in the group of patients with steatohepatitis (10.36 times higher than the control group, $p<0.001$). Thus, it can be concluded that in patients with NAFLD, a significant increase in the level of the anti-inflammatory cytokine IL-10 was observed in comparison with the control group, due to a compensatory mechanism, and this difference was especially pronounced in the subgroup with steatohepatitis.

Based on the results obtained, it can be said that in steatosis, especially in steatohepatitis, the levels of inflammatory cytokines IL-α and IL-6, which lead to inflammation, as well as IL-10, which suppresses inflammation, increase sharply due to the development of fatty inflammatory processes. An increase in the level of IL-10 in the serum of patients occurs due to compensatory processes and suppresses inflammatory processes. Such changes are directly related to gender (while IL-α expression was mainly characteristic of women, strong expression of IL-6 was observed more often in men), age (cytokine expression was strongest in patients aged 25–49 years) and TVI. The strongest correlations were observed with TVI, and with an increase in its index, the level of cytokines also increased. A moderate to strong positive correlation was observed between the levels of IL-α, IL - 6 and IL-10 in steatosis, especially in steatohepatitis, and the biochemical parameters ALT, AST, total bilirubin, cholesterol, triglycerides, insulin and HOMA-IR, while moderate to strong negative correlations were found with cholesterol in albumin and

LDL. A strong positive correlation was noted between conjugated bilirubin and cytokines in steatosis, and a strong negative correlation was noted between them in steatohepatitis. Therefore, the determination of the amount of conjugated bilirubin may play an important role in the differential diagnosis of nonalcoholic steatosis and steatohepatitis. The results presented confirm that increased serum cytokine concentrations indicate alterations induced by fatty liver, in particular IL-6 cytokine, which is of great informative value. It was found that IL-6 cytokine has a statistically significant effect on the risk of developing nonalcoholic steatohepatitis.

The results of research conducted over the past decade show that genetic factors play a significant role in the progressive development of NAFLD. Today, a number of scientific studies are being conducted in the world to study the genetic basis of NAFLD, develop early diagnosis of the disease and prevent its complications through the development of treatment methods. Scientific studies and analysis of the studied literature have shown that genetic testing is necessary for accurate diagnosis of the development and course of NAFLD. Currently, many studies are being conducted in Uzbekistan in the molecular genetic direction. However, in the steatosis and steatohepatitis stages of NAFLD inflammatory cytokines (IL-α, IL-6, IL-10), accumulation of lipid fractions in liver tissues, and the GCKR and its polymorphism, which are among the candidate genes for a more dangerous and aggressive course of the disease, have not been studied. The importance of clinical and genetic aspects and instrumental examination methods in the early diagnosis of nonalcoholic fatty liver disease in the diagnosis has not been sufficiently studied. Although numerous studies have been conducted to study the role of polymorphisms of various genes in the development of NAFLD, the significance of the MBOAT7 gene rs641738 G>T polymorphism in the development of NAFLD in the Uzbek population has not been fully elucidated. Therefore, the significance of the MBOAT7 gene rs641738 polymorphism in the pathogenesis of NCD was examined in a group of 98 patients diagnosed with NCD and 70 healthy controls.

The study of the relationship between the wild and mutant alleles of the MBOAT7 gene rs641738 polymorphism and the occurrence of NAFLD in the main and control groups showed that the wild G allele reduces the occurrence of the disease by 30% by exerting a protective effect on the occurrence of NAFLD (RR=0.7; 95% CI: 0.611–0.862), while the mutant allele exerts an initiating effect on the occurrence of NAFLD, with a relative risk of 1.38 (95% CI: 1.16–1.64). The results were tested using chi-square and p-value indicators and their significance and reliability in the development of NAFLD were confirmed (χ^2=11.1; p<0.001).

Also, when examining the role of the genotype distribution of the studied polymorphism in the main and control groups, it was found that the G/G wild homozygous genotype has a strong protective effect on the development of the disease (OR=0.375; 95% CI: 0.199–0.709) and the significance of the results obtained was confirmed (χ^2=7.8; p<0.01). On the other hand, it was found that the T/T mutant homozygous genotype has an initiating effect on the development of the disease (OR=4.74; 95% CI: 1.027 – 21.9) and increases the risk of the disease by 1.54 times (RR=1.54; 95% CI: 1.2 – 1.98), and the relationship between the mutant genotype and the development of the disease was proven to be significant (χ^2=4.7; p<0.05).

Another initiating effect of MBOAT7 deficiency in the pathogenesis of fatty liver is the disruption of the normal balance of lipogenic and lipolytic gene expression. Various studies have shown that in hepatocytes with MBOAT7 deficiency , one of the lipogenic enzymes , stearoIL-CoA desaturase , is expressed more and other lipolytic enzymes are expressed less. This slows down the oxidation of free fatty acids and their accumulation in liver cells under the influence of lipogenic substances can lead to the development of fatty liver [206,207]. It is known that the slowing down of fat oxidation is manifested by obesity and increased blood triglyceride concentrations.

The results of this study confirmed the existence of a positive statistically significant association between the MBOAT7 gene rs641738 polymorphism and NASH in the steatosis and steatohepatitis stages of nonalcoholic fatty liver disease ,

and this association was particularly pronounced in patients with advanced nonalcoholic steatohepatitis.

of the GCKR gene rs1260326 polymorphism was significantly more prevalent in the main group, no statistically significant association was found between the genotype distribution of patients with the minor allele (G/T and T/T) and the development of NSCLC. When analyzing the allele distribution of the GCKR gene rs1260326 polymorphism in the blood cells of 98 patients with NSCLC (main group), the wild G allele was detected in 74.5%, and the minor T allele in 25.5%. The results obtained during the study were checked according to the Hardy-Weinberg law. The observed results did not show statistically significant deviations from this law ($\chi^2 < 3.84$ $p > 0.05$), and the compliance of these results with the Hardy-Weinberg law was confirmed.

When studying the relationship between the indicators of the GCKR gene rs1260326 polymorphism obtained from the main and control groups and the occurrence of NCDs, it was found that the G wild-type gene allele plays a protective role in the occurrence of the disease, while the T allele has a relatively increased risk of developing NCDs in patients with a pro-inflammatory effect, and the probability of developing the disease in the main group was 1.23 times higher in relative risk (95%CI: 1.0–1.49), 1.74 times higher in odds ratio (95%CI: 1.0–3.02), while the presence of the wild-type allele reduced the risk of developing the disease by almost 20% (RR=0.8; 95% CI: 0.67–0.98), and almost two times higher in odds ratio (OR=0.57; 95% CI: 0.331–0.99). The statistical significance of these results, determined by alleles in the studied gene polymorphism, was confirmed ($\chi^2 = 3.9$ $p=0.047$).

Several studies have shown a positive association between the GCKR gene rs1260326 polymorphism and the development of NAFLD in some populations, as well as between triglyceride levels and TVI. In addition, according to the results of some studies, the conformational change of the expressed protein as a result of the T minor allele of the GCKR gene rs1260326 polymorphism also affects β cells. As a result, the disruption of the regulation of GCK in β cells by GCKR may lead to an

increase in intracellular glucose concentration and, consequently, insulin hypersecretion. The chronic course of this condition leads to the development of insulin resistance and metabolic syndrome [225,227].

The GCKR gene rs1260326 polymorphism, detected in all patients in the main group, was compared with the differences in the distribution of the C/C, C/T and T/T genotypes, as well as with some anthropometric and biochemical parameters. The results of the analysis showed that patients with minor alleles (T/T and G/T) of the GCKR gene polymorphism had a statistically significant advantage over patients with homozygous normal genotypes in terms of TVI and plasma triglycerides. Such a significant advantage was also confirmed for glucose parameters. In addition, among the different genotypes, only patients with homozygous mutant genotypes had an advantage over representatives of homozygous normal genotypes in terms of insulin levels ($p<0.05$), while the advantage shown by patients with heterozygous group was not statistically significant ($p >0.05$). For the remaining parameters, no significant difference was found between patients with wild-type homozygotes and patients with the minor allele. Thus, although the minor allele of the GCKR gene rs1260326 polymorphism prevailed in the main group with a statistically significant difference, no statistically significant association was found between patients with the minor allele (G/T and T/T) and the development of NSCLC in the distribution of genotypes.

An algorithm for predicting complications of nonalcoholic fatty liver disease based on clinical, laboratory and instrumental examination methods was developed. Diagnosis was carried out by the method of exclusion using a sequential algorithm. An algorithm for predicting complications of nonalcoholic fatty liver disease was developed based on a comparative assessment of clinical, laboratory and instrumental examination methods of nonalcoholic fatty liver disease . This algorithm allowed patients to choose the method of treatment after hospitalization and make a final diagnosis with an average time spent on diagnostic examinations, which ensured high economic efficiency by reducing disability by 30%, reducing the cost of medical care and the working time of medical personnel .

CONCLUSION

"Clinical, laboratory and molecular genetic markers of the development of non-alcoholic fatty liver disease", the following conclusions were presented :

1. The manifestation process of clinical signs in NAFLD has some important and noteworthy features, pain under the right rib, unpleasant sensation (58.06%) , stuttering (67.7%) , heartburn (61.2%), constipation (54.8%) were noted to be higher in steatohepatitis compared to steatosis .

2. Dyslipidemia (hypertriglyceridemia, decreased LDL-C, increased LDL-C) was observed in 65-85% of patients with nonalcoholic fatty liver disease . Our correlation analysis showed that in the stage of NAFLD, steatosis, steatohepatitis, and total cholesterol, LDL-C and LDL-C were negatively correlated.

3. In patients with NAFLD, an 8–16-fold increase in ONO-α, IL-6, and IL-10 was observed in the serum, and sharp changes were noted in steatohepatitis. Also, varying degrees of correlation were noted with the amount of cytokines and other biochemical parameters: moderate and strong positive correlations were observed with indicators of cytolysis and cholestasis syndromes, and moderate and strong negative correlations were observed with indicators of liver synthetic function. In steatosis, a strong positive correlation of cytokines with conjugated bilirubin was found, and in steatohepatitis - a strong negative correlation. Although ONO-α increased the risk of developing steatohepatitis from nonalcoholic steatosis by 2.54 times (95% CI: 0.85–7.56) and 3.6 times (95% CI: 0.98–13.32) in terms of odds ratio as a relative risk factor, the statistical reliability of these results was not confirmed ($p>0.05$). IL-6 was found to increase the risk of developing steatohepatitis by 6.4 times (95% CI: 1.63–25.1) and 10.4 times (95% CI: 2.29–47.2) in terms of odds ratio, and the statistical reliability of this result was confirmed;

4. In the differential diagnosis of steatosis and steatohepatitis stages of NAFLD, the sensitivity was 26–36%, specificity was 79–84%, and diagnostic

efficiency was 62–70%, which was considered good for TNF-α and average for IL-6 and IL-10.

5. The study of the relationship between the wild and mutant alleles of the MBOAT7 gene rs641738 polymorphism and the occurrence of NAFLD in the primary and control groups showed that the wild G allele reduced the occurrence of the disease by 30% by exerting a protective effect on the occurrence of NAFLD (RR=0.7; 95% CI: 0.611–0.862) , while the mutant allele exerted an initiating effect on the occurrence of NAFLD, with a relative risk of 1.38 (95% CI: 1.16–1.64). The results were tested using chi-square and p-value indicators and their significance and reliability in the development of NAFLD were confirmed (χ^2=11.1; p<0.001) .

6. In the stage of steatosis and steatohepatitis of NAFLD Although the minor allele of the GCKR gene rs1260326 polymorphism was significantly more prevalent in the main group, no statistically significant association was found between the distribution of genotypes in patients with the minor allele (G/T and T/T) and the development of NSCLC;

7. CRIME based on the algorithm developed for steatosis, stages of inflammation were evaluated and their early prevention was created for the primary joints of medicine.

PRACTICAL RECOMMENDATIONS

1. In the steatosis stage of NAFLD, additional diagnostic methods should be used, as patient complaints and clinical signs are nonspecific.

2. When dyslipidemia and increased glycemia are observed in nonalcoholic steatosis in a biochemical blood test with a control group, a treatment mechanism should be developed.

3. When determining NAFLD, it is necessary to determine the amount of cortisol and insulin.

4. To determine the stages of the disease in NAFLD, it is important to conduct an analysis of the pro-inflammatory cytokines TNF-α, IL-6 and conduct a comparative analysis with a lipidogram and biochemical cytolysis.

4. In case of high levels of cytolysis markers, molecular genetic analysis of the MBOAT7 gene rs641738 polymorphism is mandatory.

5. The developed algorithm allows patients to choose a treatment method after hospitalization and make a final diagnosis with the average time spent on diagnostic tests.

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R LIST OF ABBREVIATIONS

AG	is the main group
WHO	- World Health Organization
NG	– control group
TVI	- body mass index
γ-GTFA	- gammaglutamyltranspeptidase
ALT	- alanine aminotransferase
AST	- aspartate aminotransferase
GI	– hyperinsulinemia
GERD	- gastroesophageal reflux disease
DLP	- dyslipoproteinemia
OIT	- gastrointestinal system
IR	- insulin resistance
IFA	- enzyme immunoassay
AT	- coefficient of atherogenicity
ZPLP	- low-density lipoproteins
ZJPLP	- very low density lipoproteins
ZYuLP	- high-density lipoproteins
JNAYoX	- non-alcoholic fatty liver disease
JS	- hepatic steatosis
SG	– steatohepatitis
PTI	- prothrombin index
ЕЙОК	- free fatty acids
QD	- diabetes mellitus
HOMA-IR	– Homeostasis Model Assessment of Insulin Resistance