INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 09 July 2026
Revised: 29 July 2026
Accepted: 14 Aug 2026
Published: 31 Aug 2026

Volume 12 Issue 08, 2026
Page No - 190-197
DOI - 10.55640/ijmsdh-12-08-22

Article Citation: Tursunov, J. K., Zaribbaev, U. Z. ., Abduvaliev, A. ., & Inoyatova, F. K. . (2026). Mechanisms of Lipid Metabolism Disorders in Experimental Non-Alcoholic Fatty Liver Disease: The Role of LDLR, LOX-1, ApoE and LRP1. International Journal of Medical Science and Dental Health, 12(08), 190-197. https://doi.org/10.55640/ijmsdh-12-08-22

Mechanisms of Lipid Metabolism Disorders in Experimental Non-Alcoholic Fatty Liver Disease: The Role of LDLR, LOX-1, ApoE and LRP1

Jahongir Kh. Tursunov
Associate Professor, Department of Medical and Biological Chemistry, Tashkent State Medical University, Tashkent, Uzbekistan.

Ulugbek Z. Zaribbaev
Independent Researcher, Department of Medical and Biological Chemistry, Tashkent State Medical University, Tashkent, Uzbekistan.

Abdurakhmon Abduvaliev
Assistant, Department of Medical and Biological Chemistry, Tashkent State Medical University, Tashkent, Uzbekistan.

Firuza Kh. Inoyatova
Professor, Department of Medical and Biological Chemistry, Tashkent State Medical University, Tashkent, Uzbekistan.

Corresponding author: Jahongir Kh. Tursunov, Associate Professor, Department of Medical and Biological Chemistry, Tashkent State Medical University, Tashkent, Uzbekistan. E-mail: johongirtursunov@gmail.com.

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disorder and is closely linked to insulin resistance and the metabolic syndrome. Beyond the accumulation of triacylglycerides (TAG), disturbed hepatic cholesterol handling — mediated by the low-density lipoprotein receptor (LDLR), the lectin-like oxidised LDL receptor-1 (LOX-1), apolipoprotein E (ApoE) and LDL receptor-related protein 1 (LRP1) — has been proposed as a central pathogenetic mechanism.

Objective: To evaluate the serum protein factors involved in triacylglyceride and cholesterol metabolism during the stepwise development of experimental fatty hepatosis.

Methods: Fifty outbred white rats weighing 150–180 g were studied. Eight animals formed the intact group and received a standard vivarium diet; 42 animals received a high-fat diet (cow lard) supplemented with a 10% glucose–fructose solution (1:1) for 5 months. Serum was examined at 2, 3, 4 and 5 months. Total protein, albumin, bilirubin, urea, glucose, TAG, total cholesterol

(TC) and cholesterol in very-low-density (VLDL-C), low-density (LDL-C) and high-density (HDL-C) lipoproteins were measured, and the atherogenic index (AI) together with ALT, AST, GGT and ALP activities were determined. Insulin, LDLR, LOX-1, ApoE and LRP1 were measured by sandwich enzyme-linked immunosorbent assay. HOMA-IR, the TAG/HDL-C ratio and the metabolic index (MI) were calculated.

Results: High-calorie feeding produced a progressive increase in serum TAG (up to 2.11-fold) and TC (up to 1.93-fold), a rise in VLDL-C (up to 2.96-fold) and LDL-C (up to 4.19-fold) and a fall in HDL-C, with the AI increasing from 0.66 ± 0.03 to 3.66 ± 0.28 (5.54-fold; $P < 0.001$). Glucose rose 1.49-fold, insulin 2.73-fold and HOMA-IR 3.13-fold by month 5. Serum LDLR fell progressively (2.41-, 3.34- and 4.89-fold at 2, 3 and 4 months, with partial recovery to a 3.61-fold reduction at 5 months), whereas LOX-1 rose (1.63-, 2.03-, 2.18- and 1.94-fold). ApoE showed a biphasic pattern: a 1.52-fold decrease at 2 months followed by a rise above intact values at 4 (1.32-fold) and 5 months (1.23-fold). LRP1 was unchanged at 2 months and then decreased by 1.25-, 1.40- and 1.43-fold.

Conclusion: Prolonged high-calorie feeding reproduces fatty hepatosis accompanied by the full biochemical picture of the metabolic syndrome. The progressive decline of LDLR together with a rise in LOX-1, a biphasic ApoE response and a gradual reduction of LRP1 indicate a dysregulation of receptor-mediated hepatic cholesterol handling and suggest that these proteins merit further evaluation as early markers of fatty hepatosis.

Keywords: non-alcoholic fatty liver disease; low-density lipoprotein receptor; LOX-1; apolipoprotein E; LRP1; insulin resistance.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterised by an excessive accumulation of fat in the liver, is associated with insulin resistance (IR) and is defined by the presence of steatosis in more than 5% of hepatocytes on histological examination of liver biopsies [1,2]. Radiological criteria are also used to grade hepatosis: a proton density fat fraction above 5.6% on proton magnetic resonance spectroscopy, or quantitative assessment of the fat-to-water ratio on magnetic resonance imaging [3,4]. The concept of NAFLD covers two morphological forms with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The severity of NASH is highly variable and includes fibrosis, cirrhosis and hepatocellular carcinoma.

According to WHO data, the number of patients worldwide with NAFLD, chronic alcoholic hepatitis and liver damage caused by drugs, other medicinal substances and viruses exceeds two billion [3,5]. This is associated with metabolic disturbances in the liver and reduced resistance of hepatocytes to damaging factors (viruses, toxic substances, drugs, autoimmune processes) in the presence of obesity and type 2 diabetes mellitus. NAFLD is currently the most common liver disease, and approximately 25% of the world population is affected [3,6]. Prevalence is 20–30% in European countries and 5–18% in Asia, with a 1–2% risk of progression to cirrhosis in the general population; in NAFLD the risk of cirrhosis reaches 25% [3,4]. NAFLD is detected more often in women, and the mean age of patients is about 50 years. In the presence of metabolic syndrome, the frequency of NAFLD reaches 80%, and in obese patients it is detected in 75–100% of cases [3]. Mortality is approximately 5% and is mainly related to cardiovascular complications. The study of the cellular and molecular mechanisms of NAFLD and of the development of systemic lesions, as well as the elaboration of early diagnostic criteria, therefore has considerable scientific and practical significance.

In recent years NAFLD has been regarded as the hepatic manifestation of the metabolic syndrome. It is generally accepted that hepatic TAG accumulation is the principal feature of NAFLD. Increasing evidence, however, supports a disruption of cholesterol homeostasis in the liver and a role for free cholesterol accumulation in the pathogenesis of this condition. Several authors point to a central role of cholesterol metabolism disorders leading to chronic inflammation [7,8,9]. Low-density lipoprotein receptors (LDLR), lectin-like oxidised LDL receptor-1 (scavenger receptor, LOX-1), low-density lipoprotein receptor-related protein 1 (LRP1) and apolipoprotein E (ApoE) play important roles in hepatic cholesterol metabolism [9,10,11].

The LDLR pathway is one of the major routes of hepatic cholesterol metabolism [11]. It maintains plasma cholesterol concentrations and hepatocyte cholesterol homeostasis by modulating intracellular cholesterol uptake and endocytosis. Chronic inflammation is one of the main factors that disrupt the LDLR pathway, promoting lipid accumulation and accelerating the progression of vascular calcification, atherosclerosis and NAFLD [12]. LOX-1 is a biomarker of atherosclerosis, insulin resistance, obesity and diabetes [10,11], and serum LOX-1 levels correlate with the histological manifestations of NAFLD. ApoE is a multifunctional protein whose synthesis, secretion and metabolism are completed mainly in the liver [9,13]; it plays a key role in the metabolism of cholesterol and TAG, participating in the degradation of chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL) and other lipids through binding to its receptors. LRP1 is a member of the LDLR family and is highly expressed in hepatocytes, adipocytes, neurons, vascular smooth

muscle cells, fibroblasts and macrophages [12,14]. It exerts an atheroprotective effect, regulates processes associated with vascular integrity and participates in insulin signalling and glucose homeostasis in various tissues; its action is mediated by ApoE. In adipocytes its endocytic function increases two- to threefold after insulin exposure, and insulin also stimulates LRP1-specific uptake of chylomicron remnants in the liver, which is associated with translocation of hepatic LRP1 to the cell surface. Hepatic LRP1 is thus important for maintaining insulin sensitivity and preventing steatosis through regulation of GLUT4, and cellular GLUT4 transport depends on LRP1 expression.

Taken together, these data indicate an important role of specific proteins involved in lipid metabolism in the development of fatty liver disease. The aim of the present study was to evaluate the specific protein factors involved in triacylglyceride and cholesterol metabolism in experimental fatty liver disease.

2. Materials and Methods

2.1 Animals and experimental design

Fifty outbred white rats weighing 150–180 g and kept under standard vivarium conditions were used. Eight rats constituted the intact group and received a standard vivarium diet. Fatty hepatosis was reproduced by a standard model close to the clinical situation: 42 animals were fed a high-fat diet (cow lard) for 5 months, supplemented with a 10% glucose–fructose solution in a 1:1 ratio. Overall mortality in the experimental group was 7.1%. The study was carried out dynamically, 2, 3, 4 and 5 months after the start of the experiment, with 8–9 animals examined at each time point.

The presence of fatty liver was assessed after opening the abdominal cavity at each study time point. After two months the livers of the experimental animals appeared shiny and slightly yellow. As the pathological process progressed, the liver acquired a shiny yellowish tint and fatty streaks became visible on section, confirming the presence of fatty liver in the experimental animals.

At the corresponding time points the animals were decapitated under light ether anaesthesia, blood was collected and the liver was taken for general morphological examination. Blood was centrifuged, serum was separated, and biochemical and enzyme immunoassay tests were performed.

2.2 Ethics statement

The experimental studies were conducted in accordance with the requirements for the humane treatment of laboratory animals (European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Strasbourg, 1986) and with the principles of the Declaration of Helsinki, in the central vivarium of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan.

2.3 Biochemical analyses

Biochemical studies were performed on a MINDRAY BA-88A biochemical analyser (China) using reagents from CYPRESS Diagnostics (Belgium). Total protein, albumin, bilirubin, urea, glucose, triacylglycerides (TAG), total cholesterol (TC) and cholesterol in very-low-density (VLDL-C), low-density (LDL-C) and high-density (HDL-C) lipoproteins were determined. The cholesterol atherogenic index (AI) was calculated, and the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) were measured.

2.4 Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assays were performed on an ELISA plate analyser using commercial kits. A solid-phase sandwich ELISA was employed, based on two monoclonal antibodies directed against specific epitopes, one immobilised on the solid phase and the other conjugated with biotin. After calibration, the samples were added to the plates and bound to the immobilised antibodies; the immobilised insulin, LOX-1, LDLR, LRP-1 and ApoE proteins then interacted with the biotin-labelled secondary antibodies. The amount of bound conjugate was directly proportional to the content of insulin, LOX-1, LDLR, LRP-1 and ApoE. Streptavidin–peroxidase conjugate was subsequently added and the plates were incubated, during which a gradual colouring of the solution developed, the intensity of which was directly proportional to the amount of labelled antibody. The optical density of the analysed solutions was measured and the content of the studied proteins was calculated from a calibration curve.

2.5 Calculated indices

Tissue sensitivity to insulin was assessed using calculated indices: the HOMA-IR index [15], the TAG to HDL-cholesterol ratio [16,17] and the metabolic index (MI) [1].

2.6 Statistical analysis

Quantitative data are presented as the arithmetic mean and the standard error of the mean (M ± m). Differences between the intact and experimental groups were assessed by methods of variation statistics, and a value of $P < 0.05$ was regarded as statistically significant.

3. Results

3.1 General biochemical profile of liver injury

The experimental animals showed increased serum activity of ALT and, in particular, of AST, GGT and ALP. Hyperbilirubinaemia developed, together with a tendency towards decreased urea levels and with hypoproteinaemia due to hypoalbuminaemia. The severity of these changes depended on the duration of the experiment. These results indicate liver damage with a risk of developing steatohepatitis and liver fibrosis.

3.2 Serum triacylglycerides and total cholesterol

Serum TAG and TC levels of the experimental animals are presented in Table 1. TAG increased progressively by 1.16-fold, 1.66-fold ($P < 0.01$), 1.56-fold ($P < 0.01$) and 2.11-fold ($P < 0.001$) at 2, 3, 4 and 5 months of the experiment, respectively. By the final stage of the study a pronounced hypertriglyceridaemia was present.

The same dynamics were characteristic of TC, the values of which increased statistically significantly by 1.41-fold ($P < 0.05$), 1.68-fold ($P < 0.01$), 1.83-fold ($P < 0.001$) and 1.93-fold ($P < 0.001$) over the same periods. These results indicate the development of both hypertriglyceridaemia and hypercholesterolaemia.

Table 1. Dynamics of triacylglyceride and total cholesterol content in the blood serum of experimental animals (M ± m, n = 8–9)

Study groups and timeframes	TAG, mmol/L	Total cholesterol, mmol/L
Intact	0.73 ± 0.02	2.36 ± 0.05
NAFLD, 2 months	0.85 ± 0.015*	3.32 ± 0.096*
NAFLD, 3 months	1.21 ± 0.059*	3.96 ± 0.12*
NAFLD, 4 months	1.14 ± 0.05*	4.31 ± 0.15*
NAFLD, 5 months	1.54 ± 0.060*	4.56 ± 0.31*

TAG — triacylglycerides. * — differences between the intact and the experimental groups are statistically significant ($P < 0.05$).

3.3 Cholesterol in transport lipoproteins and the atherogenic index

The changes in serum lipids also affected the cholesterol content of the transport lipoprotein fractions (Table 2). VLDL-C increased statistically significantly by 1.74-fold, 2.19-fold, 2.31-fold and 2.96-fold (all $P < 0.001$) at 2, 3, 4 and 5 months from the beginning of the experiment, respectively. LDL-C increased by 2.13-fold, 3.43-fold, 3.82-fold and 4.19-fold (all $P < 0.001$) over the same periods, while HDL-C decreased from 1.43 ± 0.04 mmol/L in intact animals to 0.98 ± 0.029 mmol/L by month 5.

Table 2. Dynamics of cholesterol content in transport lipoproteins in the blood serum of experimental animals (M ± m, n = 8–9)

Study groups and timeframes	HDL-C, mmol/L	LDL-C, mmol/L	VLDL-C, mmol/L
Intact	1.43 ± 0.04	0.67 ± 0.03	0.26 ± 0.02
NAFLD, 2 months	1.44 ± 0.064	1.43 ± 0.055*	0.45 ± 0.017*
NAFLD, 3 months	1.10 ± 0.047*	2.29 ± 0.07*	0.57 ± 0.026*
NAFLD, 4 months	1.02 ± 0.036*	2.56 ± 0.15*	0.60 ± 0.045*
NAFLD, 5 months	0.98 ± 0.029*	2.81 ± 0.20*	0.77 ± 0.010*

HDL-C, LDL-C, VLDL-C — cholesterol of high-, low- and very-low-density lipoproteins. * — differences between the intact and the experimental groups are statistically significant ($P < 0.05$).

Analysis of the atherogenic index (AI) showed a gradual increase during high-fat feeding. In intact rats the AI was 0.66 ± 0.03; by the end of the second month of the high-calorie diet it had increased 2.01-fold to 1.33 ± 0.08. In the subsequent periods the index rose to 2.63 ± 0.11 after 3 months, 3.09 ± 0.21 after 4 months and 3.66 ± 0.28 after 5 months, exceeding the values of intact rats by 3.98-fold, 4.68-fold and 5.54-fold, respectively (all $P < 0.001$).

3.4 Glucose, insulin and indices of insulin resistance

Fatty hepatosis in the experimental animals was accompanied by hyperglycaemia, with blood glucose increasing by 1.18-fold, 1.28-fold ($P < 0.05$), 1.33-fold ($P < 0.01$) and 1.49-fold ($P < 0.01$) relative to intact rats (Table 3). Insulin levels increased more markedly: by 1.71-fold after 2 months, 2.37-fold after 3 months, 2.59-fold after 4 months and 2.73-fold after 5 months (all $P < 0.001$) relative to intact values. Calculation of the HOMA-IR index revealed significant increases of 2.06-, 3.04-, 3.44- and 3.13-fold (all $P < 0.001$) over the corresponding periods.

Table 3. Dynamics of glucose, insulin and the HOMA-IR index in the blood serum of experimental animals (M ± m, n = 8–9)

Study groups and timeframes	Glucose, mmol/L	Insulin, IU/L	HOMA-IR
Intact	5.33 ± 0.22	4.35 ± 0.28	1.02 ± 0.06
NAFLD, 2 months	6.31 ± 0.13*	7.46 ± 0.39*	2.10 ± 0.12*
NAFLD, 3 months	6.81 ± 0.19*	10.30 ± 0.52*	3.10 ± 0.14*
NAFLD, 4 months	7.08 ± 0.23*	11.27 ± 0.50*	3.54 ± 0.20*
NAFLD, 5 months	7.92 ± 0.20*	11.89 ± 0.89*	3.19 ± 0.29*

HOMA-IR — homeostatic model assessment of insulin resistance. * — differences between the intact and the experimental groups are statistically significant ($P < 0.05$).

The three calculated indices of tissue insulin sensitivity are summarised in Table 4. Alongside the rise in HOMA-IR, the TAG/HDL-C ratio increased steadily from 0.51 ± 0.02 in intact animals to 1.57 ± 0.07 by month 5, whereas the metabolic index rose at 2 months (10.56 ± 0.43) and subsequently returned to values close to those of intact animals.

Table 4. Calculated indices of tissue insulin sensitivity in experimental animals (M ± m, n = 8–9)

Study groups and timeframes	HOMA-IR	TAG/HDL-C	MI
Intact	1.02 ± 0.06	0.51 ± 0.02	7.60 ± 0.33
NAFLD, 2 months	2.10 ± 0.12	0.61 ± 0.041	10.56 ± 0.43
NAFLD, 3 months	3.10 ± 0.14	1.11 ± 0.08	7.51 ± 0.42
NAFLD, 4 months	3.54 ± 0.20	1.14 ± 0.062	7.20 ± 0.33
NAFLD, 5 months	3.19 ± 0.29	1.57 ± 0.07	7.76 ± 0.32

MI — metabolic index.

As the presented data show, rats fed a high-calorie diet develop all the signs of the metabolic syndrome with a high risk of cardiovascular pathology.

3.5 LDLR, LOX-1, ApoE and LRP1

Serum LDLR content decreased progressively with the duration of the experiment (Table 5). Two months after the start of the high-calorie diet the LDLR content had fallen 2.41-fold ($P < 0.001$) compared with intact rats, and in the subsequent periods of 3 and 4 months it continued to decrease by 3.34-fold and 4.89-fold (both $P < 0.001$), respectively. By the final period of the study the LDLR content had risen slightly compared with the

previous period and was 3.61-fold lower than in intact rats, indicating a degree of stabilisation of the process.

Serum LOX-1 showed the opposite pattern, increasing progressively with the duration of the experiment (Table 5). Two months after the start of the high-calorie diet LOX-1 had increased 1.63-fold ($P < 0.01$) compared with intact rats, and at 3 and 4 months it continued to rise by 2.03-fold and 2.18-fold (both $P < 0.001$), respectively. By the final period of the study LOX-1 had decreased slightly compared with the previous period but remained 1.94-fold higher ($P < 0.001$) than in intact rats.

ApoE showed variable changes depending on the duration of the experiment (Table 5). Two months after the start of the high-calorie diet ApoE had decreased 1.52-fold ($P < 0.01$) compared with intact rats. At 3 months the values had risen and approached those of intact animals; the upward trend persisted at 4 months, when values exceeded those of intact rats by 1.32-fold ($P < 0.05$). By the final stage of the study the ApoE content had decreased slightly compared with the previous period and was 1.23-fold higher ($P < 0.05$) than in intact rats.

Serum LRP1 decreased with the duration of the experiment (Table 5). Two months after the start of the high-calorie diet the LRP1 content did not change significantly and remained within the range of the intact group. In the subsequent periods, at 3, 4 and 5 months, it decreased gradually by 1.25-fold ($P < 0.05$), 1.40-fold ($P < 0.01$) and 1.43-fold ($P < 0.01$), respectively.

Table 5. Dynamics of LDLR, LOX-1, ApoE and LRP1 content in the blood serum of experimental animals (M ± m, n = 8–9)

Study groups and timeframes	LDLR, ng/mL	LOX-1, pg/mL	ApoE, ng/mL	LRP1, ng/mL
Intact	59.77 ± 2.86	51.01 ± 2.30	120.07 ± 16.53	6.61 ± 0.05
NAFLD, 2 months	24.80 ± 1.42*	82.94 ± 4.12*	79.21 ± 8.03*	6.65 ± 0.23
NAFLD, 3 months	17.91 ± 1.15*	103.79 ± 8.45*	124.89 ± 12.76	5.30 ± 0.18*
NAFLD, 4 months	12.23 ± 1.40*	111.34 ± 7.90*	158.84 ± 21.19*	4.71 ± 0.24*
NAFLD, 5 months	16.55 ± 2.14*	99.07 ± 4.85*	147.64 ± 16.88*	4.63 ± 0.27*

LDLR — low-density lipoprotein receptor; LOX-1 — lectin-like oxidised LDL receptor-1; ApoE — apolipoprotein E; LRP1 — LDL receptor-related protein 1. — *differences between the intact and the experimental groups are statistically significant ($P < 0.05$).*

4. Discussion

Despite the established view that hepatic TAG accumulation is central to the development of NAFLD, there is substantial evidence that impaired hepatic cholesterol metabolism, leading to chronic inflammation, is equally important. LDLR, LOX-1, LRP1 and ApoE play a significant part in this impairment. The LDLR protein regulates cholesterol uptake by hepatocytes and endocytosis from the liver; a reduction in LDLR recycling on the hepatocyte surface increases plasma LDL concentrations, cholesterol accumulation and foam-cell formation in the liver.

In the present experiment serum LDLR fell progressively as fatty hepatosis developed. As noted above, the LDLR pathway is one of the main routes of hepatic cholesterol metabolism [11]; it maintains plasma cholesterol concentrations and hepatocyte cholesterol homeostasis by modulating intracellular cholesterol uptake and endocytosis, a process in which PCSK9 participates. Increased PCSK9 activity reduces LDLR recycling on the cell surface and promotes lysosomal degradation of the receptor, which lowers the amount of LDLR and raises plasma LDL. Chronic inflammation, which is characteristic of NAFLD, leads to accumulation of lipids in the blood and accelerates the progression of vascular calcification, atherosclerosis and NAFLD [12]. Inflammatory stress also disrupts the feedback regulation of LDL and thereby causes excess cholesterol deposition in the liver [12]; increased LDL expression mediated by inflammatory stimuli is therefore a factor contributing to the progression of NAFLD. Our findings are consistent with this concept, since the fall in LDLR occurred in parallel with the rise in LDL-C shown in Table 2.

LOX-1, a biomarker of atherosclerosis, insulin resistance, obesity and diabetes, may also be useful in the early diagnosis of fatty liver disease, since NAFLD is now regarded as a manifestation of the metabolic syndrome. Structurally, LOX-1 is a membrane glycoprotein that binds and degrades oxidised LDL, and it may therefore participate in the development of fatty liver disease, in which chronic hepatic inflammation is present. In patients with NAFLD, serum LOX-1 rises as metabolic disorders worsen [10,11], which has been attributed to insulin resistance as a

common pathophysiological mechanism of these disorders. An increase in serum LOX-1 has also been described in patients with endothelial dysfunction and pronounced oxidative stress [10]. On the basis of the present results it can be suggested that determination of serum LOX-1 may be of value in the early prediction of fatty hepatosis. It is possible that high serum LOX-1 levels, by promoting endothelial dysfunction of the hepatic vessels, further provoke fibrotic changes around the portal vessels and the central vein.

ApoE is a component of VLDL and chylomicrons and is produced in the liver. A defect in ApoE structure resulting in synthesis of the ApoE2 isoform, which does not interact with receptors, leads to increased concentrations of chylomicron remnants and of very-low-, low- and intermediate-density lipoproteins, and hence to hyperchylomicronaemia, hypertriglyceridaemia, hypercholesterolaemia, early atherosclerosis and xanthomatosis. ApoE is a polymorphic protein: the ε2 allele has a low affinity for LDL receptors whereas the ε4 allele has a higher affinity [13,18]. The wave-like changes in total ApoE content identified in the present work may therefore reflect the expression patterns of the different isoforms — the decrease at 2 months being associated with suppression of both isoforms, followed by a gradual increase in the subsequent periods driven by expression of the ε4 isoform. There is evidence that in patients with NAFLD carrying the ε2 allele, serum total cholesterol and LDL-C are lower than in patients carrying the ε4 allele [5,9,13].

The gradual decrease in LRP1 observed after the second month indicates a disruption of insulin signal transduction, since in hepatocytes LRP1 maintains sensitivity to insulin and prevents fatty degeneration of the liver by regulating the transport function of GLUT4 [12,14]. LRP1 is highly expressed in hepatocytes and, together with ApoE, mediates the endocytosis and degradation of chylomicron and VLDL remnants. The parallel decline of LRP1 and the rise in HOMA-IR observed in the present study are consistent with this mechanism.

Taken as a whole, the long-term use of a high-calorie diet in the present model led to a lipid profile corresponding to types 4 and 5 hyperlipoproteinaemia (familial hypertriglyceridaemia), a heterogeneous group of conditions characterised by hypertriglyceridaemia and hypercholesterolaemia. In this setting hyperinsulinaemia increases the synthesis of VLDL and LDL, the accumulation of cholesterol and triglycerides, and the systemic development of atherosclerotic changes in the blood vessels. Serum HDL-C concentrations below 0.91 mmol/L are currently regarded as indicating a high risk of cardiovascular events, whereas levels above 1.56 mmol/L are considered protective; LDL-C correlates more closely with the risk of atherosclerosis than total cholesterol. In the present experiment HDL-C fell to 0.98 mmol/L and LDL-C rose more than fourfold, while the atherogenic index increased 5.54-fold, which places the animals in the high-risk range.

5. Conclusion

Rats fed a high-calorie diet for a prolonged period develop fatty hepatosis manifested by hypertriglyceridaemia, hypercholesterolaemia, disturbed cholesterol content in the transport lipoprotein fractions, hyperglycaemia and hyperinsulinaemia — that is, by the full biochemical picture of the metabolic syndrome. In the blood serum, LDLR decreases progressively against a background of increasing LOX-1, the severity of both changes depending on the duration of the experiment. ApoE decreases after 2 months and then increases as fatty hepatosis progresses, whereas LRP1 is unchanged at 2 months and decreases gradually thereafter. These proteins therefore reflect distinct stages of receptor-mediated disturbance of hepatic cholesterol handling and deserve further study as candidate early markers of fatty hepatosis.

References

1. Shakhrun OO. Formation of cardiometabolic disorders in non-alcoholic fatty liver disease associated with insulin resistance [dissertation]. Moscow; 2019. 317 p. (In Russ.)
2. Valenti L, Al-Serri A, Daly AK, Galmozzi E, Rametta R, Dongiovanni P, et al. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatology. 2010;51:1209–17.
3. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
4. Lazebnik LB, Golovanova EV, Turkina SV, et al. Non-alcoholic fatty liver disease in adults: clinical presentation, diagnosis, treatment. Guidelines for therapists, third version. Eksperimental'naya i Klinicheskaya Gastroenterologiya. 2021;185(1):4–52. doi:10.31146/1682-8658-ecg-185-1-4-52 (In Russ.)
5. Liu YL, Patman GL, Leathart JB, Piguet AC, Burt AD, Dufour JF, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol. 2014;61:75–81.
6. Valenti L, Alisi A, Galmozzi E, Bartuli A, Del Menico B, Alterio A, et al. I148M patatin-like phospholipase domain-containing 3 gene variant and severity of pediatric

nonalcoholic fatty liver disease. Hepatology. 2010;52:1274–80.

7. Brus TV, Vasiliev AG, Trashkov AP. The main biochemical markers in non-alcoholic fatty liver disease of various severity (experimental study). Patologicheskaya Fiziologiya i Eksperimental'naya Terapiya. 2022;66(1):44–51. doi:10.25557/0031-2991.2022.01.44-51 (In Russ.)
8. Liang W, Menke AL, Driessen A, Koek GH, Lindeman JH, et al. Establishment of a general NAFLD scoring system for rodent models and comparison to human liver pathology. PLoS One. 2014;9(12):e115922. doi:10.1371/journal.pone.0115922
9. Liu S, Weng R, Gu X, Li L, Zhong Z. Association between apolipoprotein E gene polymorphism and nonalcoholic fatty liver disease in Southern China: a case–control study. J Clin Lab Anal. 2021;35:e24061. doi:10.1002/jcla.24061
10. Reyes C, Nova-Lamperti E, Duran-Sandoval D. Loxin reduced the inflammatory response in the liver and the aortic fatty streak formation in mice fed with a high-fat diet. Int J Mol Sci. 2022;23(13):7329. doi:10.3390/ijms23137329
11. Zhang Y, Ma KL, Ruan XZ, Liu BC. Dysregulation of the low-density lipoprotein receptor pathway is involved in lipid disorder-mediated organ injury. Int J Biol Sci. 2016;12(5):569–79. doi:10.7150/ijbs.14027
12. Au DT, Strickland DK, Muratoglu SC. The LDL receptor-related protein 1: at the crossroads of lipoprotein metabolism and insulin signaling. J Diabetes Res. 2017;2017:8356537. doi:10.1155/2017/8356537
13. Deprince A, Hennuyer N, Kooijman S, Pronk ACM, et al. Apolipoprotein F is reduced in humans with steatosis and controls plasma triglyceride-rich lipoprotein metabolism. Hepatology. 2023;77:1287–302.
14. Jaeschke A, Hui DY. LRP1 and its interacting partners in tissue homeostasis. Curr Opin Lipidol. 2021;32(5):301–7. doi:10.1097/MOL.0000000000000776
15. Arutyunov GP, Martynov AI, Spassky AA. Guide to internal medicine. Moscow: GEOTAR-Media; 2015. 800 p. (In Russ.)
16. Bakulin IG, Sandler YuG, Keiyan VA, Rotin DL. A non-invasive method of steatosis assessment in chronic liver diseases. Terapevticheskii Arkhiv. 2016;88(2):49–57. (In Russ.)
17. Roitberg GE, Shakhrun OO, Platonova OE. The main forms and clinical–laboratory variants of non-alcoholic fatty liver disease. Russian Journal of Rehabilitation Medicine. 2017;(3):28–33. (In Russ.)
18. Nobili V, Donati B, Panera N, Vongsakulyanon A, Alisi A, Dallapiccola B, et al. A 4-polymorphism risk score predicts steatohepatitis in children with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr. 2014;58:632–6.