CLUSTER ANALYSIS OF THE PATHOGENETIC RELATIONSHIPS OF METABOLIC PARAMETERS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE ON THE BACKGROUND OF HYPERTENSION

Professor Oleg Babak, PhD student Anna Bashkirova, Kharkiv, Ukraine, Kharkiv National Medical University

DOI: https://doi.org/10.31435/rsglobal_ws/31102019/6717

The aim of the study was to conduct a cluster analysis of pathogenetic relationships between metabolic parameters, endothelial lipase levels, the severity of steatosis, and clinical parameters in patients with non-alcoholic fatty liver disease with hypertension. To analyze pathogenetic relationships, a cluster analysis was performed with the distribution of parameters into 4 clusters using the Ward's method. The most dense metabolic link by cluster analysis endothelial lipase forms with NAFLD liver fat score (2.639 cu), HbA1C (2.084 cu), total cholesterol (2.272 cu), and alcohol units (2.797 cu).

KEYWORDS: NAFLD, hypertension, endothelial lipase, cluster analysis.

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of impaired liver function in adults and children [1]. NAFLD covers the histological spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH), progressive fibrosis and cirrhosis [2]. Simple steatosis without fibrosis or inflammation in most cases has a benign clinical course, but often leads to an increase in mortality [3]. The possible role of NAFLD as a risk factor for the development of cardiovascular diseases has been discussed for a long time, and only recent data have demonstrated the existing relationship between these conditions [4]. Insulin resistance is often detected in patients with NAFLD, as in patients without obesity and diabetes [5]. NAFLD is often associated with components of the metabolic syndrome, such as type 2 diabetes mellitus (T2DM), obesity, hypertension, and dyslipidemia [7]. However, an increasing number of patients with a normal body mass index (BMI) have been described, with central obesity and latent insulin resistance. [6] Several studies have shown that adopting a healthy lifestyle, reducing weight, and proactively correcting individual components of the metabolic syndrome can help prevent, slow down, or reverse liver damage associated with NAFLD [8].

Endothelial lipase (EL) is a strong determinant of the structural and functional properties of high density lipoproteins (HDL) [9]. EL is a new marker of cardiovascular risk, which is closely associated with dyslipidemia and insulin resistance and has hardly been studied in the presence of NAFLD [10]. Regardless of this, NAFLD increases the risk of premature cardiovascular disease and related mortality, therefore, research and monitoring of the metabolic function of the liver and early detection of accumulation of EL, as well as the relationships between them, are of great importance.
The purpose of the study was to conduct a cluster analysis of pathogenetic relationships between metabolic parameters, EL levels and clinical parameters in patients with liver steatosis on the background of hypertension.

Materials and methods 80 patients have been examined on the basis department of internal medicine №1 of Kharkiv National Medical University and National Institute of Therapy named by L.T. Malaya of National Academy of Medical Sciences of Ukraine. The patients have been divided into three groups according to the severity of liver steatosis. The first group consisted of 16 patients with hypertension without laboratory or instrumental signs of liver steatosis (hypertension group). Patients who, in addition to hypertension, had signs of steatosis during ultrasound and normal level of transaminases (ALT, AST), formed a group with moderate liver steatosis (MLS, n = 20). Patients with hypertension who, in addition to the echoscopic features of hepatic steatosis had increased level of transaminases, were assigned to the group with severe liver steatosis (group SLS, n = 24). The control group consisted of 20 practically healthy individuals. The patients' ages ranged from 45 to 60 years, with an average age of 52.12 + 5.24 years. Among them 28 were female (46.66%) and 32 were male (53.33%).

For identification of liver steatosis and its severity we have used liver fat index (NAFLD liver fat score), which includes such indicators as the presence of metabolic syndrome and T2DM, serum insulin level, AST and the ratio AST/ALT and is calculated by the formula [11]:

\[
\text{NAFLD liver fat score} = -2.89 + 1.18 \times \text{metabolic syndrome (yes}=1/\text{no}=0) + 0.45 \times \text{type 2 diabetes (yes}=2/\text{no}=0) + 0.15 \times \text{fasting serum Insulin (mU/L)} + 0.04 \times \text{fasting serum АSТ(U/L)} - 0.94 \times \text{AST/ALT}. 
\]

The FIB-4 index has been used to identify liver fibrosis, which includes indicators such as AST, ALT, platelet count, and is calculated by the formula [12]:

\[
\text{FIB4} = \text{Age (years)} \times \text{AST (IU/L)} / \text{platelet count (×109/L)} \times \sqrt{\text{ALT (IU/L)}} 
\]

Serum endothelial lipase (EL) concentration was determined by enzyme-linked immunosorbent assay using Aviscera Bioscience INC reagent kit (USA) using a Labline 90 enzyme immunoassay analyser.

For excluding the alcoholic genesis of NAFLD all patients have been interviewed to determine alcohol units. This test has international standardization and allows detecting alcohol abuse by the formula:

\[
\text{Alcohol units} = \text{amount (liters)} \times \text{alcoholic strength (％)} \times 0.789
\]

Alcohol abuse was eliminated by less than 14 units per week regardless of gender [13].

In order to monitor the implementation of dietary recommendations, we have used a questionnaire designed by the original questionnaire, which asked patients about the consumption of 15 basic foods that are not recommended for overweight, carbohydrate metabolism disorders and liver steatosis.

The statistical processing of the survey data has been performed using Microsoft Exel and Statistica 7.0 using standard methods of virion statistics.

Results and discussion. Results of studies are presented in table 1.

Table 1. Anthropometric, laboratory and surrogate ratios indicating the severity of liver steatosis

| Parameter                      | Control, n=20 | Hypertension group, n=16 | MLS group, n=20 | SLS group, n=24 | Significance of difference, P |
|--------------------------------|---------------|--------------------------|----------------|----------------|-----------------------------|
|                                | Mean          | SD           | Mean          | SD           | Mean          | SD           | Mean          | SD           | Mean          | SD           |                                    |
|                                | 0             | 1             | 2             | 3             | 4             | 5             | 6             | 7             | 8             | 9             | 10                        |
| AST/ALT, U                    | 0.73          | 0.34         | 0.95          | 0.26         | 1.19          | 0.38        | 1.75          | 0.77        | 12, 23, 13     |                          |                          |
| ALT, U/L                      | 18.15         | 7.26        | 22.44         | 6.29         | 24.65         | 7.19        | 62.54         | 40.78       | 23, 13         |                          |                          |
| AST, U/L                      | 11.45         | 3.78        | 24.56         | 7.84         | 22.90         | 10.18       | 38.71         | 20.70       | 23, 13         |                          |                          |
| AP, mmol/l                    | 1334,90       | 464,11      | 1422.50       | 302,46      | 1457,13       | 384,29      | 1834,06       | 690,13      | 13, 23         |                          |                          |
| NAFLD liver fat score         | -1.93         | 0.65        | -0.308        | 1.14        | 2.308         | 2.43        | 4.48          | 3.21        | For all groups < 0.001 |                          |                          |
| Fib-4                         | 0.43          | 0.16        | 1.07          | 0.36         | 1.14          | 0.72        | 1.36          | 0.63        | With control - all groups < 0.0001 | 13, 23           |                          |
| BMI, kg/m2                    | 21.44         | 1.57        | 25.91         | 3.42         | 30.00         | 2.79        | 29.04         | 5.44        | 01, 02, 03, 12 |                          |                          |
| WC, cm                        | 75.50         | 6.83        | 79.31         | 8.58         | 98.08         | 10.53       | 104.10        | 8.67        | 02, 03, 12, 13, 23 |                          |                          |
| WC/height, U                  | 0.44          | 0.03        | 0.47          | 0.04         | 0.57          | 0.05        | 0.60          | 0.04        | 01, 02, 03, 12, 13, 23 |                          |                          |
Continuation of table 1

|     | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| SBP, mm Hg | 116.00 | 161.56 | 17.77 | 163.89 | 17.54 | 169.17 | 22.20 | 01, 02, 03 |
| DBP, mm Hg | 73.50 | 101.56 | 7.47 | 102.78 | 8.26 | 101.46 | 9.94 | 01, 02, 03 |
| Cholesterol, mmol/l | 3.85 | 0.77 | 5.25 | 1.47 | 5.74 | 0.85 | 5.80 | 1.42 | 01, 02, 03 |
| Triglycerides, mmol/l | 0.92 | 0.16 | 1.13 | 0.38 | 1.70 | 0.83 | 1.96 | 0.67 | 0.37 | 12, 13, 23 |
| HDL, mmol/l | 1.77 | 0.28 | 1.47 | 0.42 | 1.42 | 0.30 | 1.20 | 0.27 | 13, 23 |
| LDL, mmol/l | 2.36 | 0.46 | 3.45 | 1.14 | 3.34 | 0.85 | 3.75 | 1.25 |
| VLDL, mmol/l | 0.38 | 0.05 | 0.56 | 0.16 | 0.70 | 0.40 | 0.92 | 0.31 | 13, 23 |
| EL, ng / ml | 8.23 | 2.47 | 10.54 | 2.69 | 13.21 | 5.59 | 13.71 | 3.71 | 01, 02, 03, 12, 13 |
| Diet | 2.36 | 0.81 | 2.57 | 0.53 | 2.64 | 1.15 | 2.08 | 0.86 |
| Alcohol units | 4.26 | 2.27 | 4.29 | 1.82 | 6.39 | 2.99 | 6.62 | 2.98 | 02, 03, 12, 13 |
| Fasting glucose, mmol/l | 4.36 | 0.72 | 5.01 | 0.60 | 6.32 | 1.75 | 5.73 | 0.91 | 12, 13 |
| Fasting insulin, mU/l | 7.91 | 3.71 | 17.77 | 6.86 | 24.51 | 9.49 | 33.28 | 13.82 | 12, 13, 23 |
| HOMA-IR | 1.55 | 0.85 | 3.61 | 1.80 | 7.02 | 4.76 | 8.35 | 5.25 | 12, 13 |
| HbA1C, % | - | - | 5.40 | 0.63 | 6.64 | 1.76 | 5.79 | 0.49 | 12, 23, 13 |

For the analysis of pathogenetic relationships, a cluster analysis was performed. The graph of parameter merging using Ward's method showed that it is advisable to distribute data into 3-4 clusters (Fig. 1).

![Plot of Linkage Distances across Steps](image_url)

**Fig. 1. Cluster aggregation of data parameters**

The first and second cluster illustrates the existence of offline hypertension and the close relationship of hyperinsulinism with BMI.

The third cluster covered liver steatosis associated with alcohol consumption, compensation for carbohydrate metabolism (by HbA1C) and the level of total cholesterol and EL.

The fourth cluster demonstrates the connection of lipid profile parameters with the patient’s nutritional preferences (Table 2).
Table 2. Clustering of model components containing parameters of lipid-carbohydrate metabolism with hypertension and liver steatosis

| Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 |
|-----------|-----------|-----------|-----------|
| Parameter | Mean      | Parameter | Mean      | Parameter | Mean      | Parameter | Mean      |
| SBP       | 33,04     | Fasting insulin | 8,520     | HbA1C     | 2,084     | Triglycerides | 0,840     |
| DBP       | 33,04     | BMI       | 8,520     | EL        | 5,386     | HDL       | 1,231     |
|           |           |           |           | Cholesterol | 2,72    | LDL       | 1,864     |
|           |           |           |           | Alcohol units | 2,797   | VLDL      | 1,470     |
|           |           |           |           | NAFLD liver fat score | 2,639 | Diet | 1,306     |
|           |           |           |           | WC/height | 1,472     |           |           |

Grouping the results of the examination of patients allowed us to identify 4 main clusters. Cluster 1 - overweight patients with abdominal fat distribution and moderate hypertension, moderate hyperinsulinism with prediabetic levels of HbA1C, increased levels of total cholesterol, LDL and borderline HDL, moderate steatosis (table 3).

Table 3. Basic statistical analysis of clinical and laboratory parameters Cluster 1

| Parameters                  | Valid N | Mean  | Minimum | Maximum | Variance | Std.Dev. | Coef.Var. |
|-----------------------------|---------|-------|---------|---------|----------|----------|-----------|
| WC/height                   | 13      | 0,5391| 0,3593  | 0,6221  | 0,00544  | 0,073755 | 13,68212  |
| Fasting insulin            | 13      | 25,0715| 15,7000 | 46,0500 | 93,55990 | 9,672637 | 38,58015  |
| HbA1C                      | 13      | 6,1092 | 4,3300  | 10,3000 | 2,36916  | 1,539207 | 25,19477  |
| EL                         | 13      | 12,0465| 7,0665  | 17,4200 | 9,18047  | 3,029928 | 25,15198  |
| Cholesterol                | 13      | 5,9615 | 4,0200  | 7,7900  | 1,40600  | 1,185748 | 19,88996  |
| Triglycerides              | 13      | 1,4846 | 0,7900  | 4,1600  | 0,73911  | 0,859715 | 57,90828  |
| HDL                        | 13      | 1,4046 | 0,6900  | 2,0000  | 0,13968  | 0,373734 | 26,60755  |
| LDL                        | 13      | 3,7492 | 2,2800  | 5,3500  | 0,86937  | 0,932402 | 24,86917  |
| VLDL                       | 13      | 0,6277 | 0,1900  | 1,8700  | 0,16587  | 0,407270 | 64,88377  |
| SBP                        | 13      | 142,6923| 130,0000| 150,0000| 52,56410 | 7,250111 | 5,08094   |
| DBP                        | 13      | 94,6154| 80,0000 | 100,0000| 56,08974 | 7,489309 | 7,91553   |
| BMI                        | 13      | 27,5394| 16,8525 | 32,4500 | 17,56233 | 4,190744 | 15,21728  |
| Alcohol units              | 13      | 6,4231 | 2,0000  | 9,2000  | 5,46692  | 2,338145 | 36,40226  |
| Diet                       | 13      | 2,7692 | 1,0000  | 4,0000  | 0,85897  | 0,926809 | 33,46809  |
| NAFLD liver fat score      | 13      | 2,1543 | -0,8161 | 6,1263  | 3,98455  | 1,996134 | 92,65719  |

Cluster 2 included patients with grade 1 obesity with severe abdominal fat distribution and severe hypertension, a pre-diabetic level of HBA1C, an increase in total cholesterol, triglycerides, LDL and a distinct decrease in HDL and severe liver steatosis (Table 4).
Table 4. Basic statistical analysis of clinical and laboratory indicators of representatives of Cluster 2

| Parameters         | Valid N | Mean    | Minimum | Maximum | Variance | Std.Dev. | Coef.Var. |
|--------------------|---------|---------|---------|---------|----------|----------|-----------|
| WC/height          | 11      | 0.5934  | 0.5058  | 0.7317  | 0.0038   | 0.06164  | 10.38688  |
| Fasting insulin    | 11      | 53.0082 | 35.3300 | 73.3500 | 172.3410 | 13.12787 | 24.76574  |
| HbA1C              | 11      | 6.0109  | 4.8600  | 7.4400  | 0.9214   | 0.95992  | 15.96965  |
| EL                 | 11      | 13.6655 | 7.7600  | 19.7200 | 21.8332  | 4.67261  | 34.19283  |
| Cholesterol        | 11      | 6.4600  | 4.1500  | 8.5500  | 1.4985   | 1.22414  | 18.94954  |
| Triglycerides      | 11      | 2.5227  | 0.9700  | 5.6900  | 1.8036   | 1.34230  | 21.77624  |
| HDL                | 11      | 1.0718  | 0.7600  | 1.5600  | 0.0545   | 0.23340  | 53.23534  |
| LDL                | 11      | 4.2218  | 1.9400  | 6.4000  | 1.8807   | 1.37138  | 32.48310  |
| VLDL               | 11      | 1.0982  | 0.3700  | 2.5600  | 0.4095   | 0.63995  | 58.27362  |
| SBP                | 11      | 175.9091| 160.0000| 180.0000| 54.0909  | 7.35465  | 4.18094   |
| DBP                | 11      | 105.0000| 100.0000| 120.0000| 45.0000  | 6.70820  | 6.38877   |
| BMI                | 11      | 30.0625 | 22.9481 | 48.3343 | 51.2784  | 7.16089  | 23.82002  |
| Alcohol units      | 11      | 6.1909  | 1.5000  | 10.0000 | 8.6669   | 2.94396  | 47.55298  |
| Diet               | 11      | 2.9091  | 1.0000  | 4.0000  | 1.0909   | 1.04447  | 35.90352  |
| NAFLD liver fat score | 11      | 6.8779  | 0.9228  | 10.9828 | 11.5463  | 3.39799  | 49.40435  |

Cluster 3 was composed of overweight patients with abdominal fat distribution, a slight increase in insulin at normal HbA1C, a slight increase in total cholesterol and LDL, normal triglycerides and marginal HDL (Table 5).

Table 5. Basic statistical analysis of clinical and laboratory indicators of representatives of Cluster 3

| Parameters         | Valid N | Mean    | Minimum | Maximum | Variance | Std.Dev. | Coef.Var. |
|--------------------|---------|---------|---------|---------|----------|----------|-----------|
| WC/height          | 23      | 0.5448  | 0.4606  | 0.6875  | 0.00439  | 0.066239 | 12.1574   |
| Fasting insulin    | 23      | 18.1643 | 4.8600  | 37.1000 | 85.67632 | 9.256150 | 50.9578   |
| HbA1C              | 23      | 5.6678  | 4.3700  | 7.2800  | 0.61653  | 0.785192 | 13.8535   |
| EL                 | 23      | 11.2209 | 5.3300  | 18.9900 | 10.31109 | 3.211089 | 28.6171   |
| Cholesterol        | 23      | 5.3009  | 2.8400  | 6.9900  | 1.65284  | 1.285627 | 24.2531   |
| Triglycerides      | 23      | 1.3804  | 0.7500  | 2.6900  | 0.29569  | 0.543770 | 39.3912   |
| HDL                | 22      | 1.3318  | 0.8000  | 2.3000  | 0.11832  | 0.343977 | 25.8276   |
| LDL                | 22      | 3.2109  | 1.0000  | 5.1600  | 1.38308  | 1.176042 | 36.6265   |
| VLDL               | 23      | 0.6991  | 0.3400  | 1.5000  | 0.10728  | 0.327538 | 46.8493   |
| SBP                | 23      | 168.2609| 150.0000| 180.0000| 53.65613 | 7.325034 | 4.3534    |
| DBP                | 23      | 103.0435| 100.0000| 120.0000| 31.22530 | 5.87960  | 5.4229    |
| BMI                | 23      | 28.1174 | 22.6003 | 37.1255 | 13.17259 | 3.629407 | 12.9080   |
| Alcohol units      | 23      | 5.3000  | 1.5000  | 11.5000 | 8.36909  | 2.892938 | 54.5837   |
| Diet               | 23      | 3.0000  | 1.0000  | 4.0000  | 0.90909  | 0.953463 | 31.7821   |
| NAFLD liver fat score | 23      | 0.8359  | -2.7277 | 4.9742  | 4.40681  | 2.099239 | 251.1388  |

Cluster 4 is the least numerically representative, but the most unexpected. It included patients with severe abdominal obesity, diabetic levels of HbA1C, moderate hyperinsulinism, with an increase in total cholesterol, TG, LDL and a decrease in HDL (Table 6).
Table 6. Basic statistical analysis of clinical and laboratory indicators of representatives of Cluster 4

| Parameters       | Valid N | Mean   | Minimum | Maximum | Variance | Std.Dev. | Coef.Var. |
|------------------|---------|--------|---------|---------|----------|----------|-----------|
| WC/height        | 5       | 0.5782 | 0.4821  | 0.6180  | 0.0032   | 0.05692  | 9.84298   |
| Fasting insulin  | 5       | 21.9720| 16.1700 | 27.5400 | 26.5516  | 5.15283  | 23.45179  |
| HbA1C            | 5       | 6.6280 | 5.4200  | 9.9600  | 4.8687   | 2.20652  | 34.86912  |
| EL               | 5       | 13.9380| 9.2300  | 18.2800 | 14.5143  | 3.80977  | 27.33367  |
| Cholesterol      | 5       | 5.6600 | 4.6000  | 6.7600  | 0.7388   | 0.85951  | 15.18561  |
| Triglycerides    | 5       | 2.2500 | 1.2300  | 3.2900  | 0.8322   | 0.91222  | 40.54322  |
| HDL              | 5       | 1.1440 | 0.7800  | 1.6100  | 0.1012   | 0.31817  | 27.81177  |
| LDL              | 5       | 3.5060 | 2.4400  | 4.5000  | 0.6001   | 0.77468  | 22.09585  |
| VLDL             | 5       | 1.0000 | 0.5000  | 1.4800  | 0.1811   | 0.42562  | 42.56172  |
| SBP              | 5       | 203.0000| 190.0000| 240.0000| 445.0000| 21.09502| 10.39164  |
| DBP              | 5       | 114.0000| 100.0000| 130.0000| 130.0000| 11.40175| 10.00154  |
| BMI              | 5       | 30.1405| 24.8016| 33.9100| 12.8248| 3.58118| 11.88161  |
| Alcohol units    | 5       | 6.8800 | 4.5000  | 11.5000| 10.6970| 3.27063| 47.53818  |
| Diet             | 5       | 2.6000 | 2.0000  | 3.0000  | 0.3000   | 0.54772  | 21.06625  |
| NAFLD liver fat score | 5    | 1.7530 | 0.2018  | 2.9370  | 1.5633   | 1.25032  | 71.32395  |

For better visualization, we have reduced the average values of the parameters for the clusters into a common table (Table 7), which allows us to compare trends.

Table 7. The average values of clinical and laboratory indicators with the distribution of clusters

| Parameters       | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 |
|------------------|-----------|-----------|-----------|-----------|
| WC/height        | 0,54      | 0,59      | 0,54      | 0,58      |
| Fasting insulin  | 25,07     | 53,01     | 18,16     | 21,97     |
| HbA1C            | 6,11      | 6,01      | 5,67      | 6,33      |
| EL               | 12,05     | 13,67     | 11,22     | 13,94     |
| Cholesterol      | 5,96      | 6,46      | 5,30      | 5,66      |
| Triglycerides    | 1,48      | 2,52      | 1,38      | 2,25      |
| HDL              | 1,40      | 1,07      | 1,33      | 1,14      |
| LDL              | 3,75      | 4,22      | 3,21      | 3,51      |
| VLDL             | 0,63      | 1,10      | 0,70      | 1,00      |
| SBP              | 142,69    | 175,91    | 168,26    | 203,00    |
| DBP              | 94,62     | 105,00    | 103,04    | 114,00    |
| BMI              | 27,54     | 30,06     | 28,12     | 30,14     |
| Alcohol units    | 6,42      | 6,19      | 5,30      | 6,88      |
| Diet             | 2,77      | 2,91      | 3,00      | 2,60      |
| NAFLD liver fat score | 2,15 | 6,88 | 0,84 | 1,75 |

The lowest variability of characteristics in the first cluster is inherent in indicators of blood pressure, BMI and insulin concentration, and the largest - in the severity of liver steatosis.

The lowest variability in the second cluster is inherent in blood pressure and anthropometric parameters, as well as indicators of carbohydrate metabolism. The variability of the severity of steatosis is half that of the previous group.

Cluster 3 from cluster 1 is distinguished by lower numbers of blood pressure, less severe liver steatosis and less alcohol abuse. The indicated group is determined by the relative stability of lipid
profile parameters, the stability of carbohydrate metabolism compensation, but the high variability of NAFLD. Thus, it is understood that the formation of steatosis is not latent even under conditions of a moderate shift in metabolic parameters.

Cluster 4 from cluster 2 is distinguished by pronounced hypertension, low insulin values, less compensation for carbohydrate metabolism, but also less severity of liver steatosis. In addition, alcohol abuse is the highest in this group, and the lowest adherence to dietary recommendations. The fact that dyslipidemia is isolated is also obvious, which is confirmed by the data of a large population study under the auspices of NHANES, which included more than 23 thousand Americans, in patients with hepatic pathology with high levels of transaminases lipid profiles with low LDL and high HDL can be recorded, which may be caused by a defect in the synthesis of lipoproteins or a violation of the synthetic function of the liver and a marker of latent hepatopathies [14].

**Conclusions.** 1. Clustering of patient examination results demonstrates a reliable distribution of groups according to the severity of liver steatosis.

2. In case of non-compliance with dietary recommendations and the use of alcohol even within acceptable limits, the progression of liver steatosis occurs even against the background of minimal metabolic disturbances

3. The presence of genetically determined hyperlipidemia in combination with insulin resistance is an unfavorable background in the implementation of the clinical manifestations of metabolic disorders.

**REFERENCES**

1. Estes, C.; Razavi, H.; Loomba, R.; Younossi, Z.; Sanyal, A.J. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018, 67, 123–133.

2. Younossi, Z.M.; Koenig, A.B.; Abdelatif, D.; Fazel, Y.; Henry, L.; Wyner, M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016, 64, 73–84.

3. Younossi, Z.; Anstee, Q.M.; Marietti, M.; Hardy, T.; Henry, L.; Eslam, M.; George, J.; Bugianesi, E. Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention. Nat. Rev. Gastroenterol. Hepatol. 2018, 15, 11–20.

4. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. Liver Int 2006; 26: 856-863.

5. Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, Karim R, Lin R, Samarasinghe D, Liddle C, Weltman M, George J. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology 2002; 35: 373-379.

6. Marchesini G, Marzocchi R, Agostini F, Bugianesi E. Nonalcoholic fatty liver disease and the metabolic syndrome. Curr Opin Lipidol 2005; 16: 421-427.

7. Estes, C.; Razavi, H.; Loomba, R.; Younossi, Z.; Sanyal, A.J. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018, 67, 123–133.

8. Kumari RSP, Vipula VA, Reddy BS, Nagadeepa W, Reddy BLN. Predictors of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in patients with type-2 diabetes mellitus. Int J Med Sci Public Health 2017;6:372-376.

9. Schilcher I, Ledinski G, Rudulović S, et al. Endothelial lipase increases antioxidative capacity of high-density lipoprotein. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;1864(10):1363–1374. doi:10.1016/j.bbalip.2019.06.011

10. Junji Kobayashi. Which is the Best Predictor for the Development of Atherosclerosis Among Circulating Lipoprotein Lipase, Hepatic Lipase, and Endothelial Lipase? Journal of Atherosclerosis and Thrombosis, 2019, Volume 26, Issue 9: 758-759.

11. Kotronen A, Peltonen M, Hakkarainen A et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology. vol. 137, no. 3: 865–872.

12. Sterling, R. K., Lissen, E., Clunieck, N., Sola, R., Correa, M. C., Montaner, J., Sulkowski, M., Torriani, F. J., Dieterich, D. T., Thomas, D. L., Messinger, D. and Nelson, M. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology, 2006, 43: 1317-1325. doi:10.1002/hep.21178

13. Department of Health. UK Chief Medical Officers’ Alcohol Guidelines Review: summary of the proposed new guidelines. London: Department of Health. 2016.

14. Jiang ZG, Mukamal K, Tapper E, Robson SC, Tsugawa Y Low LDL–C and High HDL–C Levels Are Associated with Elevated Serum Transaminases amongst Adults in the United States: A Cross-sectional Study. PLoS ONE, 2014,9(1):e85366. https://doi.org/10.1371/journal.pone.0085366