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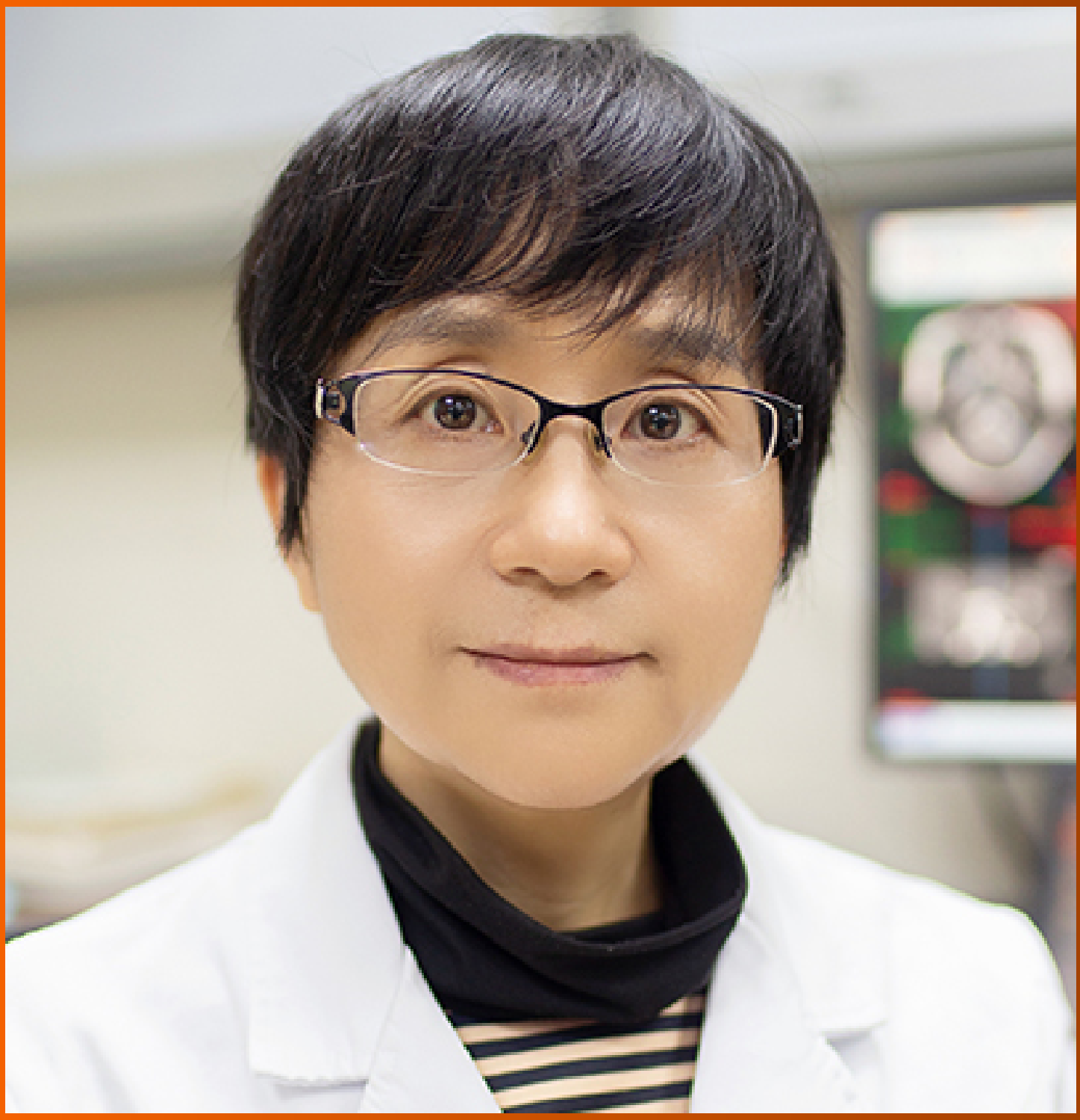

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AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

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ORIGINAL ARTICLE

Clinical Trials Study

Ursodeoxycholic acid as a means of preventing atherosclerosis, steatosis and liver fibrosis in patients with nonalcoholic fatty liver disease

Maria Nadinskaia, Marina Maevskaya, Vladimir Ivashkin, Khava Kodzoeva, Irina Pirogova, Evgeny Chesnokov, Alexander Nersesov, Jamilya Kaibullayeva, Akzhan Konysbekova, Aigul Raissova, Feruza Khamrabaeva, Elena Zueva

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Author contributions: Nadinskaia M, Maevskaya M, and Ivashkin V contributed equally to this work and should be considered as co-first authors; Maevskaya M, and Ivashkin V conceived the design; Nadinskaia M and Kodzoeva Kh analyzed the results; Nadinskaia M, and Maevskaya M wrote the original draft; Kodzoeva Kh, Pirogova I, Chesnokov E, Nersesov A, Kaibullayeva J, Konysbekova A, Raissova A, Khamrabaeva F, and Zueva E conducted the study; all the authors revised the manuscript and approved the final version.

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Abstract

BACKGROUND

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in patients with nonalcoholic fatty liver disease (NAFLD). Weight loss is a key factor for successful NAFLD and CVD therapy. Ursodeoxycholic acid (UDCA), which is one of the first-line therapeutic agents for treatment of NAFLD, is reported to have a beneficial effect on dyslipidemia and ASCVD risk because of antioxidant properties.

AIM

To evaluate the effects of 6 mo of UDCA treatment on hepatic function tests, lipid profile, hepatic steatosis and fibrosis, atherogenesis, and ASCVD risk in men and women with NAFLD, as well as to assess the impact of > 5% weight reduction on these parameters.

METHODS

An open-label, multicenter, international noncomparative trial was carried out at primary health care settings and included 174 patients with ultrasound-diagnosed NAFLD who received 15 mg/kg/d UDCA for 6 mo and were prescribed lifestyle modification with diet and exercise. The efficacy criteria were liver enzymes, lipid profile, fatty liver index (FLI), noninvasive liver fibrosis tests (nonalcoholic fatty liver disease fibrosis score and liver fibrosis index), carotid intima-media thickness (CIMT), and ASCVD risk score. To test statistical hypotheses, the Wilcoxon test, paired *t*-test, Fisher's exact test, and Pearson's chi-squared test were used.

RESULTS

The alanine aminotransferase (ALT) level changed by -14.1 U/L (-31.0; -5.3) from baseline to 3 mo and by -6.5 U/L (-14.0; 0.1) from 3 to 6 mo. The magnitude of ALT, aspartate transaminase, and glutamyltransferase decrease was greater during the first 3 mo of treatment compared to the subsequent 3 mo ($P < 0.001$, $P < 0.01$, $P < 0.001$, respectively). At 6 mo, in the total sample, we observed a statistically significant decrease in body weight and levels of FLI: 84.9 ± 10.4 *vs* 72.3 ± 17.6, $P < 0.001$, total cholesterol: 6.03 ± 1.36 *vs* 5.76 ± 1.21, $P < 0.001$, low-density lipoprotein: 3.86 ± 1.01 *vs* 3.66 ± 0.91, $P < 0.001$, and triglyceride: 3.18 (2.00; 4.29) *vs* 2.04 (1.40; 3.16), $P < 0.001$. No effect on nonalcoholic fatty liver disease fibrosis score or liver fibrosis index was found. The CIMT decreased significantly in the total sample (0.985 ± 0.243 *vs* 0.968 ± 0.237, $P = 0.013$), whereas the high-density lipoprotein ($P = 0.036$) and 10-year ASCVD risk ($P = 0.003$) improved significantly only in women. Fifty-four patients (31%) achieved > 5% weight loss. At the end of the study, the FLI decreased significantly in patients with (88.3 ± 10.2 *vs* 71.4 ± 19.6, $P < 0.001$) and without > 5% weight loss (83.5 ± 10.3 *vs* 72.8 ± 16.7, $P < 0.001$). The changes in ALT, aspartate transaminase, glutamyltransferase, total cholesterol, and low-density lipoprotein levels were similar between the subgroups.

CONCLUSION

UDCA normalizes liver enzymes greatly within the first 3 mo of treatment, improves lipid profile and hepatic steatosis independent of weight loss, and has a positive effect on CIMT in the total sample and 10-year ASCVD risk in women after 6 mo of treatment.

Key Words: Ursodeoxycholic acid; Nonalcoholic fatty liver disease; Liver function tests; Fatty liver index; Carotid intima-media thickness; Atherosclerotic cardiovascular disease

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Core Tip: An open-label, multicenter, international noncomparative trial demonstrated the effect of ursodeoxycholic acid (UDCA) on hepatic steatosis and fibrosis,

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atherogenesis, and atherosclerotic cardiovascular disease risk in 174 ultrasound-diagnosed nonalcoholic fatty liver disease patients who received 15 mg/kg/d UDCA for 6 mo and were prescribed lifestyle modifications with diet and exercise. UDCA had a bidirectional positive effect on the liver and cardiovascular system in patients with and without > 5% weight loss: It improved liver enzymes, lipid profiles, and hepatic steatosis in addition to improving carotid intima-media thickness and atherosclerotic cardiovascular disease risk.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is currently the leading cause of liver disease and liver transplantation in developed countries; the number of people with this pathology is steadily growing[1,2]. NAFLD-related morbidity in the world is approximately 25%, being the highest in Middle Eastern and South American countries, while in Europe and Asia, the morbidity is approximately the same[3].

According to the DIREG 1, DIREG_L_01903, and DIREG 2 studies, up to 27% of the population suffers from NAFLD in Russia[4]. In Kazakhstan, the morbidity is almost 30%[5], and in Uzbekistan, it reaches 37%[6]. Among the NAFLD risk factors, obesity is considered to be one of the key factors: a body mass index (BMI) increase of 1 kg/m^2 is associated with a 13%-38% increased risk of NAFLD development[7]. Such a high morbidity puts this disease among the most important diseases in primary health care.

NAFLD is often associated with cardiovascular diseases (CVDs), which have become the main cause of decreased life expectancy in patients[8,9]. According to one prospective study with over almost three decades of follow-up, 30% of deaths in patients with NAFLD were due to CVD, and 19% were due to liver disease[10].

The gold standard methods for the diagnosis of NAFLD are liver biopsy, proton magnetic resonance spectroscopy, and quantitative fat/water selective magnetic resonance imaging.

An ultrasound examination (US), a less expensive and more accessible method, is preferred for hepatic steatosis detection in primary health care settings. NAFLD is diagnosed after steatosis secondary causes are excluded. At all stages of the disease, the following validated scales are used: the fatty liver index (FLI), nonalcoholic fatty liver disease fibrosis score (NFS), and liver fibrosis index (FIB-4)[11].

Validated scales are also used to assess the CVD risk in patients with NAFLD. To accomplish this task, the Atherosclerotic Cardiovascular Disease (ASCVD) 2013 Risk Calculator and the Framingham Risk Score (2008) are used, the results of which, according to a recent study, correlate with the severity of steatosis according to US data and fibrosis severity, as assessed by the NFS and FIB-4[12].

In a number of studies, it has been noted that hepatic steatosis is an early predictor of coronary atherosclerosis and is associated with an increase in carotid intima-media thickness (CIMT)[13,14] as well as with uncalcified atherosclerotic plaque formation[15].

There is currently no approved standard therapy for NAFLD. The main factor in successful treatment is weight loss, which is a key link in both NAFLD itself and CVD pathogenesis[16]. Among the NAFLD drug treatments, those that affect various disease pathogenesis links may be considered, including increased sensitivity to insulin (pioglitazone, rosiglitazone and liraglutide), lipid-lowering agents (statins), and antioxidant and cytoprotective drugs such as ursodeoxycholic acid (UDCA), vitamin E, obeticholic acid, and omega-3 fatty acid-polyunsaturated fatty acids[17-24].

Several antioxidant mechanisms may explain the beneficial effect of UDCA on dyslipidemia and CVD risk. UDCA treatment seems to protect against iron-dependent and hydroxyl radical-dependent oxidative damage, inhibit lipid peroxidation products, and prevent reactive oxygen species-induced oxidative stress by activation of the PI3K/Akt/Nrf2 pathway in hepatocytes[25-33]. Recent studies demonstrated that

the oxidative stress products increase significantly along with the thickening of artery intima, and elevated peroxidative glutathione redox status is associated with atherosclerosis progressing[34,35].

Study Purpose: To evaluate the effects of 6 mo of UDCA treatment on liver function tests (LFT), lipid profile, hepatic steatosis and fibrosis, atherogenesis, and CVD risk in men and women with NAFLD, as well as to assess the impact of > 5% weight reduction on these parameters.

MATERIALS AND METHODS

An open international noncomparative study with the code USPEH –Ursodeoxycholic acid as a means of preventing atherosclerosis, steatosis and liver fibrosis in patients with nonalcoholic fatty liver disease – was carried out at primary health care settings.

The study protocol passed the review procedure and was approved at a meeting of an independent interdisciplinary committee on the ethical review of clinical trials in each center of the Russian Federation, Kazakhstan and Uzbekistan. The study took place from November 1, 2017, until August 31, 2018.

Inclusion criteria

Age over 18; proven NAFLD case based on US abdominal data; FLI index value > 60; the physician's decision to prescribe UDCA regardless of the patient's inclusion in the study; and availability of the patient's written informed consent to participate in the program and use of personal data in accordance with the legislation of the participating countries.

Non-inclusion criteria

Pregnancy; hepatic decompensation (serum albumin ≤ 35 g/L, international normalized ratio ≥ 1.2, platelets < 150 × 10^9/L); UDCA allergy in past medical history; presence of atherosclerosis complications; use of statins; use of other drugs that potentially affect the studied parameters; use of medications in past medical history associated with secondary hepatic steatosis development (amiodarone, methotrexate, tamoxifen, glucocorticoids, valproic acid, and antiretroviral drugs); unhealthy alcohol use (40 g ethanol per day for men and 20 g ethanol per day for women); scores on the AUDIT (Alcohol Use Disorders Identification Test) questionnaire > 8 for both men and women; type 1 diabetes mellitus; parenteral nutrition; fasting; and presence of a secondary etiology of liver disease (viral, metabolic, autoimmune, cholestatic, or drug etiology).

Exclusion criteria

A patient's decision to discontinue participation in the study at any stage; acute hepatocellular or cholestatic injury that occurred during the study: Increased alanine aminotransferase (ALT), aspartate transaminase (AST), glutamyltransferase (GGT), or alkaline phosphatase levels by two or more times; and the need to take other drugs that potentially affect the studied parameters, arising during the study.

To select study participants, a total of 207 Caucasian patients from regional registries of patients with NAFLD were screened as follows: 150 people from 3 centers in the Russian Federation (Moscow, Tyumen, Chelyabinsk), 47 people from 3 centers in Kazakhstan (Almaty, Nur-Sultan, Shymkent), and 10 people from 1 center in Uzbekistan (Tashkent).

The inclusion criteria were met by 183 patients who had been receiving daily UDCA (Ursosan®) therapy at a dose of 15 mg/kg body weight for 6 mo. In addition, total sample were given standard recommendations to modify their lifestyle and diet: strength or aerobic exercise for at least 150 min per week, Mediterranean diet, and consumption of no more than 1500 kcal/d[36].

Each patient was assessed according to the following parameters: weight, height, BMI (weight, kg/height, m^2), waist circumference (WC), smoking, alcohol consumption, metabolic syndrome criteria according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[37], complete blood count and LFT, and lipid profile.

The criteria for the treatment effectiveness evaluation were as follows: LFT [ALT, AST, and GGT upper limit of normal (ULN) = 40 U/L]; lipid profile [total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG)]; noninvasive hepatic steatosis assessment by the FLI; noninvasive fibrosis assessment by the NFS and FIB-4; 10-year and lifetime ASCVD risk; and CIMT.

FLI was calculated using the formula FLI = e^y /(1 + e^y) × 100, where y = 0.953 × ln (TG, mg/dL) + 0.139 × BMI, kg/m^2 + 0.718 × ln (GGT, U/L) + 0.053 × WC, cm - 15.745).

FLI index values that exceeded a value of 60 corresponded to a high probability of hepatic steatosis, indicators from 30 to 59 constituted the "gray zone", and a result less than 30 excluded the likelihood of hepatic steatosis[38].

The noninvasive liver fibrosis assessment was carried out using the NFS score, which was calculated by the formula NFS = -1.675 + [0.037 × age (years)] + [0.094 × BMI (kg/m^2)] + [1.13 × Impaired fasting glucose/diabetes (yes = 1, no = 0)] + (0.99 × AST/ALT ratio) – [0.013 × platelet count (× 10^9/L)] – [0.66 × albumin (g/dL)] URL: https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score. Fibrosis index values of -1.455 and below have made it possible to exclude the presence of advanced liver fibrosis, and a value of more than 0.675 testified in favor of the F3-F4 fibrosis stages[39].

Another method for liver fibrosis assessment was the calculation of the fibrosis index FIB-4 according to the formula FIB-4 = age (years) × AST (U/L)/platelets (10^9/L) × √ ALT (U/L). A FIB-4 value less than 1.45 excluded the presence of severe liver fibrosis, and a value greater than 3.25 indicated the presence of advanced fibrosis.

The risk of developing complications from the cardiovascular system was assessed using the ASCVD 2013 calculator. In accordance with the age limits, the CVD risk over 10 years in patients over 40 years of age and the risk over a lifetime in those under 59 years of age were calculated. A program presented in the public domain was used for calculation[40].

The CIMT was assessed with a standard method in accordance with the European Society of Cardiology recommendations. CIMT was measured from longitudinal images of both the right and left common carotid arteries during B-mode ultrasonography as the distance from the echogenic lumen-intima interface to the echogenic media-adventitia interface; the highest value for each patient was used for analysis[41]. Values of the 95th percentile for the corresponding age and sex were used as the ULN[42].

All data were entered into the patient's Case Report Form. After 3 mo of the study, 9 patients were excluded due to acute hepatocellular or cholestatic injury associated with nonsteroidal anti-inflammatory drug intake and alcohol consumption during the study. The study was completed by 174 patients who were included in the final analysis (Figure 1).

To assess treatment effectiveness, the comparisons were made for the total sample and for men and women separately. The body weight, BMI, WC, and LFT were compared between baseline and 3 mo as well as between 3 and 6 mo of the treatment. The lipid profile, FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT were compared between baseline and the end of the follow-up (Figure 2).

Considering that the patients were given dietary and lifestyle recommendations, it was assumed that some patients would lose weight by the end of the study, which in itself could affect the parameters studied. Based on this assumption, a subgroup analysis with and without weight loss > 5% from baseline was planned.

Statistical processing

For the statistical processing of the study results, all data from the case report forms were entered by two researchers (M.N., Kh.K.) independently into a database created on the basis of Excel spreadsheets (Microsoft, United States). In case of data discrepancies, the indicators were manually checked from the case report forms. The missing data for the studied parameters were 2.1% ± 0.8%. Data are presented as absolute and relative indicators, mean ± SD for normally distributed values and for the rest of the values, as median (Me) and the 25th and 75th percentiles-interquartile range (IQR). To test statistical hypotheses, the Wilcoxon test, paired *t*-test, Fisher's exact test, and Pearson's chi-squared test were used. The critical value of the statistical significance level, when testing the null hypotheses, was equal to 0.05. Statistical analysis was performed using SPSS Statistics v.23.0 (IBM Corporation, United States).

RESULTS

The study involved 121 (69.5%) men and 53 (30.5%) women aged 24 to 68 years. The patients' baseline data are presented in Table 1. Among the concomitant diseases, type 2 diabetes mellitus (T2DM) was diagnosed in 54 (31.0%) patients, and arterial hypertension (AH) was diagnosed in 41 (23.6%) patients. Tobacco smoking was noted

Table 1 Baseline characteristics of the study patients

Parameter	Total sample (*n* = 174)	Men (*n* = 121)	Women (*n* = 53)	*P* value
Age, years, Me (IQR)	45.2 ± 10.1	42.9 ± 8.7	50.7 ± 10.5	< 0.001
T2DM	54 (31.0)	35 (28.9)	19 (35.8)	0.466
AH	41 (23.6)	27 (22.3)	14 (26.4)	0.695
Smoking	58 (33.3)	45 (37.2)	13 (24.5)	0.146
Obesity, classes I-III	121 (69.5)	79 (65.3)	42 (79.2)	0.097
Metabolic syndrome, NCEP ATP III	79 (45.4)	45 (37.2)	34 (64.2)	0.002

Data are presented as mean ± SD or *n* (%). Me: Median; IQR: Interquartile range; T2DM: Type 2 diabetes mellitus; AH: Arterial hypertension; NCEP ATP III: National cholesterol education program adult treatment panel III.

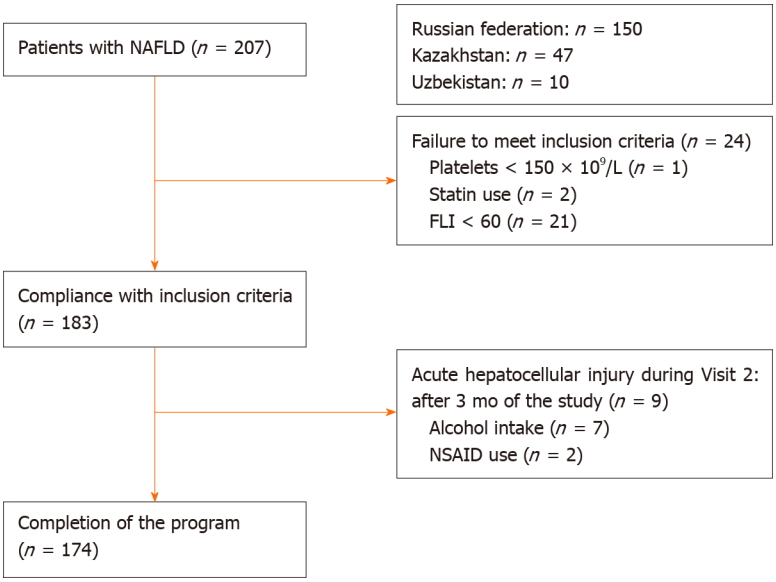

Figure 1 Patient enrollment flowchart. NAFLD: Nonalcoholic fatty liver disease; FLI: Fatty liver index; NSAID: Nonsteroidal anti-inflammatory drug.

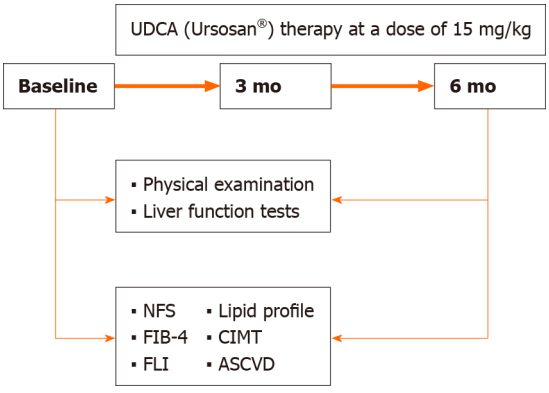

Figure 2 Scheme of the study. UDCA: Ursodeoxycholic acid; NFS: Nonalcoholic fatty liver disease fibrosis score; FIB-4: Liver fibrosis index; FLI: Fatty liver index; CIMT: Carotid intima-media thickness: ASCVD: Atherosclerotic Cardiovascular Disease.

in every third patient. Obesity (Classes I-III) was observed in 121 (69.5%) patients, and the remaining patients were overweight. Seventy-nine (45.4%) patients met the NCEP ATP III criteria for metabolic syndrome. The mean age of women was significantly higher than that of men ($P < 0.001$); the metabolic syndrome was more common in women compared with men ($P < 0.002$). Men and women did not differ in frequency of T2DM, AH, tobacco smoking, and obesity (classes I-III) (Table 1).

Analysis within the total sample and by sex

During the study, smoking status, need for AH treatment, and the number of T2DM cases did not change.

As compared with their initial levels, body weight, BMI, and WC decreased significantly ($P < 0.001$) in men and women after 3 mo of treatment and continued to reduce between 3 and 6 mo ($P < 0.001$) (Table 2). No significant difference was reported in body weight change between the 0- to 3-mo and 3- to 6-mo intervals, whereas the WC was greatly reduced between baseline and 3 mo of treatment ($P < 0.001$).

After 3 mo of treatment, 11 (6.3%) patients lost > 5% weight, whereas at the end of treatment, 54 (31%) patients had > 5% weight reduction, a 3-mo difference being statistically significant ($P < 0.001$) (Table 2).

The levels of ALT, AST, and GGT decreased significantly from baseline to 3 mo and from 3 to 6 mo. The ALT level initially exceeded 39.9 U/L in 116 (66.7%) of patients but decreased to 64 (36.8%) by the 3rd mo and to 40 (23%) by the end of the study. Low-normal ALT values (0-19.9) were noted in 5 (2.8%) at baseline, in 15 (8.6%) at 3 mo, and in 26 (14.9%) after treatment. The ALT level changed by -14.1 U/L (IQR = -31.0 U/L to -5.3 U/L) from baseline to 3 mo and by -6.5 U/L (IQR = -14.0 U/L to 0.1 U/L) from 3 to 6 mo. Similar changes were seen with AST and GGT levels. From baseline to 3 mo, the levels of AST and GGT decreased by -4.0 U/L (IQR = -12.0 U/L to 1.0 U/L) and -5.0 U/L (IQR = -15.0 U/L to 2.0 U/L), respectively. From 3 to 6 mo, AST and GGT levels dropped by -2.0 U/L (IQR = -7.0 U/L to 2.2 U/L) and -3.0 U/L (IQR = -8.0 U/L to 2.0 U/L), respectively.

The magnitude of ALT, AST, and GGT decrease was greater during the first 3 mo of treatment compared to the subsequent 3 mo ($P < 0.001$, $P < 0.01$, $P < 0.001$, respectively). The baseline ALT, AST, and GGT levels did not differ between the sexes, in contrast to the rates of change of these parameters over the trial. Men had a significant decrease in ALT, AST, and GGT levels both from baseline to 3 mo and from 3 to 6 mo, whereas women had the only significant decrease in ALT over the both periods. The AST and GGT levels decreased to normal levels during the first 3 mo of treatment in most women (Table 2).

During the study, there was a statistically significant change in lipid profile: a decrease in the TC, TG, and LDL levels in the total sample and by sex. The HDL level did not change significantly in men, but significantly increased in women (Table 3).

By the end of the study, the FLI had decreased to a value of < 30 in one men, and in another 40 patients [24 (20%) men 16 (30%) women], it had gone into the "gray zone." No significant changes in fibrosis were noted according to the NFS and FIB-4.

The CIMT decreased significantly by the end of 6 mo in the total sample. When men and women were analyzed separately, the rate of CIMT change remained close to significant with P values of 0.073 and 0.052, respectively. At the same time, no statistically significant changes in the proportion of persons with reference values exceeding the ULN for the corresponding sex and age were established (Table 3).

A significant decrease in the 10-year ASCVD risk score was observed only in women ($P = 0.003$). The same patient's 10-year risk with optimal risk factors was 1.5 (0.9; 2.9) in both sexes.

The lifetime ASCVD risk did not change during the study and remained significantly increased relative to lifetime risk with an optimal risk factor of 5.0 (5.0; 8.0).

Analysis within the subgroup

Weight loss of more than 5% of the initial weight was observed in 54 patients (31%); in 54 patients (31%), the weight decreased to 5% of the initial weight; in 35 patients (20%), it did not change; and in 31 patients (18%), it increased by an average of 3%. A comparison was made between subgroups with a weight loss of more than 5% and all remaining patients.

The delta of the studied parameters ALT, AST, GGT, TC, and LDL did not differ between the subgroups (Table 4). In the subgroup with more than 5% weight loss, the FLI baseline was higher, and during the study, there was a more pronounced decrease than in the other group. By the end of the study, the subgroups with and without weight loss of more than 5% did not differ in FLI. Additionally, in the subgroup with a weight loss of more than 5%, there was a tendency toward a more pronounced decrease in TG (P was close to statistically significant).

Table 2 Changes in clinical variables and liver function tests from baseline during the trial

Parameter	Baseline	3 mo	6 mo
Weight (total sample), kg	94.8 (86.7; 102.1)	93.0 (86.0; 100.0)[c]	92.9 (85.0; 98.3)[c]
Men	95.0 (92.0; 104.2)	94.0 (90; 101.1)[c]	93.7 (88.7; 100.0)[c]
Women	86.7 (82.0; 96.0)	85.0 (80.0; 94.8)[c]	85.0 (79.0; 95.0)[b]
Δ total sample, kg		-1.0 (-2.4; 0.0)	-1.0 (-2.4; 0.0)
Weight loss > 5% (total sample)		11 (6.3)	54 (31)[c]
Men		8 (6.6)	39 (32.2)[c]
Women		3 (5.6)	15 (28.3)[b]
BMI (total sample), kg/m^2	31.2 (29.4; 34.0)	30.9 (29.3; 33.3)[c]	30.6 (29.0; 33.1)[c]
Men	30.7 (29.0; 33.3)	30.4 (29.0; 32.6)[c]	30.1 (28.4; 32)[c]
Women	32.0 (30.7; 36.2)	31.5 (30.1; 34.6)[c]	31.6 (29.7; 34.4)[b]
Δ total sample, kg/m^2		-0.4 (-0.9; 0.0)	-0.3 (-0.8; 0.0)
Waist circumference (total sample), cm	102.0 (97.0; 111.8)	100.0 (96.0; 108.0)[c]	100.0 (94.0; 106.0)[c]
Men	103.0 (98.0; 112.0)	102.0 (97.0; 110.0)[c]	100 (97.0; 106.0)[c]
Women	99.0 (93.0; 106.0)	98.0 (92.0; 105.0)[c]	97.0 (90.0; 102.0)[c]
Δ total sample, cm		-2.0 (-3.0; 0.0)	0.0 (-2.0; 0.0)[c]
ALT (total sample), U/L	53.0 (34.0; 78.0)	35.0 (26.0; 45.0)[c]	29.0 (24.0; 38.0)[c]
Men	55.8 (37.0; 78.0)	38.0 (29.0; 46.0)[c]	32.0 (25.9; 41.0)[c]
Women	44.0 (30.8; 69.0)	28.5 (21.6; 38.0)[c]	26.0 (16.5; 33.2)[c]
Δ total sample, U/L		-14.1 (-31.0; -5.3)	-6.5 (-14.0; 0.1)[c]
ALT (total sample) 10-19.9/20-39.9/≥ 40 U/L	5 (2.8)/53 (30.5)/116 (66.7)	15 (8.6)/95 (54.6)/64(36.8)[b]	26 (14.9)/108 (62.1)/40 (23.0)[c]
Men	1 (0.8)/35 (28.9)/85 (70.2)	5 (4.1)/64 (52.9)/52 (43)[c]	10 (8.3)/79 (65.3)/32 (26.4)[a]
Women	4 (7.5)/18 (34)/31 (58.5)	10 (18.9)/31 (58.5)/12 (22.6)[c]	16 (30.2)/29 (54.7)/8 (15.1)
AST (total sample), U/L	31.0 (24.0; 42.0)	26.5 (21.0; 34.0)[c]	25.0 (21.0; 29.0)[c]
Men	29.1 (23.5; 42.0)	26.0 (21.0; 33.0)[c]	25.0 (21.0; 28.0)[c]
Women	32.0 (24.0; 42.0)	28.0 (22.0; 35.0)[c]	26.0 (23.0; 32.0)
Δ total sample, U/L		-4.0 (-12.0; 1.0)	-2.0 (-7.0; 2.2)[b]
GGT (total sample), U/L	36.0 (26.0; 48.0)	28.0 (21.0; 38.0)[c]	26.0 (19.0; 35.0)[c]
Men	36.0 (28.0; 46.0)	31.0 (24.0; 41.0)[c]	26.0 (21.0; 35.0)[c]
Women	35.0 (23.0; 53.0)	23.0 (18.0; 30.0)[c]	21.0 (12.0; 34.0)
Δ total sample, U/L		-5.0 (-15.0; 2.0)	-3.0 (-8.0; 2.0)[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$. Data are presented as median (IQR) or *n* (%). BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate transaminase; GGT: Glutamyltransferase.

DISCUSSION

The NAFLD prevalence rate in the population, as well as associated complications and risk factors, is growing steadily. Thus, a 10-fold increase in hepatocellular carcinoma related to NAFLD has been reported over the past decade. Moreover, it has been shown that patients with more advanced NAFLD are 4 times more likely to have a fatal CVD event and twice as likely to suffer a nonfatal CVD event[43]. These data demonstrate the urgency of NAFLD-related problems and the need to find a modern drug to treat it effectively.

Male sex is one of the nonmodifiable risk factors for NAFLD and ASCVD. In our study, the number of men with NAFLD was 2 times higher than the number of

Table 3 Changes in laboratory and imaging variables from baseline during the trial

Parameter	Baseline	6 mo	*P* value
TC (total sample), mmol/L	6.03 ± 1.36	5.76 ± 1.21	< 0.001
Men	5.99 ± 1.39	5.77 ± 1.24	0.003
Women	6.11 ± 1.32	5.73 ± 1.16	0.019
LDL (total sample), mmol/L	3.86 ± 1.01	3.66 ± 0.91	< 0.001
Men	3.81 ± 1.04	3.67 ± 0.90	0.033
Women	4.0 ± 0.94	3.65 ± 0.93	0.006
HDL (total sample), mmol/L	1.24 ± 0.32	1.24 ± 0.27	0.910
Men	1.24 ± 0.33	1.21 ± 0.22	0.160
Women	1.23 ± 0.29	1.31 ± 0.34	0.036
TG (total sample), mmol/L	3.18 (2.00; 4.29)	2.04 (1.40; 3.16)	< 0.001
Men	3.13 (2.10; 4.29)	2.04 (1.4; 2.79)	< 0.001
Women	3.45 (1.80; 4.36)	2.26 (1.35; 3.62)	< 0.001
FLI (total sample)	84.9 ± 10.4	72.3 ± 17.6	< 0.001
Men	86.3 ± 9.0	73.6 ± 17.2	< 0.001
Women	81.9 ± 12.7	69.4 ± 18.4	< 0.001
FLI (total sample) ≥ 60/30-59/< 30	174 (100)/-/-	133 (76.4)/40 (23.0)/1 (0.6)	< 0.001
Men	121 (100)/-/-	96 (79)/24 (20)/1 (1)	< 0.001
Women	53 (100)/-/-	37 (70)/16 (30)/-	< 0.001
NFS (total sample) < -1.455 (F0-F2), *n* (%)	141 (81.0)	148 (85.0)	0.353
Men	102 (84.3)	112 (92.6)	0.071
Women	39 (76.6)	34 (64.2)	0.402
FIB 4 (total sample) < 1.45 (F0-F1), *n* (%)	157 (90.2)	163 (93.7)	0.256
Men	111 (91.7)	114 (94.2)	0.615
Women	46 (86.8)	49 (92.5)	0.402
CIMT (total sample), mm	0.985 ± 0.243	0.968 ± 0.237	0.013
Men	0.993 ± 0.224	0.977 ± 0.217	0.073
Women	0.967 ± 0.284	0.947 ± 0.276	0.052
CIMT (total sample) exceeding ULN for the corresponding age and sex	143 (84)	139 (82)	0.549
Men	103 (85.1)	101 (83.5)	0.860
Women	40 (75.5)	38 (72)	0.826
ASCVD (total sample, *n* = 112) 10-year risk	5.1 (2.9; 9.1)	4.8 (2.6; 8.0)	0.053
Men (*n* = 71)	6.0 (3.6; 11.1)	5.8 (3.4; 8.8)	0.720
Women (*n* = 41)	3.5 (2.3; 7.8)	3.2 (2.0; 6.0)	0.003
ASCVD (total sample, *n* = 152) lifetime risk	50 (39; 60)	50 (39; 64)	0.370
Men (*n* = 112)	50 (46; 69)	50 (46; 69)	0.870
Women (*n* = 40)	39 (39; 50)	39 (39; 50)	0.160

Data are presented as median (IQR) or *n* (%). TC: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; FLI: Fatty liver index; NFS: Nonalcoholic fatty liver disease fibrosis score; FIB-4: Liver fibrosis index; ULN: Upper limit of normal; ASCVD: Atherosclerotic Cardiovascular Disease.

women, which is consistent with the NAFLD prevalence data in other populations[44-46]. The patients' average age in our study was 45 years, which generally corresponds to the NAFLD epidemiological study data. Thus, according to individual studies, in Europe, the average age of patients with NAFLD is 56 years in Italy and 58 years in Spain[47,48]. In Asia, this parameter is lower; in the Chinese population, the average age is 45 years, and in the Japanese population, it is 51 years[49,50]. In a NAFLD study conducted in Kazakhstan, the patients' average age was 55 years[5].

It is well known that NAFLD and CVD share common modifiable risk factors[43]. In our study, one-third of patients had T2DM, most (69.5%) of the observed participants were obese (Classes I-III obesity), and the rest were overweight. A total of 45.4% of patients met the criteria for metabolic syndrome based on the NCEP ATP III, which is consistent with a large-scale epidemiological study data conducted by Younossi *et al*[3], in which the number of patients with metabolic syndrome was 42.5%.

Factors released from fatty liver that could link NAFLD to CVD are proinflammatory and proatherogenic cytokines (IL-6, tumor necrosis factor-alpha), procoagulant factors (fibrinogen, factors VII and VIII, plasminogen activator type 1 inhibitor), and pro-oxidant factors (reactive oxygen species); other pathogenic mechanisms include progression of insulin resistance and dyslipidemia[10,13].

In this study, patients were given lifestyle and dietary modifications, and UDCA was prescribed. For 6 mo of the study, there was a statistically significant decrease in weight, BMI, and WC, which is associated with the adherence of a certain proportion of the subjects to the recommendations on lifestyle modification and diet, which were discussed with patients prior to the UDCA administration and three months later.

In a randomized study by Wong *et al*[51], the participation of patients with NAFLD in lifestyle and diet modification programs contributed to a decrease in body weight, liver TG content and disease remission achievement. At the same time, in a study by Dudekula *et al*[52], it has been shown that in a primary care setting, prescribing only lifestyle recommendations for significant (> 5%) weight loss in NAFLD patients is insufficient. In this study, the degree of weight loss was correlated with the frequency of outpatient visits.

During the study, a statistically significant decrease in ALT level was achieved; the number of patients whose ALT level exceeded 40 U/L decreased almost 3-fold. The Me ALT reduction was 45.3%. A decrease in ALT levels in NAFLD patients during treatment with UDCA has been demonstrated in previous studies. For example, in a randomized controlled trial by Ratziu *et al*[19], high-dose UDCA therapy for one year was associated with a decrease in ALT level by 28.3% and ALT level normalization in a quarter of the patients, regardless of weight loss. An even more pronounced decrease in ALT level during a 6-mo course of UDCA at a dose of 15 mg/kg/d, as in our study, was noted in a prospective study by Ozel Coskun *et al*[20]: The ALT level decreased after therapy by 54% in patients with histologically confirmed NAFLD.

In addition, during the study, there was a significant decrease in AST and GGT levels by 6 and 10 U/L, respectively, which was repeatedly noted in other similar studies[21-24]. The percentage of AST reduction was 19.4% and 27.8% for GGT, which is consistent with previously mentioned publications: a decrease in AST of 18.9% and GGT of 62% in a study by Ratziu *et al*[19], and a decrease in AST of 43% and GGT of 41% in a study by Ozel Coskun *et al*[20]. A statistically significant decrease in AST levels of 8.5 U/L and GGT of 16.5 U/L was also demonstrated after a relatively short (3-wk) course of UDCA 20 mg/kg/d[53].

In comparison with other studies, we also analyzed the rates of LFT change during the first and subsequent 3-mo intervals. The magnitude of ALT, AST, and GGT decrease was significantly higher during the first 3 mo of treatment, whereas the rates of weight and BMI change were the same in both periods.

Improvement in LFT is probably associated with the antioxidant effect of UDCA, the ability to suppress the production of tumor necrosis factor-alpha, which is associated with an improvement in LFT and histological findings[54,55].

Positive changes have also been observed in relation to lipid profile. The Me TC during follow-up decreased significantly by 0.27 mmol/L, which is consistent with the results of a recently published meta-analysis, which, based on an analysis of 20 studies, demonstrated a significant decrease in TC with UDCA therapy by 0.36 mmol/L[56]. The Me of other lipid parameters (LDL and TG) also decreased during the study. The HDL level increased significantly only in women.

Administration of UDCA improves the lipid spectrum by decreasing cholesterol absorption and synthesis and the activity of the farnesoid X-receptor and increasing the synthesis of bile acids[56].

The effect of UDCA therapy on the FLI has not been previously shown. In our study, the FLI, a noninvasive assessment of steatosis, decreased significantly. This is

Table 4 Comparison of the parameter decrease degree in subgroups with weight loss of more and less than 5% from baseline to the end of treatment

Parameter	Weight loss > 5% (*n* = 54)	Weight loss ≤ 5% (*n* = 120)	*P* value
ΔALT, U/L	-21.1 (-45.0; -6.0)	-25.0 (-42.5; -6.0)	0.683
ΔALT, %	-46 (-63; -18)	-43 (-54; -23)	0.281
ΔAST, U/L	-6.0 (-15.0; 1.6)	-5.0 (-18.0; 1.0)	0.673
ΔAST, %	22 (-41; 0)	-17 (-42; 0)	0.446
ΔGGT, U/L	-5.0 (-17.0; 0)	-8.0 (-22.5; 0)	0.492
ΔGGT, %	-19 (-41; 0)	-32 (-50; 0)	0.354
ΔTC, mmol/L	-0.10 (-0.66; 0.30)	-0.10 (-0.57; 0.2)	0.666
ΔTG, mmol/L	-1.04 (-1.80; -0.23)	-0.70 (-1.33; -0.11)	0.079
ΔLDL, mmol/L	-0.20 (-0.7; 0.2)	-0.14 (-0.58; 0.3)	0.401
FLI			
Initially	88.3 ± 10.2	83.5 ± 10.3	0.002
After 6 mo	71.4 ± 19.6[c]	72.8 ± 16.7[c]	0.916
ΔFLI	-14.6 (-21.8; -6.3)	-8.45 (-17.9; -2)	0.003

[c]$P < 0.001$. Δ is the difference in indicators after 6 mo and at baseline. The minus sign indicates a decrease in the parameter by the end of the study.

due to a decrease in the parameters included in the FLI algorithm, including BMI, WC, GGT, and TG. At the end of the program, 1/4 of the patients moved to the "gray zone". Similarly, Laurin *et al*[22] previously reported a histologic improvement in steatosis after UDCA treatment.

The literature contains a limited number of clinical studies evaluating the effects of drug therapy on fibrosis in patients with NAFLD. In our work, liver fibrosis was assessed using the NFS and FIB-4 scales, which have similar diagnostic value according to the Sun meta-analysis[57]. We observed no significant effect on fibrosis, which is consistent with a 52-wk study by Parikh *et al*[58] using the NFS scale to compare the fibrosis severity before and after UDCA therapy. Notably, in another study, there was a decrease in fibrosis severity when assessed using the FibroTest, but the study duration and the UDCA dose were higher than those in our trial[19].

NAFLD is currently known to be associated with increased CIMT, an early predictor of atherosclerosis and CVD. In our study, patients achieved a statistically significant decrease in CIMT with UDCA treatment. Similar data have been demonstrated in the prospective Coscun study (6 mo of UDCA at a dose of 15 mg/kg/d). The mechanism for reducing CIMT appears to be associated with the antioxidant, anti-inflammatory, and hypolipidemic effects of UDCA, as well as its effect on insulin resistance[20]. In turn, CIMT reduction plays an important role in CVD prevention. Notably, CIMT, exceeding the ULN for the corresponding sex and age, remained unchanged during the study, which can probably be explained by the short duration. The duration of cardiac studies, which showed a more pronounced decrease in CIMT, was 24 and 36 mo[59].

In our study, the impact of UDCA on CVD risk was assessed using the ASCVD risk calculator for the first time. We found a statistically significant decrease in the 10-year ASCVD risk only in women. Of all the parameters assessed in ASCVD, this one was due to a decrease in the TC level in both sexes and the HDL level only in women.

At the same time, in the present study, the predicted 10-year risk of CVD at the end of 6 mo was 3 times higher than the same patient's 10-year risk with optimal risk factors. There was no reduction in the predicted lifetime CVD risk. Indeed, it was 10 times higher than the same individual's lifetime risk with optimal risk factors.

Achieving more significant reductions in CIMT and ASCVD risk appears to take longer and requires control of other modifiable risk factors such as sedentary lifestyle, T2DM, AH, and smoking. Cardiological and endocrinological studies have shown that regular physical activity for 1 year or more, smoking cessation, blood pressure control, and glycemic control using new-generation hypoglycemic agents such as sodium–glucose cotransporter 2 inhibitor (dapagliflozin) or inhibitor of dipeptidyl peptidase-4 (sitagliptin) contribute to CIMT and ASCVD risk decrease[60-65].

Weight loss is believed to be a key factor in successful NAFLD treatment and in reducing the risk of CVD. A recent meta-analysis has shown clinical and laboratory improvements in NAFLD patients with 5%-10% weight loss[66]. To assess the effect of weight loss on the studied efficacy parameters in our patients, we divided them into two subgroups: weight loss of more than 5% and weight loss of 5% or less. The cutoff point of 5% was chosen due to the short 6-mo study period.

When comparing groups, there was no statistically significant difference in absolute and relative reductions in ALT, AST, GGT, TC, and LDL levels. At the same time, in the group with a weight loss of more than 5%, we observed a close to significant decrease in TG level and a significant decrease in FLI steatosis. Since the FLI formula includes the GGT, TG, BMI, and WC values, it is likely that the steatosis improvement in the group of patients with a decrease in body weight of more than 5% is associated with a greater change in the values of the last three parameters. However, even in patients who did not achieve more than 5% weight loss, a statistically significant decrease in the FLI index was observed.

A recent meta-analysis[66], which assessed the relationship between weight loss and LFT, found that weight reduction resulted in a decrease in ALT by –9.81 U/L; 95%CI: -13.12; -6.50. In our study, patients with a weight loss of more than 5% had a decrease in ALT levels by an average of 21.1 U/L; this reduction is greater than that in the meta-analysis, demonstrating the UDCA effectiveness. Moreover, in the current study, both the subgroups with and without a loss of > 5% body weight achieved significant improvement in FLI, while the above mentioned meta-analysis did not show any differences in FLI under UDCA therapy.

In addition, in contrast to the meta-analysis data, our study achieved a statistically significant decrease in FLI both in the subgroup with a weight loss of more than 5% and in the subgroup without weight loss; in the meta-analysis, the weight loss effect on FLI was not established. The study was conducted in a primary health care setting, which expands the possibilities of its transfer to regular practice. Some limitations of our study should also be noted, namely, the open design, the absence of a control group, and the relatively short follow-up period.

CONCLUSION

The study suggests that 6-mo UDCA therapy at a dose of 15 mg/kg/d may improve ALT, AST, GGT, TC, and TG levels and FLI in the primary care setting independent of weight loss. A positive effect of UDCA on ALT, AST, and GGT levels is greater during the first 3 mo of treatment. Our study also demonstrates a beneficial effect of UDCA on the progression of CIMT in both sexes and reduction in 10-year CVD risk in women. Further long-term studies with control groups are needed to confirm these findings.

ARTICLE HIGHLIGHTS

Research background

Nonalcoholic fatty liver disease (NAFLD) is currently the leading cause of liver disease and liver transplantation in developed countries. Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in patients with NAFLD. Weight loss is a key factor for successful NAFLD and cardiovascular disease therapy. Ursodeoxycholic acid (UDCA), which is one of the first-line therapeutic agents for treatment of NAFLD, is reported to have a beneficial effect on dyslipidemia and ASCVD risk because of antioxidant properties.

Research motivation

The main motivation was our wish to improve the treatment outcomes of patients with NAFLD. Each author of our international study had a personal positive experience of treating NAFLD with UDCA. We sincerely wanted to combine our efforts to gain a new knowledge.

Research objectives

To evaluate the effects of 6-mo administration of UDCA on liver function tests (LFT), lipid profile, hepatic steatosis and fibrosis, carotid intima-media thickness (CIMT), and ASCVD risk in total sample with NAFLD, separately in men and women, in patients

with and without > 5% weight loss.

Research methods

An open international noncomparative study was carried out at primary health care settings. The study was completed by 174 patients who were included in the final analysis and received UDCA (Ursosan®) therapy at a dose of 15 mg/kg body weight daily for 6 mo. In addition, total sample was given recommendations to modify lifestyle behaviors and diet. The body mass index, waist circumference, and LFT were compared between baseline and 3 mo as well as between 3 and 6 mo of the treatment. The lipid profile, fatty liver index (FLI), nonalcoholic fatty liver disease fibrosis score, liver fibrosis index, 10-year and lifetime ASCVD risk, and CIMT were compared between baseline and the end of the follow-up.

Research results

The magnitude of LFT decrease was greater during the first 3 mo of treatment compared to the subsequent 3 mo. At 6 mo, in the total sample, we observed a statistically significant decrease in body mass index, waist circumference, and levels of FLI ($P < 0.001$), total cholesterol (TC) ($P < 0.001$), low-density lipoprotein (LDL) ($P < 0.001$), triglyceride (TG) ($P < 0.001$), and the CIMT ($P = 0.013$), whereas the high-density lipoprotein (HDL) ($P = 0.036$) and 10-year ASCVD risk improved significantly only in women ($P = 0.003$). No effect on nonalcoholic fatty liver disease fibrosis score, and liver fibrosis index was found. At the end of the study, the FLI decreased significantly in patients with and without > 5% weight loss; the changes in LFT, TC, TG, and LDL levels were similar between the subgroups.

Research conclusions

The study suggests that 6-mo UDCA therapy at a dose of 15 mg/kg/d may improve LFT, TC, LDL, and TG levels, FLI, and CIMT in total sample with NAFLD. These changes are observed independent of sex and weight loss. UDCA has also a beneficial effect on HDL and 10-year ASCVD risk in women.

Research perspectives

Further long-term studies with control groups are needed to confirm these findings. For further research, we suggest to compare lipid profile and hepatic steatosis between baseline to 3 mo and 3 to 6 mo; evaluate the effects of long-term UDCA therapy (during 1-year follow-up or more) on HDL and 10-year and lifetime risk ASCVD in men and women.

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