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Effect of Ursodeoxycholic acid on lipid profile in NAFLD patients

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A B S T R A C T

Nonalcoholic fatty liver (NAFLD) is the most common liver disease. Hyperlipidemia, particularly hypertriglyceridemia is a major risk factor in NAFLD. Serum lipids reduction is important in these patients. However, despite this importance, few studies have been done about UDCA on serum lipid levels in these patients. The aim of this study is to evaluate UDCA effect on lipid profile in NAFLD patients. In this cohort study, NAFLD patients referring to Azadi and Sheykh Al-Reis Clinics in Tabriz (Iran) from 2009 to 2014 (a total of 2485 patients on different treatments) were enrolled, and 94 patients using UDCA who met inclusion criteria were studied. Patients received Metformin as a treatment base and were studied for 3 months. Before and after UDCA administration, LDL was 79.24 ± 1.99 vs. 80.75 ± 2.30 (P = 0.24), HDL was 44.66 ± 1.60 vs. 45.78 ± 1.42 (P = 0.44), TG was 171.30 ± 7.25 vs. 173.64 ± 10.52 (P = 0.8), cholesterol was 190.78 ± 5.37 vs. 183.52 ± 3.96 (P = 0.15). Liver ultrasound grading improved 3 months after UDCA administration. UDCA therapy has a significant role in disease progression and improving ultrasound grading in NAFLD patients. UDCA has meaningful effect on lipid profile.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is an increasingly common cause of chronic liver disease world-wide. It comprises a disease spectrum ranging from benign hepatic steatosis to non-alcoholic steatohepatitis (NASH) with inflammation and liver cirrhosis (1). In the United States, NAFLD is the most common cause of chronic liver disease, with an estimated prevalence of 20–30% and an estimated prevalence of 3.5–5% for NASH (2,3).

No treatment has been proven to be effective in nonalcoholic fatty liver disease (NAFLD) and/or steatohepatitis (NASH). General measures of risk reduction, such as weight loss in obese patients, effective treatment of hyperlipidemia and diabetes mellitus (if present) are usually recommended. Other methods currently in use include: weight loss drugs (orlistat), physical activity, oral antidiabetic medications (metformin, troglitazone, pioglitazone, and rosiglitazone), cytoprotective agents [taurine, ursodeoxycholic acid (UDCA)], hypolipidemics (clofibrate, gemfibrozil, bezafibrate, atorvastatin, and other HMG-CoA reductase inhibitors), several antioxidants, and a combination of different therapies (diet and UDCA, vitamin E and pioglitazone) (4-9).

Ursodeoxycholic acid (UDCA) has cytoprotective, anti-apoptotic, membrane stabilizing, anti-oxidant and immunomodulative effects (10); So UDCA has been recommended in the treatment of NASH and in the prevention of cholelithiasis during weight reduction. However, Clinical trials of UDCA in NASH therapy have yielded ambiguous results (10-12).

As regards that hyperlipidemia, particularly hypertriglyceridemia is a major risk factor in NAFLD, serum lipids reduction is important in these patients. However, despite this importance, few studies have been done about UDCA on serum lipid levels in these patients.

Materials and Methods

This article is a part of a broader cohort study with total of 2485 NAFLD patients that were under different treatments (orlistat, metformin, pioglitazone, UDCA, clofibrate, gemfibrozil, atorvastatin, avitamin E and other supplements). 94 NAFLD patients (liver steatosis in ultrasound) referring to Azadi and Sheykh Al-Reis Clinics in Tabriz (Iran) from 2009 to 2014 (a total of 2485 patients) were enrolled, and 94 patients using UDCA who met inclusion criteria were studied. Patients received metformin as a treatment base and were studied for 3 months.

Patients drinking more than 20 grams of alcohol daily, using drugs that induce hepatic steatosis such as prednisone, corticosterone, amiodarone, calcium channel blockers, tamoxifen, methotrexate, positive viral markers or confirming lab studies of Wilson disease and autoimmune diseases, cholestatic liver disease, advanced kidney or liver disease, heart disease, hyper or hypothyroidism, gastric bypass surgery, rapid weight loss, TPN (Total Parental Nutrition), cachectic patients and patients receiving drugs such as statins (lovastatin, atorvastatin, simvastatin), fenofibrate, gemfibrozil that have effect on blood lipids, were excluded from the study.

Selected patients were receiving 500 mg metformin and 900 mg UDCA daily.The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (Alp), fasting blood glucose (FBS) and lipid profile (total cholesterol, LDL, HDL, TG) were measured using

enzymatic methods at the beginning and end of the study. LDL cholesterol level was determined using the formula Fried-Wald (13):

Total cholesterol - (5 / triglycerides + cholesterol HDL) = LDL-C (mg / dl).
If triglyceride level was higher than 300 mg / dl, LDL cholesterol was measured independently (14).

Total cholesterol and triglyceride measure was performed using the kit with cholesterol oxidize and glycerol phosphates oxidize by enzymatic colorimetric method, respectively. Serum HDL cholesterol was measured after precipitation of the solution of apolipoproteins and phosphotengestinic acid. LDL cholesterol calculated using the Fried-Wald formula (15).

Patients' weights were measured and recorded while wearing minimal clothes and no shoes using a digital scale Seca meticulous, with 100 g accuracy. Their heights were measured using a tape while standing up and shoulders in normal position without shoes. BMI calculated by weight (kg) on height (m^2).

Data analysis

After entering data into a computer and data analyzing, they will be normalize using appropriate statistical conversions if the data is not normal. Measurements repeatability method was used for dependent quantitative variables using below structure by Minitab 16 software:

$$VDV = ID + \theta^{\square}_{DrugGroup} + \theta_{Time\ (DrugGroup)} + \beta_1 + \cdots + \beta_k + Error$$

In this structure VDV is dependent variable variations (TG, HDL, LDL, Total Cholesterol) and ID is individual difference and $\theta^{\square}_{DrugGroup}$ is drug act on dependent variable and $\theta_{Time\ (DrugGroup)}$ is drug time process act on dependent variable in three consecutive times and $\beta_1 + \cdots + \beta_k$ are confounding variables, and Error covers the other changes.

Statistics T2 Hotelling was used for studying coincidence of them. $\bar{\chi} \pm SE$ was mentioned for the results of quantitative variables and percentages for qualitative variables were presented. The average difference was significant when P value was less than 0.05. In this study, TG, HDL, LDL and Total Cholesterol were considered as dependent variables and age, sex and BMI as confounding variables. Statistical analysis was investigated by using frequency, percentage and mean difference test for quantitative variables and chi square test for qualitative variables.16SPSS ™ and MiniTab statistical software were used in this study. P-value less than 0.05 were considered statistically significant.

Result and Discussion

Data was collected for 94 patients using UDCA, at the end of the study. 55 patients (58.5%) were male and 35 patients (37.2%) were female. The mean age of patients was 44.84 ± 1.25 (Min = 14, Max = 71 years old). The results of the variations of anthropometric indices, fasting blood glucose, lipid profile and liver enzymes of NAFLD patients using UDCA in three months period, are shown in Tables 1 and 2. Figure 1 is presenting the results of the fatty liver grades in patients before and after the treatment, on the basis of the ultrasound findings. Figures 2 to 4 show changes in liver enzymes value between two groups (before and after UDCA use) in 95% confidence interval.

Fatty liver disease is one of the important causes of the chronic liver disease in

children and adults, which usually is found associated with obesity, resistance to insulin and even in those without diabetes. It seems that fatty liver in some cases despite the absence of other underlying risk factors is not necessarily a benign phenomenon and has the ability to progress to fibrosis and cirrhosis of the liver (16).

It has been said that NAFLD is in association with the components of metabolic syndrome, including obesity, diabetes and hyperlipidemia (1).

Considering the fact that lifestyle modifications such as weight loss and physical activity can decrease most of NAFLD risk factors, therefore these methods have been proposed as the main choice for the treatment of these patients (17, 18). Ursodeoxycholic acid (UDCA) is an anti-inflammatory agent that is widely used as treatment of liver disease and also is used in gallstones treatment. Some long-term clinical trial studies including Ratziu et al. study showed that UDCA causes improvement in the levels of liver enzymes, serum markers of fibrosis and metabolic parameters, safely and effectively(19). Also, Laurin et al. observed significant reductions in serum levels of alkaline phosphatase (Alp), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) in patients whom were treated with 13-15 mg / kg / day UDCA, in their one year study (20). These results are similar to our study.

Table.1 Comparison of changes in values of anthropometric indices before and after UDCA use

	Before UDCA	After UDCA	P value*
height	167.46 ± 1.19		
weight	85.92 ± 1.55	84.56 ± 1.58	<0.0001
BMI	30.94 ± 0.60	30.49 ± 0.60	<0.0001
Waist	105.01 ± 1.04	103.54 ± 1.01	<0.0001

*Data are presented as Mean ± SE.

Table.2 Comparison of changes in values of FBS, lipid profile and liver enzymes before and after UDCA use

	Before UDCA	After UDCA	P value*
FBS	98.87 ± 2.18	98.68 ± 2.03	0.83
LDL	75.57 ± 10.5	65.28 ± 6.9	0.24
HDL	45.04 ± 1.56	45.06 ± 1.33	0.44
TG	170.94 ± 7.15	170.06 ± 9.86	0.80
Total Cholesterol	190.59 ± 5.2	185.06 ± 3.9	0.15
AST	37.75 ± 2.49	31.62 ± 1.62	0.001
ALT	61.44 ± 4.15	47.14 ± 3.2	<0.0001
Alp	230.34 ± 12.46	210.47 ± 11.38	0.009

*Data are presented as Mean ± SE.

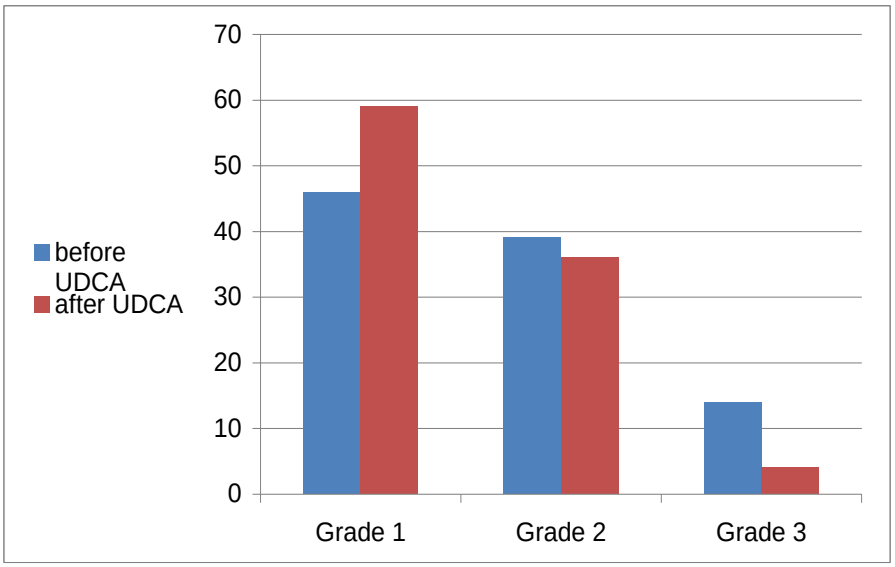

Figure.1 Comparison of changes in percentage of patients with each fatty liver grades before and after UDCA use

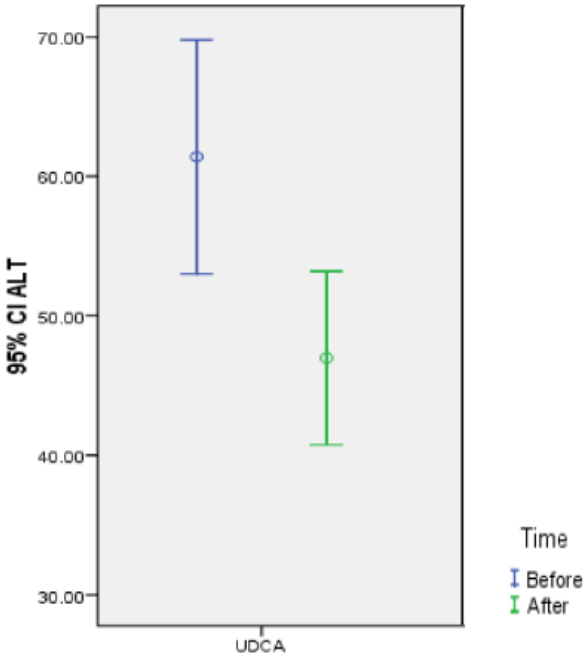

Figure.2 Comparison of changes in ALT value between two groups in 95% confidence interval: before UDCA (blue) and after UDCA (green)
CI= confidence interval

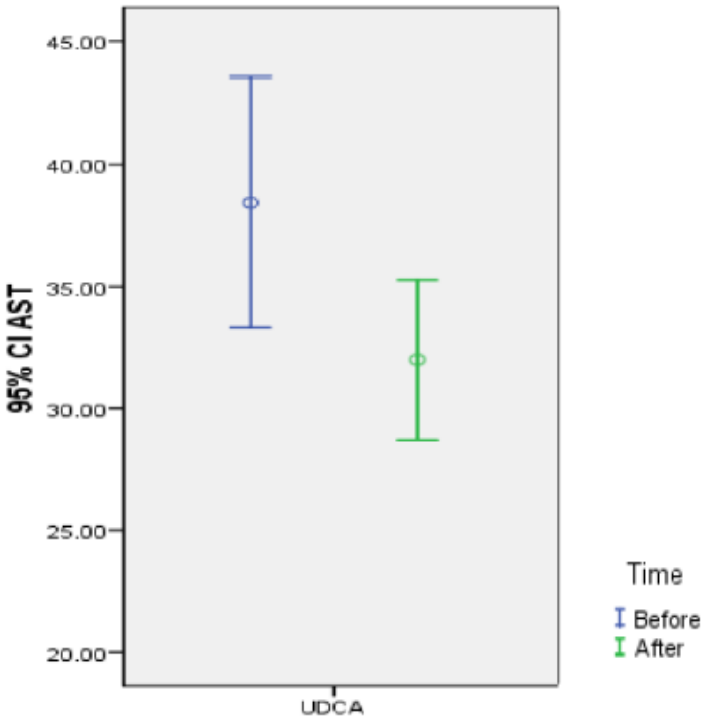

Figure.3 Comparison of changes in AST value between two groups in 95% confidence interval: before UDCA (blue) and after UDCA (green)
CI= confidence interval

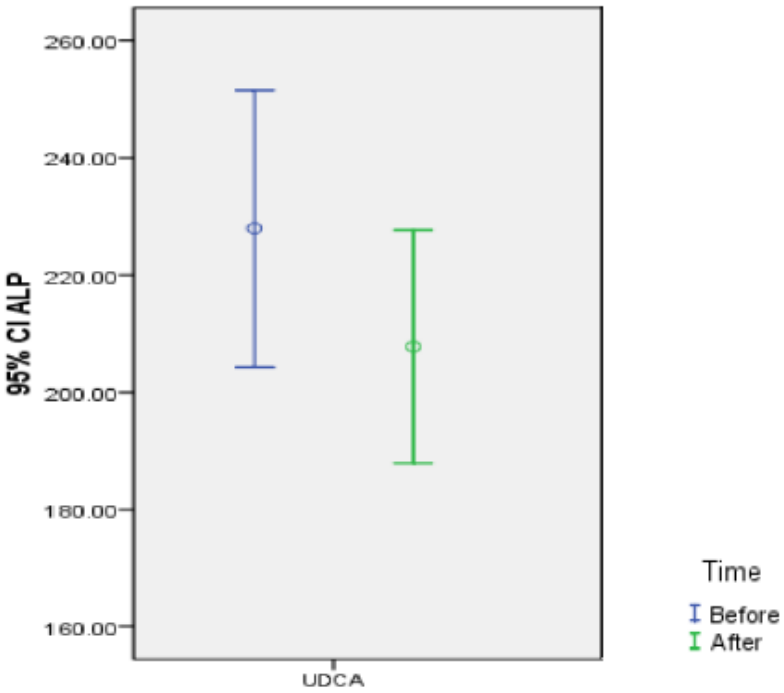

Figure.4 Comparison of changes in Alp value between two groups in 95% confidence interval: before UDCA (blue) and after UDCA (green)
CI= confidence interval

In the present study, the average of all three markers (AST, ALT and Alp) decreased significantly, in the UDCA receiving group. Serum aspartate aminotransferase (AST) level reduced from 37.75 ± 2.49 to 31.62 ± 1.62, and serum ALT reduced from 61.44 ± 4.15 to 47.14 ± 3.2, and Alp reduced from 230.34 ± 12.46 to 210.47 ± 11.38. (As is seen, decrease in ALT level is more than the other two, which can be very important in treatment aspect. The recorded all three above enzymatic markers levels changes were statistically significant. (P was 0.001, <0.0001 and 0.009 in order for AST, ALT and Alp).

As mentioned, Laurin et al. observed significant reduction in fatty liver grade in one year study of patients treated with 13-15 mg / kg / day UDCA (20). Also S Yang et al. showed in their study that *taurine-conjugated ursodeoxycholic acid* oral administration reduces hepatic steatosis through multiple metabolic pathways including the regulation of lipogenesis gene expression in rats (21).On the other hand, no significant differences were observed between UDCA and placebo use in some clinical studies including Duvnjak's study (22). Our study leads to the similar results of S Yang and his colleagues study. Following results were obtained in liver grade study of patients, using ultrasound criteria:

At the beginning of our study, 47.9% of patients had Grade I fatty liver, 37.2% Grade II and 14.9 % Grade III. After 3 months period of 900 mg UDCA administration, 59.6% patients got Grade I fatty liver, 36.2% Grade II and 4.3% Grade III, finally. Shift from higher fatty liver grades to lower grades is seen according to ultrasound criteria that was statistically significant (P <0.0001).

In this study, weights and waist circumferences reduction was seen.Weight average was 85.92 ± 1.55 before UDCA and 84.56 ± 1.58 kg after three month UDCA use and waist circumference average was 105.01 ± 1.04 and 103.54 ± 1.01 cm before and after that (decrease was statistically significant in both cases and P <0.0001 in both). The average fasting blood glucose (FBS) level was 98.87 ± 2.18 before the study and was 98.68 ± 2.03 after 3 months UDCA use which did not show significant changes (P = 0.83).

In the study of UDCA effect on patients' lipid profile, significant reduction was observed in serum LDL-cholesterol levels after 3-month treatment period which was optimal for therapy. No significant difference was observed in serum TG before and after UDCA use. Serum TG level was 170.94 ± 7.15 mg/dl before and 170.06 ± 9.86 after treatment (This variation was not statistically significant and P was 0.8). There was also a small increase in serum HDL level from baseline level of 45.04 ± 1.56 to 46.06 ± 1.33 that was not statistically significant (P = 0.44).

Conclusion

According to our study, the use of UDCA has a significant and meaningful effect on disease improvement and recovery in patients with NAFLD. Three months of UDCA use, not only improves anthropometric indices and fatty liver grade, but also decreases liver enzymes, improves lipid profile control, increases HDL and decreases blood sugar level. Regarding to improvement of anthropometric indices in this three months study period, improvement in fatty liver grade can be due to both the lifestyle changes and the medication, simultaneously.

Since recently, the goal of NAFLD treatment is trying to modify risk factors such as suitable diet, weight loss, exercise, and also avoiding oxygen free radicals damages, we can prevent and improve this situation and reduce the liver complications by recommending these methods besides appropriate medications use. So, the administration of this regime would be recommended in NAFLD patients.

Conflict of interest

Authors have no conflict of interest. This article is a part of a broader cohort study with total of 2485 NAFLD patients that were under different treatments.

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