

Evaluation of L-Carnitine Efficacy in the Treatment of Non-Alcoholic Fatty Liver Disease among Diabetic Patients: A Randomized Double Blind Pilot Study

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ABSTRACT

AIM: Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide and while its pathophysiology is still unverified, most of the present theories are based on Insulin resistance and oxidative stress as key factors. According to role of L-Carnitine in the process of fatty acid oxidation and glucose metabolism, it seems that this drug could be potentially effective in the treatment of diabetic patients suffering from NAFLD. This study has been designed to evaluate this potential therapeutic effect.

METHOD: 60 type 2 diabetic patients with NAFLD based on

sonographic findings and elevated serum transaminases randomly divided into 2 groups. The intervention group (A) treated with L-Carnitine 750mg TDS while the control group (B) received placebo. After 3 months intervention the level of liver transaminases and sonographic degree of fatty liver compared between 2 groups.

RESULT: After three months of intervention, in group A the level of AST decreased from 122.7 ± 13.6 to 96.3 ± 7 while in group B raised from 125 ± 14 to 126 ± 11 ($p < 0.001$). The level of ALT in group A declined from 124.5 ± 11.3 to 82.1 ± 5.2 and in placebo group decreased from 120 ± 10.8 to 115.1 ± 6.3 ($p < 0.001$). In comparison of average level of AST and ALT between 2 groups, we found a meaningful decline in the serum level of liver transaminases in group A ($p < 0.001$) while there were no significant reduction in serum level of Cholesterol, TG and FBS ($p > 0.05$) and also the sonographic degree of fatty liver didn't change among 2 groups.

CONCLUSION: It seems that L-Carnitine is effective in treatment of NAFLD among diabetic patients and could be a potential therapeutic approach in such patients. We recommend these findings to further be verified in future studies (www.irct.ir/IRCT2014020316348N2).

Key words: NAFLD; L-Carnitine; Liver transaminases; Diabetic patients

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Abbreviations

TDS: tree times / day

TG: triglyceride

FBS: fasting blood sugar

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) results from accumulation of fatty droplets in human hepatocytes and its prevalence is increasing worldwide due to overweight and obesity epidemic and sedentary life style among communities^[1,2]. NAFLD represent a spectrum of clinical and pathologic situations and range from simple steatosis to nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis and finally hepatocellular carcinoma^[3-5]. This condition is one of the most common liver diseases among western countries, currently 2 to 3 times more prevalent than hepatitis B, C and or alcohol related liver disorders and consider as the most common reason of disturbed liver function tests^[6,7]. Its prevalence has been reported to be about 10 to 24% in general population and up to 75% among obese subjects^[3,8,9]. Recent surveys in eastern countries have also revealed an increasing incidence of fatty liver due to changes in life style, tendency toward sedentary life, low physical activity, central obesity and diabetes Mellitus type 2 and population based studies estimated its prevalence about 15 to 30% of community and comparable to western countries^[5,10-14].

The term of NASH is used to show the severity of hepatocytes injury and its similarity to alcoholic steatohepatitis without any history of alcohol consumption^[3,8]. The risk factors of NASH include insulin resistance, oxidative stress, stellate cell activation, cellular apoptosis and infiltration of inflammatory cytokines^[3,9,15-18]. Concomitance of NASH with abdominal obesity, hypertension, dyslipidemia and glucose intolerance has been known as Metabolic or X syndrome and Diabetes Mellitus type 2 (T2DM) as a complication of obesity has been found in 34 to 74% of cases of NASH^[9,19-21].

The most common clinical presentation of these patients include elevation of liver transaminases during routine laboratory exams though hepatomegaly is also prevalent. ALT and AST have been elevated in 70-100% of patients and usually the AST/ALT ratio is less than 1 although a normal transaminase level cannot exclude histological involvement of liver^[4,10,22].

The higher plasma concentration of free fatty acids among obese people per se could be a risk factor for T2DM and based on overlap of insulin resistance and obesity between NASH and T2DM, it is supposable that effective medications on each condition be able to affect positively the other one^[23,24]. L-Carnitine affects intracellular reactions and could decrease response of inflammatory mediators by restriction of oxidative stress. It also stabilize the cellular wall by inhibiting transmission of fatty acids, detoxification of their toxic metabolites, regulation of intra mitochondrial Acyl CoA/CoA ratio and increasing catabolism of glucose^[25-28].

Based on increasing prevalence of non-alcoholic fatty liver and T2DM, their concordance and recent alteration of nutritional and life style among communities, evaluation of these conditions is important and according to role of L-Carnitine in fatty acid oxidation and glucose catabolism, it seems that this drug be able to positively affect the type II diabetic patients who concomitantly involved by nonalcoholic fatty liver. So this randomized pilot study designed to evaluate the potential therapeutic effects of L-Carnitine on fatty liver of diabetic patients.

METHODS

In this randomized double blind pilot study, 60 type 2 diabetic patients whom also diagnosed concomitantly as non-alcoholic fatty liver based on sonographic findings and elevated liver transaminases included during a 2 months period. The target community selected

from diabetic patients who attended in endocrinology outpatient clinics of Ahvaz Jundishapur University. Inclusion criteria included known history of diabetes Mellitus type 2, AST and ALT elevation, sonographic findings compatible with fatty liver, absence of any history of viral hepatitis, hemochromatosis, Wilson disease, autoimmune hepatitis, alpha 1 antitrypsin deficiency and or and chronic liver disease and elevated serum TG and cholesterol level. Exclusion criteria included any history of significant chronic liver disease, history of gastroplasty of jejunoileal bypass surgery, consumption of hepatotoxic medication during last 6 months and significant alcohol consumption (more than 10 g for female and 20 g for male/ day). Before study, every participants requested to sign an informed consent and then, they randomly divided into two groups. The randomization performed by using random numbers which allocated to consecutive participants.

The patients allocated in intervention group (group A) received L Carnitine tablet 750 mg TDS for 3 months while the other group (group B) treated with placebo. The serum levels of FBS, TG, Cholesterol, AST and ALT determined at the beginning of the study and also the sonographic grade of fatty liver recorded. After 3 months, at the end of study again, the serum level of fasting blood sugar, lipid profile and liver transaminases measured and a liver sonography performed for the patients. Then the collected DATA analyzed by using paired t test and SPSS software. During study period, the patients were requested to contact and report their physician any side effect or any other unpredicted problem and also they were free to leave study any time if they want. During the study, all of the authors had access to the study data and reviewed and approved the final manuscript and study protocol arranged based on CONSORT check list. This study has been approved by ethical committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS.REC.1392.199) and also registered in Iran Registration of Clinical Trials as IRCT2014020316348N2.

RESULTS

Overall in this randomized clinical pilot study 60 patients included and during study 6 patients did not completed the study due to lack of attendance in regular visits, incompleteness of their DATA and/ or their own demand. So finally 54 patients finished the study course and considered for final analysis (Figure 1) of them 38 patients (70.4%) were male. Based on their sonographic reports, 10 of participants had grade1 of fatty liver, 20 allocated as grade 2 and 24 diagnosed as grade 3. Their blood sugar was under control with oral agents. The participants randomly divided into 2 groups. The demographic and baseline laboratory characters of two groups had not any significant difference statistically (Table 1).

The patients in intervention group (group A) treated with L- Carnitine 750 mg TDS while group B received placebo. We did not make any change in their therapeutic regimen for diabetes Mellitus and or hypercholesterolemia. After three months of intervention, the serum level of liver transaminases, Cholesterol, TG and FBS of participants in 2 groups determined (Table 2). In group A the level of AST decreased from 122.7 ± 13.6 to 96.3 ± 7 while in group B raised from 125 ± 14 to 126 ± 11 ($p < 0.001$). The level of ALT in group A declined from 124.5 ± 11.3 to 82.1 ± 5.2 and in placebo group decreased from 120 ± 10.8 to 115.1 ± 6.3 ($p < 0.001$) (Figure 2). The serum cholesterol level before and after study period were 213 ± 40 and 189 ± 34 in group A and 224 ± 54 and 193 ± 24 in group B and did not reveal any significant decline ($p = 0.814$). Results of serum TG as well as fasting blood sugar in two groups were also comparable and did not show any meaningful result ($p > 0.05$, Table 2). In ad-

dition, their follow up ultrasonography did not show any significant change in comparison with baseline reports.

DISCUSSION

The pathogenesis of fatty liver is multifactorial and it seems that insulin resistance and oxidative stress have an important role in accumulation of fatty droplets in hepatocytes^[6,7,9,16-18]. Based on this multifactorial pathogenesis, most efforts for management of fatty liver have been focused on treating the risk factors that are commonly associated with metabolic syndrome and beside lifestyle modification and encourage to weight loss as fundamental steps^[29-33], a number of medical and supplementary therapies have been studied. These include antioxidants such as vitamin E, Co Q10 and Dark chocolate, insulin sensitizers such as pioglitazone and metformin and cytoprotective agents such as ursodeoxycholic acid^[34-38]. In the current study, we evaluated any potential efficacy of L-Carnitine 750 mg TDS as an antioxidant that can also affect intracellular metabolism and fatty acids transmission^[25-28]. L-Carnitine (β -hydroxy- γ -trimethylaminobutyric acid) is a small water soluble molecule which essential for the normal oxidation of fats by the mitochondria and is involved in the trans esterification and excretion of acyl-CoA esters, the oxidation of branched chain α -ketoacids, and removal of potentially toxic acyl Carnitine esters from within mitochondria^[27]. In the absence of L-Carnitine, the accumulation of free fatty acids in the cytoplasm produces a toxic effect on the cell, and an energy deficit arises from the unavailability of fatty acids within the mitochondria^[39].

In a study in China, L-Carnitine supplements ameliorated fatty liver in type 2 diabetic mice by increasing fatty acid oxidation and decreasing the L-Carnitine/ acetyl L-Carnitine ratio in the liver and they concluded oral administration of L-Carnitine protected mitochondrial function in liver^[40] and these protective effects confirmed in another study by Jun, Dae Won, *et al*^[41].

In a study conducted by Malaguarnera *et al* in Italy, the NASH patients treated with L-Carnitine 2 gr daily and At the end of the study, L-Carnitine-treated patients showed significant improvements in the parameters of AST, ALT, γ -GT, total cholesterol, LDL, HDL, TG, glucose and histological scores and they concluded L-Carnitine supplementation to diet could be useful for improving liver function, glucose plasma level, lipid profile, HOMA-IR, and histological manifestations of NASH^[28]. Our findings revealed a very dramatic decline in serum level of liver transaminases (AST, ALT) among intervention group ($p < 0.001$) that was similar to results of Malaguarnera study and could be interpreted as decreasing inflammation and accordingly fibrogenesis in liver. But we did not found any significant change in serum level of cholesterol, TG and FBS level in treated patients in comparison with placebo group ($P > 0.05$) (Table 2).

In a Korean study, 12 weeks of treatment with carnitine-ornitine complex resulted a significantly higher rate of normalization of serum ALT level (17.9% vs 89.7%, $p < 0.001$) in comparison with placebo^[42] that was also similar to findings of current study and they concluded that carnitine-ornitine complex improves serum ALT and may improve hepatic steatosis in patients with diabetes and NAFLD. But they also revealed a significant decrease in HbA1c in the treatment group ($-0.33 \pm 0.82\%$, $p = 0.007$) and this decrease was in contrary to our study ($p = 0.299$). Accordingly another Korean study reported the Carnitine to be able to improve liver profile and peripheral blood mitochondrial DNA copy number and suggest that Carnitine activate the mitochondria, thereby contributing to the

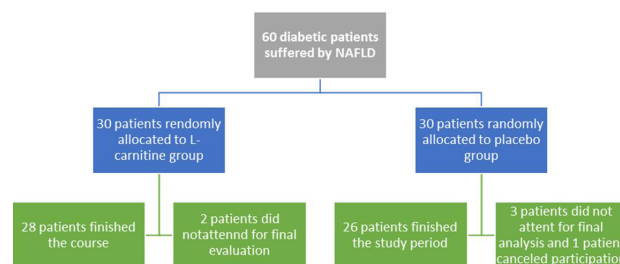


Figure 1 Flow chart of study (NAFLD: nonalcoholic fatty liver).

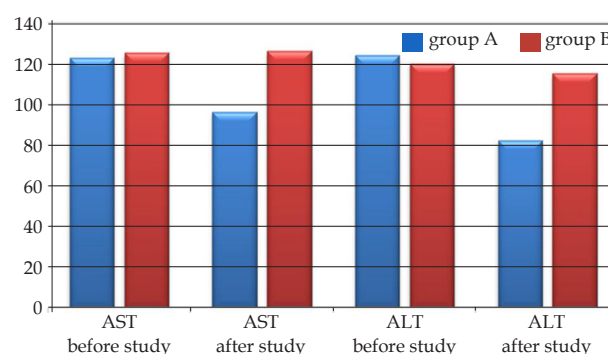


Figure 2 The serum level of liver transaminases, before and after study period in 2 groups; group A: L-Carnitine group, group b: placebo group.

Table 1 Demographic and laboratory characters of 2 groups.

Demographic and laboratory character	L-Carnitine group (A)	Placebo group (B)	P Value
Age	60 ± 5	59 ± 9	0.148
Male/female	21/7	17/9	0.448
BMI (kg/m ²)	28.6 ± 4.6	29.5 ± 3.6	0.204
AST	122.7 ± 13.6	125.3 ± 14	0.142
ALT	124 ± 11.3	120 ± 10.8	0.067
Cholesterol (mg/dL)	213 ± 40	224 ± 54	0.157
TG (mg/dL)	210 ± 89	202 ± 95	0.488
FBS (mg/dL)	172 ± 63	175 ± 68	0.135
Hb A ₁ C	9.2 ± 1.3	9.1 ± 1.8	0.299

Table 2 Laboratory results of both groups before and after study.

Laboratory variable	Group A		Group B		P Value
	Before study	After study	Before study	After study	
AST (IU/L)	122.7 ± 13.6	96.3 ± 7	125.3 ± 14	126.1 ± 11	< 0.001
ALT (IU/L)	124 ± 11.3	82.1 ± 5.2	120 ± 10.8	115 ± 6.2	< 0.001
Cholesterol (mg/dL)	213 ± 40	189 ± 34	224 ± 54	193 ± 24	0.814
TG (mg/dL)	210 ± 89	197 ± 75	202 ± 95	196 ± 63	0.757
FBS (mg/dL)	172 ± 63	165 ± 55	175 ± 68	169 ± 51	0.445
Hb A ₁ C	9.2 ± 1.3	8.9 ± 1.2	9.1 ± 1.8	8.8 ± 1.8	0.302

improvement of NAFLD^[43].

Shakerhosseini in 2005 investigated the effects of oral L-Carnitine administration 3gr daily on fasting plasma glucose, HbA1c and lipid parameters in 18 patients with diabetes mellitus type II for a period of 12 weeks^[25]. They found no significant changes in LDL-C, HDL-C, HbA1C or in total cholesterol (TC) between the two groups similar to our results and concluded L-Carnitine increases fasting triglycerides in type II diabetic patients while significantly lowers fasting plasma glucose.

The common point of almost all of the mentioned studies is the significant decline in serum level of liver transaminases secondary to treatment with L-Carnitine among patients suffered by NAFLD and based on population based follow up studies, patients with NASH and especially those with elevated liver enzymes, are at increased risk

of death compared with the general population^[44-46]. So this decline in serum level of liver transaminases can be interpreted as survival benefit and highlighting the therapeutic efficacy of L-Carnitine as a safe and easily accessible option for treatment of fatty liver. And base on more rapid progression of fatty liver among diabetic patients^[9,18,19], it seems logic that L-Carnitine be recommended for them as a therapeutic option or at least as an additive to their medications even without any unwanted effect on the level of serum sugar.

During the current study, the sonographic follow up of patients in either group did not shown any significant changes. This matter could be explained by the short course of study (3 months) and usually sonographic changes of fatty liver necessitate longer time periods to be clinically recordable.

CONCLUSION

It seems that L-Carnitine with dose of 750 mg TDS significantly decreases the serum levels of liver transaminases among diabetic patients suffered by fatty liver and is effective in treatment of NAFLD. This supplementary medication could be a potential therapeutic approach in such patients and is worthwhile to be added to their therapeutic regimen. We recommend these findings to further be verified by future studies.

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CONFLICT OF INTEREST

The authors declare to have any conflict of interest.

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