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Data from a randomized and controlled trial of L-Carnitine prescription for the treatment for Non-Alcoholic Fatty Liver Disease

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Abstract:
Non-alcoholic fatty liver disease (NAFLD) consists of a range of complication. The disease describes clinical , para clinical and pathological conditions from simple steatosis in non-alcoholic steato hepatitis (NASH) to fibrosis, cirrhosis and hepato cellular carcinoma. Therefore, it is of interest to evaluate the grade of fatty liver and Liver Function Test in NAFLD patients. We collected samples and data from 80 patients referred to gastrointestinal clinic of Emam Reza hospital with sonography diagnosed NAFLD and were evaluated in two groups in a randomized clinical trial. The effects of L-Carnitine (500 mg) prescription twice a day on liver enzymes and echogenicity changes in case group was documented and compared with the control group. The mean age of the patients was 40.7±8 in the age range of 25 to 62 years old with 66 (82.5%) male and 14 (17.5%) female patients. Data show that fatty liver changes were not significantly different in the two groups (P=0.23). It is observed that the ALT was the only enzyme with significant changes (P=0.01) after a 24-week interval. It is also noted that the difference in fatty liver sonographic grading was also significant in the two groups (P=0.0001). Thus, proper therapeutic protocols can be adopted beside diet and weight loss to control the disease trend in consideration to the significant changes observed both in enzymatic levels and sonographic grading between the two groups of patients with NAFLD.

Key words: L-carnitine, Liver Function, NAFLD.

Background:
Non-alcoholic Fatty Liver Disease is defined as accumulated lipid in hepatocytes, more than 5% of liver weight, in the absence of virus infections and alcohol usage (more than 30 gmper day),including a wide spectrum of liver damage, on the one hand hepatic steatosis and the other hand non-alcoholicSteatohepatitis related to fibrosis,necrosis, inflammation and hepatocellular cancer **[1-3]**. Fibrosis caused by NASH has seen in 40% of very fat patients**[4]**. According to a theory called "two-hit",the changing and progressing of the simple steatosis to hepatic steatosis and advanced fibrosis is caused by two hits **[5]**, in which the first hit leads to insulin-resistant accumulated lipid in the liver and the second one due to the accumulatedlipid in liver causes oxidative stress and then facilitatedinflammation, progressing steatosis and fibrosis **[6, 7].** This disease led to hepatic cirrhosis and finally death **[8]**. The prevalence of NAFLD in20-30% of general people in the Western countries, and the prevalence of NASH in 3-5% of them is estimated **[9, 10]**. Whereas,the prevalence of this disease was less in Asian countries but increased because of mellitus diabetes, metabolic syndrome and changing life style **[11].** Also the prevalence of that among male is more than female, it`s common inwomen especially after menopause **[12].** Most of people who were receiving treatment for this disease, were

diagnosed with high level of ALT and AST enzymes in which the serum level of ALT is more than AST, so ALT to AST ratio is less than 1 **[13].** This disease is the most common reason for abnormal values of liver enzymes in current decades **[14].** We can point to the other laboratory disorders such as fasting blood sugar,LDL-TG, etc **[15].** In fact,there must be an inflammatory and damage intensity of parenchyme and fibrosis ranking system in order to determine the prognosis and evaluated effect of treat interventions during disease **[16].** Currently, there is nocertain treatment for NAFLD,so it seems necessary to find new treatment approach,replacing or helping current treatment for fatty liver. L-Carnitine with chemical formula (B-hydroxy-N-TrimetylAminobutyric Acid) has animportant role in fatty acids Beta-oxidation with long strain in mitochondria and energy synthetis in cell **[17, 18]**, which finally causes fatty oxidation and storing glycation **[19]**. With respect to antioxidativequality of L-carnitine and improving the endothelial function **[20, 21],** we were to evaluate the effect of L-carnitine in and sonographic evidences in treatment of non-alcoholic fatty liver disease.

Methodology:

Population

In a randomized and controlled clinical trial study, we examined 80 patients' withgastroenterologydisorders in Emam Reza and Sheikh Alrais centers in Tabriz. We then divided them into control and intervention groups each including 40 patients, with known sonographic evidences based on Liver steatose, while other causes of fatty liver had been rejected.

Study entrance criteria

The patient criteria include NAFLD with liver steatose in sonography of the liver having liver function test with greater than 40mg/dl.

Study exit criteria

Diabetic patients

Other reasons increasing liver enzymes: viral infections,hereditary diseases such as hemachromatosis, Wilson`s disease, auto immunity hepatitis and drugs causing drug hepatitis Alcohol consumption more than 10 gr for female and 20 gr for male Sonographic and laboratory evidences confirming cholestatic Diseasestriglyceride more than 500 mg/dl in individuals

ClinicalTrial

This study has been done onJune 2012-July 2014. At first patients' height and weight by stadiometer and Seca scales with 0.1kg and 0.5 cm precisionrespectively and BMI by standard formula have been measured **[22]**. There was a questionnaire for each patient including personal information,gender,age, past experience of diseasesespecially high blood pressure, overweight, hyper lipidemia, ALT and AST quantities and sonographic evidences.Exercising and on low fat diet were recommended to both groups. Group A patients received treatment L-carnitine tablet 250mg every 12 hours and group B was considered as controlgroup.In 24 weeks,ALT and AST test and sonographyof liver were done in order to determine fatty liver`s grade.

Sonography and LaboratoryTests

After and before intervention,sonography of patients in each group was done by radiologist who was not aware of biochemical liver tests, with Siemens G40 and pruvconex, and 3.46 MHz frequency after 8 hours fasting.The fatty liver grade was classified as Grade I,Grade II, and Grade III according to sonographiccriteria **(Figure 1).** After 12-14 hours fasting,ALT and AST quantities for all patients at the first and end of the period were measured by Pars Azmoon kit (made in Iran) and auto analyzer (Hitachi 747, Japan).

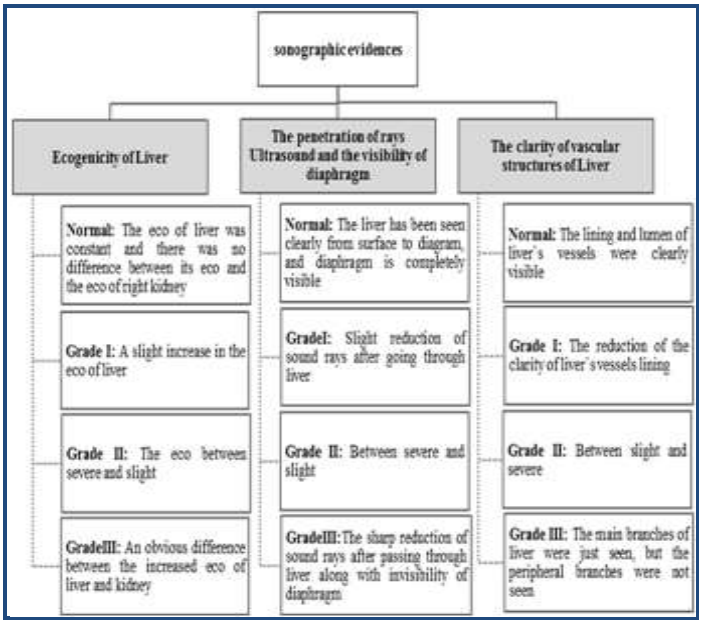

Figure 1: The grading of accumulated lipid intensity in liver according to sonographic evidences

Statistical Analysis

The data was analyzed and compared by SPSS version 16 using Qui-Square forqualitative variables and Student T-test for quantitativevariables and registered byMean ±SD into percentage and frequency.

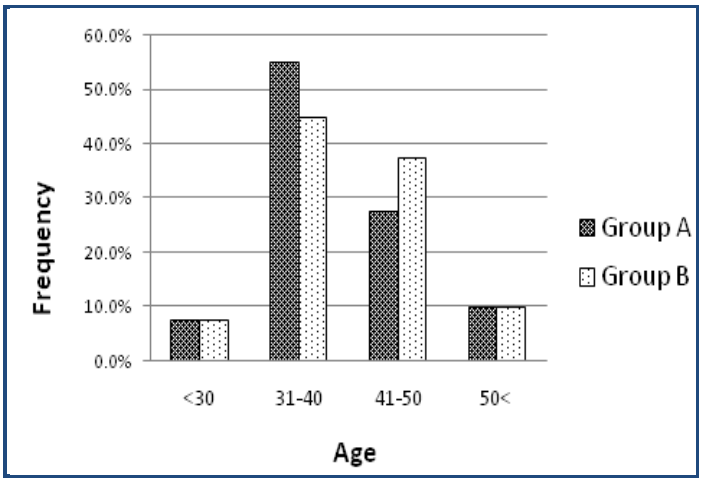

Figure 2: Comparison of sample frequency in different age groups, between two groups

Results:

On the whole in 80 patients with NAFLD, 66individuals were men (82.5 %) and 24 individualswere women (17.5 %). They were divided into two groups A and B,so that there were 23 men (82.5 %) and 7 women(17.5 %) in each group. After the analysis, there was no significant statistical difference between

two groups (p=0.61).The average age in all patients was40.7±8 years old which was in the range of 25-36 years **(Figure 2).** The average age in group A and group B was 40.3±7.8and 41.1±8.3 years old respectively. The age difference between twogroups of patients was not significant (p=0.65). The most frequency of patients'age was 30-41 years old and the least frequency was +50 years old. Patients were divided into 4 groups according to sonographic evidences **(Figure 1).** Therefore,before intervention, there were 7 individuals Grade I, 31 individuals Grade II and 2 individuals Grade III in group A **Table 1 (see supplementary material),** 22 individuals Grade I, 17 individuals Grade II and 1 individual Grade III in group B **(Table 1).**Variances after and before interventionin group A were significant in ALT,AST, BMI, weight and sonographic grade **(Table 1).** Variances after and before intervention in group B in BMI and weight was significant, but in ALT,AST and sonographic grade was significant (**Table 1).**

Discussion:

NAFLD was identified for the first time in people without alcohol usage experience in 1980 **[23]**. In fact, this disease includes a wide range of disorders from accumulated lipid in big vesicular form to accumulated lipidwith inflammation, cirrhosis and hepatic damage **[24]**. In fact, when NAFLD appears that fat comprises 5-10% of liver's weight **[25-27].** The prevalence of this is 34-46 % in adults, although the prevalence of it is 21.5-31.5 % in Iran **[28-30].** There is have been no certain treatment for NAFLD so far, but losing weight, controllingmetabolic syndromes like diabetes and hyperlipidemia, taking antioxidant drugs like Vitamin D and those which are sensitive to insulin are recommended **[31, 32].** It is suggested to take Thiazolidinedione family drugs such as Pioglitazone and Rosiglitazone, although it calls for more investigations in comprehensiveresearch projects **[33]**. In the present study, the effects of L-carnitine prescription on Liver function test and sonographic evidences were evaluated. The results indicated decrease in weight and BMI,after and before intervention, in both groups; moreover, this decreasewas significant in group A. InBahrami *et al*.,2003 study which was done on 53 NAFLD patients, the average weight of patients wasmore than control group,so that patients had high BMI and 10 % weight addition to their idea weight **[34].** In our study before any intervention, both groups were homogenized in terms of BMI and weight, so that there was no significant statisticaldifference. The role of BMI and weight in fatty liver hasbeen the topic of many studies. In the past, BMI was the more important independent predictor agent of accumulated fat in liver **[35, 36].** Other researcheshave accentuated that the peripheral accumulated lipid is a more important predictor agent in comparison with BMI **[37, 38].** So according to the significant reduction in BMI and weight effected by taking L-carnitinedaily in intervention group, this drug can be considered as an effective drug and can be prescribed for NAFLD patients . In this present, the reduction of serum level of Liver enzymes andsonographic grade was significant in both groups, but 9 individuals in group A, after 24-week period, had normal sonographic grade. According to these results, it can be claimed that L-carnitine 500mg prescribed cannot be considered as an absolute treatmentto improve serum levels of Liver enzymes and sonographic grade in NAFLD patients. While in the results of Malaguarnera et al.,2010 study that evaluated laboratory parameters,BMI,weight and histological observed Liver after taking L-carnitine 1000mg twice in 24 weeks,indicated CRP, TNF-α and lipid profile reduction and significant improvement in histological fatty Liver **[39]**. The difference between the results ofMalaguarnera`s study and this one can be because of the drug dosage during the treatment. In Biefort et al.,2006 study which evaluated the effect of 45mg Piolitazone in 24 weeks for fatty Liver treatment, the reduction in lipid profile, ALT and sonographic view was significant, in contrast AST quantity reduction was not significant **[40]**. We can refer to Hong & Lee `s study about the effect of other drugs on improving NAFLD patients in which anyone presented a different report about improving Liver function by taking Resveratrol **[41, 42].** In Celinski et al.,2014 has claimed that melatonin can be used in the treatment ofNAFLD especially metabolism of lipid disorders,hyper triglyceridemia and hyper-LDL cholesterolemia **[43]**.

Conclusion:

A suitable treatment protocol with L-carnitinecanbeadvised, so the disease can be well controlled as per significant reduction of liver enzymes and improving sonographic grade in the comparison between both groups with NAFLD, besides losing weight and a proper diet.

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Supplementary material:

Table 1: The variances between intended indexes before and after the intervention in groups A & B

		Group A		Group B	
Variable		**Pre-Trial**	**Post-Trial**	**Pre-Trial**	**Post-Trial**
Weight		88.3±13.1	85.8±12.6**	85.2±10.7	84.7±10.2*
BMI		29.4±3.9	28.6±4**	28.6±3.2	28.4±3.1*
AST		60.5±28.3	44.9±22.8**	52.6±24.4	39.5±21.1**
ALT		81.7±40.1	51±23.5**	54.1±17.6	38.4±18.9**
Grade	I	7 (17.5%)	9 (22.5%)*	22(55%)	30 (75%)**
	II	31(77.5%)	22 (55%)*	17(42.5%)	10 (25%)**
	III	2 (5%)	…….*	1(2.5%)	…….**
	Normal	…….	9 (22.5%)*	…….	……**

Measures: weight= kg, BMI=kg/m^2, AST=mg/dl, ALT=mg/dl
Comparison within group A and within group B according to the values before the treatment:
* P = NS; ** P < 0.05