The prescription of L-Carnitine in the treatment of Non-alcoholic fatty liver disease; A randomized and controlled clinical trial

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) consists of a range of consumption. The disease comprises clinical, Para clinical and pathological conditions from simple steatosis in non-alcoholic steatohepatitis (NASH) to fibrosis, cirrhosis and finally to hepatocellular carcinoma. The purpose of this study is to evaluate the grade of fatty liver and LFT in NAFLD patients. 80 patients referred to gastrointestinal clinic of Emam Reza hospital with sonography diagnosed NAFLD were evaluated in two groups in a randomized clinical trial. The effects of BID dose of L-Carnitine (500 mg) on liver enzymes and echogenicity changes in case group was documented and compared with control group. The mean age of the patients was 40.7±8 in the age range of 25 to 62 years old. 66 (82.5%) of the patients were male and 14 (17.5%) of them were female. Fatty liver changes were not significantly different in the two groups (P=0.23). After a 24-week interval, the ALT was the only enzyme with significant changes (P=0.01). The difference in fatty liver sonographic grading was also significant in the two groups (P=0.0001). Considering the significant changes both in enzymatic levels and sonographic grading between the two groups of patients with NAFLD, proper therapeutic protocols can be adopted beside diet and weight loss to control the disease trend.

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

INTRODUCTION

Non-alcoholic Fatty Liver Disease is defined as accumulated lipid in hepatocites, more than 5% of liver weight, in the absence of virus infections and alcohol usage (more than 30 gm per day), including a wide spectrum of liver damage, on the one hand hepatic steatosis and the other hand non-alcoholic Steatohepatitis related to fibrosis, necrosis, inflammation and hepatocellular cancer (Byrne, 2009; Bahrololumi, 2014; Neuschwander-Tetri, 2003). Fibrosis caused by NASH has seen in 40% of very fat patients (Harrison, 2003). According to a hyptosis called "two-hit",the changing and progressing of the simple steatosis to hepatic steatosis and advanced fibrosis is caused by two hits (Day, 1998), 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 (Petta, 2009; Videla, 2004). This disease led to hepatic cirosis and finally death (McClain, 2004). 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 (Ruhl, 2004; Ahad Eshraghian, 2013). Whereas, the prevalence of this disease was less in Asian countries but increased because of mellitus diabetes, metabolic syndrome and changing life style (Zolfaghari, 2014). Also the prevalence of that among male is more than female,it`s common in women especially after menopause (Matteoni, 1999). 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. This disease is the most common reason for abnormal values of liver enzymes in current decades (Chen, 2008). We can point to the other laboratory disorders such as fasting blood sugar, LDL-TG, etc. (Laroussi, 2002). In fact,there must be an inflammatory and damage intensity of parancism and fibrosis ranking system in order to determine the prognosis and evaluated effect of treat interventiovs during disease (Dokmeci, 2007). 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- Trimetyl Aminobutyric Acid) has animportant role in fatty acids betaoxidasion with long strain in mithocondrya and energy synthetis in cell, which finally causes fatty oxidation and storing glycation (Gülçin, 2006). With respect to antioxidativequality of L-carnitine and improving the endothelial function (Mansour, 2006;

Byrne, 2009), we were to evaluate the effect of L-carnitine in and sonographic evidences in treatment of non-alcoholic fatty liver disease.

MATERIALS & METHODS

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

Study entrance criteria: Having NAFLD with liver steatose in sonography of the liver

Liver function test more than 40mg/dl

Study exit criteria: Diabetic patients:

Other reasons increasing liver enzymes: viral infections, hereditary diseases such as hemacromatosis, Wilson`s disease, auto immunity hepatitis and drugs causing drug hepatitis

Alcohol consumption more than 10 gm for female and 20 gm for male

Sonographic and laboratory evidences confirming cholestatic

Diseases triglyceride more than 500 mg/dl in individuals

Clinical trial: 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 precision respectively and BMI by standard formula have been measured (Bahrololumi, 2014). There was a questionnaire for each patient including personal information, gender, age, past experience of diseases especially 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 control group. In 24 weeks, ALT and AST test and sonography of liver were done in order to determine fatty liver`s grade.

Sonography and laboratory tests: 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 sonographic criteria (Table 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).

Statistical analysis: The data was analyzed and compared by SPSS version 16 using Qui-Square for qualitative variables and Student T-test for quantitative variables and registered by Mean ±SD into percentage and frequency.

Table.1.The grading of accumulated lipid intensity in liver according to sonographic evidences

Ecogenicity of Liver	**Normal:** The eco of liver was constant and there was no difference between its eco and the eco of right kidney. **Grade I:** A slight increase in the eco of liver **Grade II:** The eco between severe and slight **Grade III:** An obvious difference between the increased eco of liver and kidney.
The penetration of rays Ultrasound and the visibility of diaphragm	**Normal:** The liver has been seen clearly from surface to diagram, and diaphragm is completely visible. **GradeI:** Slight reduction of sound rays after going through liver **Grade II:** Between severe and slight **Grade III:** The sharp reduction of sound rays after passing through liver along with invisibility of diaphragm.
The clarity of vascular structures of Liver	**Normal:** The lining and lumen of liver`s vessels were clearly visible. **Grade I:** The reduction of the clarity of liver`s vessels lining. **Grade II:** Between slight and severe **Grade III:** The main branches of liver were just seen, but the peripheral branches were not seen

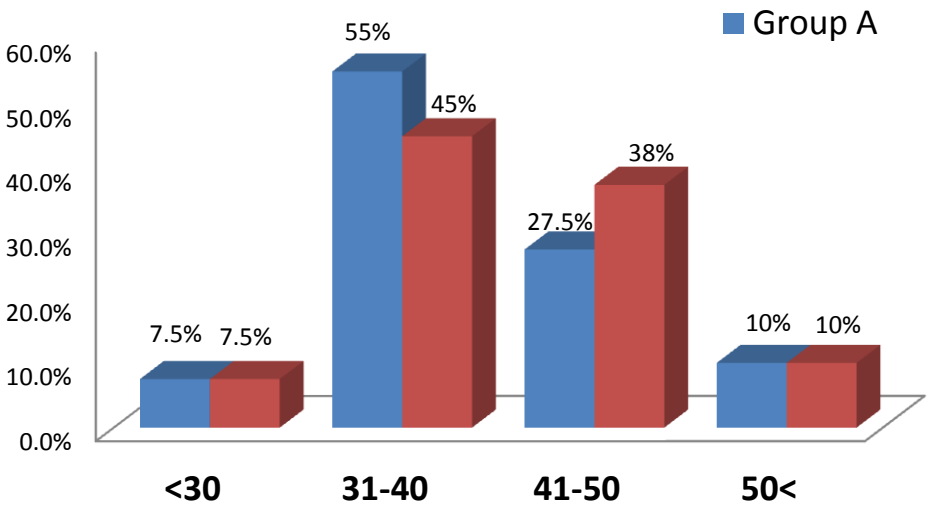

Figure.1.Compare of frequencydifferent age groups, between two groups

RESULTS AND DISCUSSION

On the whole in 80 patients with NAFLD, 66individuals were men (82.5 %) and 24 individuals were 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 1). 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 two groups 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 (Table 1). Therefore, before intervention, there were 7 individuals Grade I, 31 individuals Grade II and 2 individuals Grade III in group A (Table 2), 22 individuals Grade I, 17 individuals Grade II and 1 individual Grade III in group B (Table 3).Variances after and before interventionin in group A were significant in ALT, AST, BMI, weight and sonographic grade (Table 2). Variances after and before intervention in group B in BMI and weight was significant, but in ALT, AST and sonographic grade was significant (Table 3).

NAFLD was identified for the first time in people without alcohol usage experience in 1980 (Neuschwander-Tetri, 2003). In fact, this disease includes a wide range of disorders from accumulated lipid in big vesicoular form to accumulated lipid with inflammation, cirosis and hepatic damage (Harrison, 2003). In fact, when NAFLD appears when fat comprises 5-10 % of liver's weight (Day, 1998; Petta, 2009; Videla, 2004). The prevalence of this is 34-46 % in adults, although the prevalence of it is 21.5-31.5 % in Iran (McClain, 2004; Bellentani, 2010; Ruhl, 2004). 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 (Ahad Eshraghian, 2013; Zolfaghari, 2014). It is suggested to take Thiazolidinedione family drugs such as Pioglitazone and Rosiglitazone, although it calls for more investigations in comprehensiveresearch projects (Matteoni, 1999). In the present study, the effects of prescribed L-carnitine 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 decrease was significant in group A. In Bahrami et al., 2003 study which was done on 53 NAFLD patients, the average weight of patients was more than control group, so that patients had high BMI and 10 % weight addition to their idea weight. In our study before any intervention, both groups were homogenized in terms of BMI and weight, so that there was no significant statistical difference. The role of BMI and weight in fatty liver has been the topic of many studies. In the past, BMI was the more important independent predictor agent of accumulated fat in liver (Chen, 2008; Laroussi, 2002). Other researchers have accentuated that the peripheral accumulated lipid is a more important predictor agent in comparison with BMI (Dokmeci, 2007) 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 Bid in 24 weeks, indicated CRP, TNF-α and lipid profile reduction and significant improvement in histological fatty Liver (Arazi, 2013). The difference is between the results of Malaguarnera `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 (Gülçin, 2006). 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 (Mansour, 2006; Tobias, 2014). In Celinski et al., 2014, it has claimed that melatonin can be used in the treatment of NAFLD especially metabolism of lipid disorders,hyper triglyceridemia and hyper-LDL cholesterolemia (Ekhlasi, 2013).

Table.2.The variances between intended indexes before and after the intervention in group A

Variable	Pre-Trial		Post-Trial		P Value
Weight	88.3±13.1		85.8±12.6		P=0.006
BMI	29.4±3.9		28.6±4		P=0.005
AST	60.5±28.3		44.9±22.8		P=0.008
ALT	81.7±40.1		51±23.5		P=0.0001
Grade	I	7 (17.5%)	I	9 (22.5%)	P=0.06
	II	31(77.5%)	II	22 (55%)	
	III	2 (5%)	III	…….	
	Normal	…….	Normal	9 (22.5%)	

Measures: Weight= kilogram, BMI=kg/m^2, AST=mg/dl, ALT=mg/dl

Table.3.The variances between intended indexes before and after the intervention in Group B

Variable	Pre-Trial		Post-Trial		P Value
Weight	85.2±10.7		84.7±10.2		P=0.11
BMI	28.6±3.2		28.4±3.1		P=0.17
AST	52.6±24.4		39.5±21.1		P=0.0001
ALT	54.1±17.6		38.4±18.9		P=0.0001
Grade	I	22 (55%)	I	30 (75%)	P=0.02
	II	17(42.5%)	II	10 (25%)	
	III	1 (2.5%)	III	…….	
	Normal	…….	Normal	……	

Measures: weight= kg, BMI=kg/m^2, AST=mg/dl, ALT=mg/dl

CONCLUSION

According to the significant reduction of liver enzymes and improving sonographic grade in the comparison between both groups with NAFLD, besides losing weight and a proper diet, a suitable treatment protocol with L-carnitine can be taken, so the disease can be well controlled and finally treated.

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