Effect of Weight Reduction on Liver Enzyme in Obese Post-menopausal Women with Chronic Hepatitis

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ABSTRACT

Background: *The prevalence of obesity and overweight has risen at an alarming rate over the past 20 years. In addition to increasing the risk of the development of type 2 diabetes, hypertension, excess body weight also has a risk factor for progression of fibrosis in chronic liver diseases such as chronic hepatitis and non-alcoholic fatty liver disease. The menopause transition results in a reduction in resting metabolic rate, physical activity, energy expenditure, and leads to an increase in fat mass and abdominal adipose tissue accumulation. These changes increase the risk of bad prognosis of already existed liver disease.* ***Purpose of the study:*** *to investigate the effect of 3 months aerobic exercise training with weight loss on alanine aminotransferase (ALT) in patients with chronic hepatitis C,* ***Methodology:*** *20 obese postmenopausal women with body mass index (BMI) > 30 kg\m^2 suffered from hepatitis C participated in the study followed a regimen of restricted diet of 1000-1200 Kcal\day, in addition to a program of aerobic exercise training on a treadmill 3 times\week for 25 minutes, for 3 months, ALT, BMI and waist hip ratio (WHR) were measured before starting the study then after (J and 12 weeks of training.* ***Results:*** *showed that serum ALT levels fell progressively with weight loss (P < 0.0001), in parallel to highly significant decrease in BMI and WIIR (P < 0.001) after 12 weeks of intervention through diet control and aerobic exercises.* ***Conclusions:*** *Weight loss in patients with chronic hepatitis C associated with a reduction in abnormal liver enzyme, weight reduction may provide an important adjunct treatment strategy for patients with chronic hepatitis C.*

Key words: *chronic hepatitis C, liver enzyme, exercise, diet.*

INTRODUCTION

Hepatitis C, a blood-borne infectious disease of the liver, is transmitted through body tluids, primarily blood or blood products, and by sharing needles. Hepatitis C virus (liCV) is a major cause of chronic liver disease with an estimated 170 million chronic carriers worldwide. Most infections are persistent and the majority of eases develop chronic liver disease with various outcomes, ranging from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Although the therapy of chronic HCV has improved substantially during the last decade, complete recovery occurs in less than 50% of treated patients. With the standard regimen of interferon (IFNJ alpha-2b in combination with ribavirin for 24-48 weeks, a sustained virological response is achievable in only 30-60% of treated patients[19,26].

The complications of hepatitis C alarming to the need for liver transplantation due to mainly the development of fibrosis and subsequently cirrhosis; however, only about 30% of patients infected with Ihe hepatitis C virus (HCV) for 20 years will progress to cirrhosis. This suggests that other factors (such tu> obesity, smoking, alcohol abuse) in addition to the virus itself must augment or accelerate the hepatotoxicity and fibrogenic capacity of IICV[5,27].

The prevalence of obesity and overweight has risen at an alarming rale over the past 20 years. In addition to increasing the risk of the development of type 2 diabetes, hypertension, and dyslipidaemia, excess body weight also has an adverse effect on the liver[21].

Menopause is high risk lime for weight gain in women. Although the average woman gains 2-5 pounds during menopausal transition, some women are at risk for greater weight gain. There is also, a hormone driven shift in body fat distribution from peripheral to abdominal at menopause, which may increase health risks in older women[4,10].

Obesity is a risk factor for progression of fibrosis in chronic hvcr diseases such as non-alcoholic fatty liver disease and hepatitis C. It is also recognized as an independent risk factor for the progression of fibrosis in oilier chronic liver diseases[9].

Obesity encompasses a wide spectrum of liver pathology, ranging from steatosis to steatohepatitis, fibrosis, and cirrhosis. In patients with non alcoholic fatty liver disease (NAFLD), the clinical risk, factors thai are associated with liver injury include elevated body mass index (BMI). visceral adiposity (increased waist circumference), presence of type 2 diabetes, and systemic hypertension[18,22].

Obesity is an independent (actor that diminishes the eradication rate of IFN-based treatment. This confirms that obesity to be an independent negative predictor of HCV response to treatment. A number of studies have now demonstrated an association between increased BMI or visceral adiposity and hepatic steatosis and fibrosis in patients infected with HCV. In overweight patients with chronic HCV, it is recently demonstrated an association between increasing insulin levels and increasing hepatic fibrosis, suggesting that host metabolic factors also contribute to disease progression. Similarly, in patients with alcoholic liver disease, elevated BMI and lasting blood glucose were independent risk factors for hepatic fibrosis[1,15&27].

The role of increased I3M.1 and steatosis as comorbid factors in the progression of fibrosis has important therapeutic implications. Although gradual weight reduction is recommended as a first step in the management of patients with obesity related fatty liver, there is a paucity of long term outcome data on the effect of modest weight loss on liver disease or associated metabolic factors[14].

We hypothesised that weight reduction in patients with chronic HCV would be accompanied by a reduction in ALT. To investigate this hypothesis, we studied the effect of a three months weight reduction programme on liver enzyme and in 20 obese postmenopausa! women with chronic HCV.

The aim of this study was to investigate the effect of weight reduction on ALT in obese patients with hepatitis C.

MATERIAL AND METHODS

Methods

Twenty obese postmenopausal women with chronic HCV seen in the Hepatitis Management Clinic at Cairo University Hospitals were invited to participate in the study, their ages ranged from 50-60 years. Informed consent was obtained from each patient. Criteria required for entrance into the study were: (a) chronic HCV with circulating HCV RNA (detected by Amplicor HCV Monitor assay; Roche, New Jersey, USA) and abnormal serum aminotransferase levels (1.5 times the upper limit of normal) for at least 6 months; (b) overweight or obese (BMI >30 kg/m).; (c) no evidence of participation in diet reduction programs within the last 6 months.

All participants were following a low caloric diet (with allowed calories 1 GOO-1200 kcal\ day which was divided as following 50-60% carbohydrates, 20% protein, > 30% total fat and 18 gm of fiber \1000 Kcal) in addition to a program of aerobic exercise training, followed their program for 3 months.

Exclusion criteria were illegal drug use either currently or within the previous year, history of uncontrolled depression or psychosis, uncontrolled seizures, cardiac disease, any orthopedic limitation.

Exercise training protocol

Each patient was participated at exercise training program for 3 months (3 times per week) each exercise session was hold for 25 minutes. Each patient should be instructed not to eat for 3 hours before the exercise session.

The exercise training program was in the form of walking on treadmill, and asking each patient not to tightly grasp the rails because

this action reduces the workload at any stage of exercise. To overcome this problem each patient was asked to remove their hands from rails, close their fists, and place one finger on the rails to maintain balance after they accustomed to walking on the treadmill.

The exercise session was started by 5 minutes warm up which involved walking with no resistance and no inclination at the walk way of the treadmill followed by 15 minutes of walking with 15 degrees inclination at the walk way of the treadmill and adjusted speed to reach (20-40% of target heart rate (THR) in the first 6 weeks of the study then the speed was increased till reach (40-60% THR) in the second 6 weeks of the study.

The THR= [(maximal heart rate - resting heart rate)] + resting heart rate[12]. Maximum heart rate (MHR) was detected according to the equation MHR- 220-age. Then the session is ended by 5 minutes of cool down in which the intensity of the exercise was reduced to the level of the warm up.

Evaluative procedures:

Blood samples for measurement of liver enzyme ALT, BMI [equation BMI= (Weight Kg) \ (Height m^2)] and waist \ hip ratio (WHR) were measured at the beginning of the study, after 6 weeks then after 3 months of the treatment.

Statistical analysis:

All values were calculated by mean ± standard deviation (SD) in addition to using ANOVA compare between subjects at 0, 6 and 12 weeks. For all the statistical testes done, the threshold of significance was fixed at the 5% level (P-value). P-value >0.05 indicated non significant results. P-value < 0.05 indicated highly significant results.

RESULTS

In the current study, 20 patients completed the three months of weight reduction programme (a diet reduction regimen in addition to aerobic training program).

Table (1): ALT level, BMI and WHR at the beginning, after 6 and 12 weeks of the study.

	ALT (U|l)			BMI (Kg| m^2)			WHR		
	Pre-training	Post 6 weeks	Post 12 weeks	Pre-training	Post 6 weeks	Post 12 weeks	Pre-training	Post 6 weeks	Post 12 weeks
Mean	132	99	76	33.4	31.75	29.88	0.91	0.875	0.856
S.D. ±	77	69	63	1.07	1.80	0.03	0.0487	0.046	0.042
F-value	10.03			7.62			9.02		
P-value	< 0.0001			< 0.001			< 0.001		

In concerning to ALT, 17 of the 20 patients showed progressive decrease in ALT with weight loss. Overall, the mean ALT level decreased from 132 (77) to 76 (63) which showed a highly significant decrease (F= 10.03 & P < 0.0001) after 12 weeks of intervention through diet control and aerobic exercises, table (1) and fig (1).

The 20 patients who participated in this study all lost weight with a mean weight loss of 7.8 (4.2) kg with range (1.5-12.8), resulting in a mean difference (3.6) kg|m2 of BMI (F= 7.62 & P < 0.001), table (1) and fig. (2).

For WHR, there was a highly significant decrease (F= 9.02 & P < 0.001), table (1) and fig. (2), which was correspond to the highly significant decrease in both BMI and ALT.

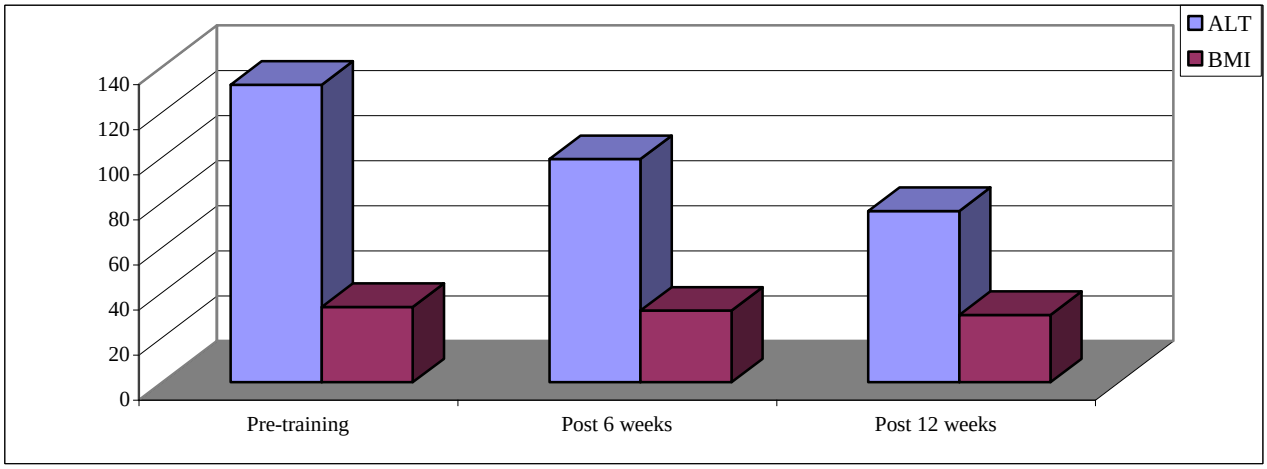

Fig. (1): Shows the ALT and BMI pr-training, post 6 weeks and 12 weeks.

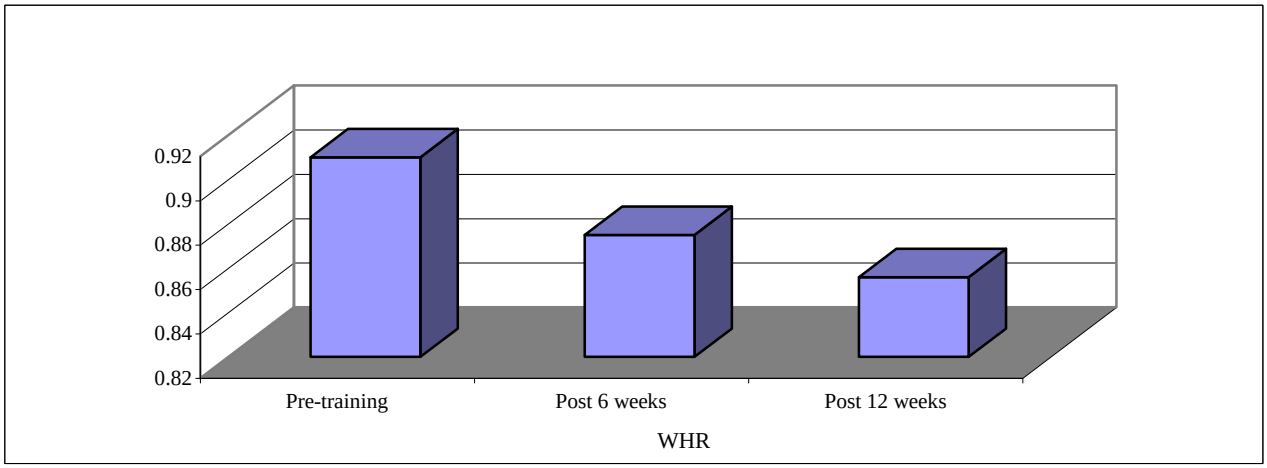

Fig. (2): Shows the WHR pr-training, post 6 weeks and 12 weeks.

DISCUSSION

Chan et al. (2004)[8], concluded that the prevalence of simple steatosis and presumed NASH was 77 and 24%, respectively. The severity of steatosis was positively correlated with BMI, raised ALT, insulin resistance and hypertryglyceridaemia. Zhu et al. (2003)[32], stated that NASH is one of the most important complications of obesity.

The severity of fatty liver was positively related to anthropometric measurements including BMI, waist and hip circumference, subscapular skinfold thickness; insulin resistance markers and homeostasis model assessment (HOMA)], raised alanine aminotransferase (ALT) and hypertriglyceridaemia[8].

The negative effect of obesity on viral clearance was independent from hepatic steatosis. This implies that these 2 intertwined factors act independently on viral clearance .While understanding the mechanisms of the observations by Dressier et al. (2003)[7], may provide new approaches to future therapies, the clinical relevance of this important report is clear. Weight loss in obese patients may improve the efficacy of HCV treatment. In addition, obesity is an independent factor that diminishes the eradication rate of IFN-based treatment. This confirms that obesity is an independent negative predictor of HCV response to treatment[14].

Obesity has an important role in the pathophysiology of steatosis in chronic HCV. Steatosis was noted in chronic liver disease with and without serum antibodies to HCV. Steatosis was found in 60% of HCV-positive and 52% of HCV-negative patients and was strongly associated with obesity[12].

The results of this study showed a highly significant decrease ($P < 0.0001$) of the ALT after 12 weeks of intervention to lose weight through diet reduction and aerobic exercises.

The decrease in ALT was associated with highly significant decrease ($P < 0.001$) in both BMI and waist\ hip ratio.

The previous results can be explained through diet restriction may also have a direct effect on the inflammatory response associated with HCV. In various rodent models, calorie restriction has been shown to reduce the intensity of inflammation and levels of proinflammatory cytokines. Arsenijevic et al. (2000), found a decrease in steatosis that associated with an increased production of reactive oxygen species which initiate lipid peroxidation, resulting in activation of hepatic stellate cells. Also, it alter the expression of mitochondrial membrane proteins, including uncoupling protein 2 which has been implicated in the generation of reactive oxygen species and lipid metabolism[9].

Most patients with chronic HCV and steatosis were in the overweight or obese weight range (26-35 kg/m2) and had significant visceral adiposity, as demonstrated by an elevated waist circumference (>94 cm in males and >80 cm in females). In these patients, loss of as little as 2.6% body weight resulted in a reduction in steatosis, with a significant association between the amount of body weight lost and the degree of change in steatosis[6,17].

Sakugawa et al. (2004), determined the prevalence of fatty liver and alanine aminotransferase (ALT) elevation in obese Japanese women and reported that ALT elevation not associated with fatty liver was frequently seen in obese women, suggesting that obesity is directly associated with the elevated ALT level in Japanese obese women.

Depending on the previously mentioned facts. There were many attempts to investigate the effects of weight reduction on the prognosis of HCV through various methods but our concern is diet reduction and\ or aerobic exercises which studied by many authors as, Sreenivasa Baba et al. (2006)[29], studied the effect of regular aerobic exercise on serum aminotransferase levels in patients with Nonalcoholic steatohepatitis (NASH) and concluded that Moderate intensity aerobic exercise helps in normalizing ALT levels in those patients.

Park et al. (1995)[24], studied the effect of weight reduction alone can improve liver function in obese patients with fatty liver and concluded that those patients showed marked improvement in ALT and AST after they lost weight. Also, Tendler et al. (2007)[30], concluded that six months of a low-carbohydrate, ketogenic diet led to significant weight loss and histological improvement of fatty liver disease.

Luyckx et al. (1998)[18], examined the factors associated with liver steatosis in severely obese subjects and to test the potential reversibility of fatty liver after weight loss and concluded that Liver steatosis in obese subjects is associated with diabetic status, higher fasting glucose and hypertriglyceridaemia. Postgastroplasty weight loss reduces liver steatosis, but seems to increase the incidence of inflammatory lobular hepatitis.

Ueno et al. (1997)[31], compared the effects of restricted diet and exercise versus no treatment in obese patients with fatty liver and conclude that restricted diet and exercise therapy, such as walking and jogging, are useful means of improving blood biochemical data and histological findings in liver tissues related to fatty liver.

Mendez-Sanchez et al. (2004)[21], investigated the effects of weight reduction and ursodeoxycholic acid administration in patients with nonalcoholic fatty liver disease and reported that beneficial effect of weight reduction, producing improvements in biochemical and imaging markers of liver disease.

Akyüz et al. (2007)[27], aimed to compare effects of metformin, rosiglitazone, and diet with exercise in nonalcoholic fatty liver disease and showed that Diet with exercise seems to be superior to metformin and rosiglitazone in decreasing ALT level after 6 as well as 12 months of interventions. Decreasing of ALT altered at month 12 compared to month 6 may be due to its fluctuations.

This study has demonstrated that weight loss in patients with chronic HCV is achievable and may result in a reduction in hepatic enzymes, despite the persistence of the virus. We believe that weight reduction may

provide an important new adjunct treatment strategy for patients with chronic HCV.

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الملخص العربي

تأثير إنقاص الوزن علي أنزيم الكبد في حالات الالتهاب الكبدي المزمن فيروس س لدي السيدات البدينات في سن ما بعد انقطاع الدورة الشهرية

تعتبر السمنة ناقوس خطر علي الصحة العامة لما تسببه من أمراض مثل الداء السكري وارتفاع ضغط الدم وكذلك زيادة تدهور حالات أمراض الكبد المزمنة. كذلك تعانى السيدات في سن ما بعد انقطاع الدورة الشهرية من زيادة وزنهن خصوصاً في منطقة البطن لما له من تأثير سلبي علي أمراض الكبد المزمنة. ومن هنا كان الهدف من هذه الدراسة معرفة تأثير إنقاص الوزن عن طريق الحمية الغذائية والتمرينات الهوائية لمدة ثلاثة أشهر علي انزيم الكبد (الانين أمينو ترانسفيريز). وقد انضمت لهذه الدراسة عشرون سيدة في سن ما بعد انقطاع الدورة الشهرية وكن يعانين من التهاب كبدي مزمن فيروس سى وقد قيمن عن طريق قياس معامل كتلة الجسم ونسبة محيط الخصر علي الحوض وكذلك انزيم الكبد (الانين امينو ترانسفيريز) قبل الاشتراك في الدراسة وبعد ستة أسابيع ثم بعد اثني عشر أسبوعاً من بدء البرنامج العلاجي. وقد أظهرت النتائج انخفاض ذو دلالة إحصائية عالية فى انزيم الكبد (الانين أمينو ترانسفيريز) بعد اثني عشر أسبوعاً من الحمية الغذائية والتمرينات الهوائية وكان هذا الانخفاض متوازياً مع الانخفاض في معامل كتلة الجسم ونسبة محيط الخصر على الحوض. ومن هنا فان إنقاص الوزن يعتبر ضرورة ملحة لما له من تأثير ايجابي علي تحسن تلك الحالات.

الكلمات الدالة: الالتهاب الكبدي المزمن – انزيمات الكبد – التمرينات – الحمية الغذائية.