

Research Article

Weight loss and improvement of hepatic fibrosis in Egyptian patients with chronic hepatitis C

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Abstract

Background: Liver fibrosis is now considered as a reversible disease. Curing the primary hepatic disease doesn't mean fibrosis improvement and steatosis could be one of the reasons responsible for this failure. Loss of weight has shown to improve fibrosis but few data is available from Egypt.

Objective: to test the effect of weight reduction on the degree of fibrosis improvement in Egyptian patients with chronic hepatitis C (CHC).

Methods: Adult patients (> 18 years) with moderate and severe steatosis who were initially investigated by liver biopsy and FibroScan to assess their stage of fibrosis before starting interferon treatment, were reassessed by FibroScan after losing $\geq 10\%$ of their weight. All patients were recruited from hepatitis C clinic, National Liver Institute (NLI), University of Menoufyia, Egypt from 2011 to 2014.

Results: Thirty CHC patients were included in the study, 20 patients with moderate and 10 with severe steatosis. Median age was 44.7 years (29-59 years) with equal sexes. The degree of fibrosis and its values improved significantly with weight loss (Mean \pm SD was 13.81 ± 7.5 kPa before and 10.98 ± 5.6 kPa after losing weight, $p < 0.01$). Three patients (10%) with severe fibrosis were down-graded to F3 and F2 after weight loss (two and one patients, respectively).

Conclusion: Weight reduction is associated with improvement of hepatic fibrosis in Egyptian patient with CHC.

Introduction

Obesity and its direct consequence nonalcoholic fatty liver disease (NAFLD) rates are increasing dramatically worldwide and steatosis becomes one of the most common hepatic histological findings [1]. Steatosis was found to be associated with liver fibrosis especially in chronic hepatitis C (CHC) with positive correlation between its grade and the fibrosis stage [2,3].

Liver fibrosis is a dynamic progressive process as long as the hepatic injurious stimulus wasn't treated. It was considered irreversible in the past but the current studies showed that fibrosis [4-6], and even cirrhosis [7,8] in some series, could be reversible.

Our study was aimed to compare the degree of hepatic fibrosis in overweight patients with CHC before and after weight loss achieved by diet and exercise, which is considered as the standard treatment of steatosis [9,10].

Methods

Adult patients (>18 years) were recruited from hepatitis C clinic, National Liver Institute (NLI), University of Menoufyia, from 2011 to 2014. Standard available treatment at that time was pegylated interferon with ribavirin, after that time we started our new protocol of treating CHC with direct acting antiviral therapies. The assessment process necessitated doing liver biopsy and transient elastography (FibroScan). All patients with alcoholic history, uncontrolled DM or endocrine dysfunction were excluded by the protocol and redirected to special clinics for better management and reassessment. The NLI protocol asked the patient with moderate or severe steatosis to lose at least 10% of his weight by food diet and practicing exercises, to improve the response to treatment. Patients were advised to follow a

diet regimen of 20% protein, 50% carbohydrate and 30% unsaturated fats prescribed by dietitian taking in consideration the different age, sex and the lifestyle of the patients with target of energy reduction of about 25 kcal/kg/day. They were also advised to practice exercise in the form of walking one hour 5 days per week. None of our patients received any medication to reduce his weight. FibroScan was done again to reassess the patient's hepatic fibrosis stage after losing weight without the need for re-biopsy.

Our retrospective study was conducted on those naïve patients eligible for interferon treatment who succeeded to lose the desired weight. We had thirty patients to be involved in the study after excluding files with incomplete data and patients with BMI > 40 kg/m², as that could affect the FibroScan result. None of our patients was alcoholic, diabetic or manifesting endocrinal dysfunction during the study.

Our study was approved from the ethical committee, NLI, University of Menoufyia.

BMI was calculated as defined by WHO [11]: bodyweight in kilograms divided by height in meters squared.

All liver biopsy specimens were analyzed according to METAVIR scoring system for assessment of fibrosis stage [12]. Steatosis was

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categorized by visual assessment as: if steatosis presents in 1-10% of hepatocytes [mild]; 11-30% [moderate]; and 31-100% [severe].

FibroScan was performed using the FibroScan apparatus (Echosens, Paris, France), with 5-MHz transducer. The fibrosis grading score used was: F0=0-2.9 kPa; F1=3-5.9 kPa; F2=6-8.9 kPa; F3=9-16.9 kPa; and F4=17-75 kPa (results were expressed in kilopascals) [13-15].

Statistical Analysis:

Data was statistically analyzed using SPSS version 21 for windows and for all the analysis a p value < 0.05 was considered statistically significant. Data are shown as mean, range or value. As appropriate, stages of fibrosis were tested against continuously-distributed variables using the Anova test. Chi-squared test was used to test two ordinal variables, while paired t test was used for pre and post values of the same variable of the same group of patients.

Results

The present study included 30 CHC patients with moderate and severe steatosis who were initially assessed by liver biopsy and FibroScan before starting interferon treatment for their fibrosis stage, activity grade and degree of steatosis. After losing 10% or more of their weight, they were followed up by FibroScan only. Our patients' median age was 44.7 years (29-59 years) with equal sexes (15 men and 15 women), table 1 shows the patients characteristics before and after losing weight. Only ALT showed significant decrease after weight loss ($p < 0.05$).

According to the histological examination there were 20 patients with moderate and 10 with severe steatosis. Table 2 shows the frequency of different grades of fibrosis between patients according to Metavir classification.

After body weight loss, our results showed great improvement of liver stiffness measured by FibroScan. Table 3 shows the frequency of different grades of fibrosis between patients before and after weight reduction. Figure 1 shows this frequency in relation to BMI before and after weight loss.

For statistical reason, we tested the FibroScan results again as values in kPa, to avoid any statistical defect when grouping patients into grades. Table 4 shows descriptive data (mean, standard deviation and range) of liver fibrosis beside BMI data before and after losing weight. It shows the highly significant improvement of liver fibrosis after weight loss ($p < 0.01$).

Discussion

Liver fibrosis reversibility is still a hot issue. Although it was considered to be a dynamic process depending on the balance between degradation and remodeling of extracellular matrix deposition by metalloproteinase enzymes and their tissue inhibitors, yet the mechanism is not completely understood. For instance, treating the cause of liver disease was thought to improve the ability of liver tissue to reverse fibrosis, but studies showed incomplete or insignificant improvement in some patients [6,7]. This means that, there are other co-factors which if treated could improve the healing response.

Increased body weight is well known to increase fat deposition in hepatocytes i.e. steatosis and it was claimed to cause liver fibrosis [16]. Studies showed that decreasing the hepatic steatosis grade by weight loss achieved by lifestyle modifications (diet and exercise) could improve hepatic fibrosis [17]. Few or scarce data are available from Egypt, in spite of the high prevalence of liver disease in our population [18].

Table 1. Descriptive data and patients' characteristics at the beginning of assessment

| Studied variables | Mean \pm SD Before losing weight | Range | Mean \pm SD After losing weight |
|-------------------|------------------------------------|--|-----------------------------------|
| Age | 44.7 \pm 8.9 | 29-59 years | |
| Male: Female | 15:15 | | |
| BMI | 33.2 \pm 2.5 | 27-36.9 kg/m ² | 29.05 \pm 1.92 |
| ALT | 49.8 \pm 15.8 | 22-88 U/L | 41.2 \pm 11 |
| AST | 49.9 \pm 16.1 | 19-79 U/L | 47.1 \pm 15.3 |
| Albumin | 4.2 \pm 0.4 | 3.6-4.9 gm/dl | 4 \pm 0.6 |
| Total bilirubin | 0.7 \pm 0.2 | 0.3-1.1 mg/dl | 0.7 \pm 0.7 |
| Direct bilirubin | 0.2 \pm 0.1 | 0.03-0.5 mg/dl | 0.15 \pm 0.08 |
| INR | 1.1 \pm 0.1 | 1-1.4 | 1.09 \pm 0.3 |
| HCV RNA level | 779.6 \pm 1385.5 | 17.5-5639.9 IU/ml \times 10 ³ | 824.2 \pm 2112 |
| FibroScan | 13.8 \pm 7.5 | 6.1-30.8 kPa | 10.98 \pm 5.57 |

N: Number, SD: Standard deviation, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, RNA: Ribonucleic Acid, INR: International Normalized Ratio, kPa: kilopascal

Table 2. Characteristics of patients' liver biopsies

| | Frequency | % |
|-------------------------|--------------------|---------------------------|
| Fibrosis stage | | |
| F1 F2 F3 F4 | 11 9 8 2 | 36.7 30 26.6 6.7 |
| Activity grade | | |
| A1 A2 A3 | 16 13 1 | 53.3 43.3 3.4 |
| Steatosis degree | | |
| No Mild Moderate Severe | 0 0 20 10 | 0 0 66.7 33.3 |
| Total | 30 | 100.0 |

Table 3. Fibrosis grades by FibroScan before and after weight reduction

| Stage of fibrosis | Before number (%) | After number (%) |
|-------------------|-------------------|------------------|
| F1 | 0(0%) | 5(16.7%) |
| F2 | 11(36.7%) | 9(30%) |
| F3 | 10(33.3%) | 10(33.3%) |
| F4 | 9(30%) | 6(20%) |
| $P < 0.01$ | | |

Table 4. FibroScan and BMI before and after losing weight

| | Mean | SD | Range | p- value |
|--------------------------------|-------|------|-----------|----------|
| FibroScan (before) kPa | 13.81 | 7.46 | 6.1-30.8 | <0.01* |
| FibroScan (after) kPa | 10.98 | 5.57 | 3.8-23.9 | |
| BMI (before) kg/m ² | 33.23 | 2.5 | 27-36.9 | <0.01* |
| BMI (after) kg/m ² | 29.05 | 1.92 | 24.2-32.5 | |

SD: Standard deviation, kPa: kilopascal. *Paired t-test

In our study we used FibroScan in the assessment of liver fibrosis as it was proved to be a reliable method to detect significant fibrosis compared to histological assessment of liver tissue [14,19], it measures liver stiffness based on the propagation speed of shear waves with overall diagnostic accuracy reaching 94% [20].

Our study goal was to test if losing significant weight could improve the degree of fibrosis in Egyptian patients suffering CHC. We included patients diagnosed with moderate or severe steatosis and compared their FibroScan results before and after losing significant weight, at

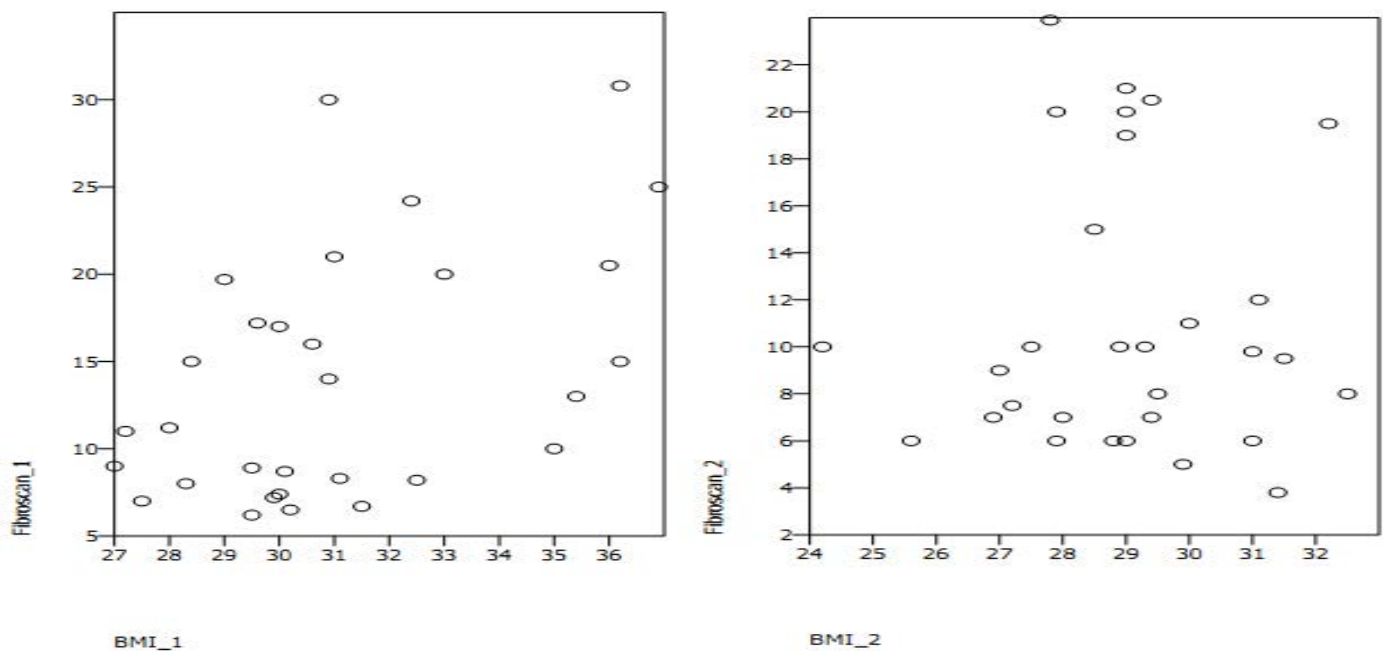


Figure 1. Scatter plot of FibroScan results according to BMI

1 = before weight loss and 2 = after weight loss

least 10% of their original weight. We used BMI [11] in the assessment of our patients' weight reduction, and we found a significant decrease in it with mean of 4.18 kg/m^2 ; $p < 0.01$.

Our main result was that there is marked improvement in the degree of fibrosis and its values in the second scan and before starting the treatment of CHC (Mean \pm SD was $13.81 \pm 7.5 \text{ kPa}$ before and became $10.98 \pm 5.6 \text{ kPa}$ after losing weight, $p < 0.01$). Three patients (10%) with severe fibrosis were down-graded to F3 and F2 after weight loss (two and one patients, respectively). This means that losing weight is an important factor for liver fibrosis healing and it could have more additive effect when treating the main cause of liver injury i.e. hepatitis C in our cases.

Our results go with Hickman *et al.* [17] who investigated 19 patients using liver biopsy before and after weight reduction and found that it was associated with improvement of fibrosis.

Also Dixon *et al.* [21], who investigated the effect of losing significant weight using laparoscopic adjustable gastric band placement on the degree of liver fibrosis and inflammation. They investigated their patients by doing two liver biopsies, before and after weight loss. They reported that significant weight loss was associated with marked improvement in hepatic necro-inflammatory changes and stage of fibrosis.

In conclusion: Weight loss is associated with hepatic fibrosis improvement. It is important to achieve significant weight loss before starting the treatment of the primary cause of the liver disease. More work is needed to find out other co-factors which, if treated could improve the response to the standard available treatments.

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