



ORIGINAL ARTICLE

Effects of lifestyle modification on liver enzyme and Fibroscan in Indian patients with non-alcoholic fatty liver disease

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Abstract

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is remarkably increasing in developing countries like India, in parallel with the increasing incidence of obesity. Lifestyle modification is a recommended treatment for NAFLD. In most of the previous studies, improvement after lifestyle modification was assessed by liver fibrosis through liver biopsy, but we cannot do a serial liver biopsy in every NAFLD patient. Liver fibrosis can also be assessed by fibroscan non-invasively in NAFLD. This study was designed to evaluate the effect of lifestyle modification on liver enzymes and Fibroscan values in a population with NAFLD.

Methods: Initially, 50 NAFLD patients were included in this prospective follow-up study; however, after 6 months of lifestyle modification, only 39 participants were studied. During both the first and second consultations, Fibroscan was carried out. All participants underwent a careful interview, anthropometry measurements and radiological and biochemical tests during every consultation.

Results: After 6 months of lifestyle modification, Fibroscan values improved significantly (8.31 ± 0.11 kPa vs 7.87 ± 0.12 kPa, $p=0.009$). Alanine aminotransferase (ALT) values also showed improvement during the second consultation (97.25 ± 2.62 U/L vs 66.69 ± 3.95 U/L, $p < 0.001$).

Conclusion: Measured by Fibroscan and liver enzymes, it has been found that lifestyle modification is an effective therapy to downgrade hepatic injury in NAFLD patients. Serial Fibroscan can be used to assess the treatment response in NAFLD patients due to its non-invasive nature.

Key words: non-alcoholic fatty liver disease; lifestyle modification; alanine aminotransferase; Fibroscan

Introduction

Non-alcoholic fatty liver disease (NAFLD) is increasingly diagnosed worldwide and is one of the common causes of abnormal liver function tests and chronic liver disease in both developed

and developing countries [1]. About 20–30% of the adult population is affected by NAFLD [2], which is a macrovesicular hepatic steatosis in the absence of alcohol consumption [3]. The primary problem in the majority of NAFLD patients is overweight

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or obesity and underlying insulin resistance. Patients with NAFLD have a 20–50% risk for progressive fibrosis, 30% risk for cirrhosis and 5% risk for hepatocellular carcinoma [4,5].

Weight loss due to diet restriction is expected to have a number of interrelated beneficial effects on NAFLD broadly related to (i) reduced hepatic free fatty acid supply, (ii) improved insulin sensitivity and (iii) reduced adipose tissue inflammation. Unfortunately, there is a lack of randomized clinical trials regarding the positive effect of foods or nutritional supplementation on NAFLD. Moderate intensity of aerobic exercise helped to normalize ALT levels in non-alcoholic steatohepatitis (NASH) patients receiving a restricted diet [6]. A decrease in the Body mass index of three points over a 3-month period also improved hepatic steatosis [7].

Approximately 10–29% of patients with NASH will develop cirrhosis within a 10-year period [8]. For this reason, early detection of liver stiffness and treatment of NAFLD are necessary to prevent NAFLD-related complications. Changes in liver functions and liver stiffness in NAFLD can be detected by alanine aminotransferase (ALT) levels and Fibroscan values, respectively. Fibroscan, which is considered an alternative to liver biopsy in staging of fibrosis, is unable to detect the etiology of liver disease [9,10].

Some studies showed that lifestyle intervention with diet and increased physical activity results in weight loss and improvement in liver enzymes as well as insulin resistance in non-alcoholic fatty liver disease [11]. Moderate exercise associated with diet modification is more effective at improving liver abnormalities than diet alone and improves NAFLD [12]. But there are no effects of only exercise on liver enzyme levels, metabolic parameters, circulatory markers of inflammation (levels of interleukin 6, tumor necrosis factor- α or C-reactive protein) and fibrosis [13].

Most of the previous studies were performed in a Western population and based on liver biopsy reports. But serial liver biopsy is not possible due to its invasive nature to assess treatment response in every NAFLD patient. Some studies showed improvement of NAFLD after lifestyle modification but some studies did not support this. This study has been designed to evaluate the effect of lifestyle modification on liver enzymes and fibroscan values in a population with NAFLD.

Methods and materials

Study design and study population

The ethical committee of Manipal Hospital, Bangalore, approves this study. In this prospective follow-up study, initially, 50 consecutive NAFLD patients attending at Department of Gastroenterology of Manipal Hospital were included between the time period of September 2014 to March 2016. The diagnostic criteria of NAFLD were elevated ALT >1.5 times the upper limit of normal (The upper limit of normal ALT is defined as 35 U/L in males and 19 U/L in females [14]) and fatty liver in ultrasonography of the abdomen. Patients with alcohol consumption, smoking, medications and toxins causing fatty liver, autoimmune and inflammatory disease, malnutrition, total parenteral nutrition, severe weight loss, viral hepatitis and metabolic liver disease (Wilson's disease, Hemochromatosis, etc.), ascites, cirrhosis, chronic illness (e.g. tuberculosis and renal failure), pregnancy, gastroplasty/bowel resection/bowel bypass surgery were excluded.

Three patients were excluded from our study because they had cirrhosis (Fibroscan score >17 kpa). Of the remaining 47 cases, only 43 participants came 6 months after their first consultation. Four patients were excluded from our study after 6 months of follow-up (second consultation), since they did not

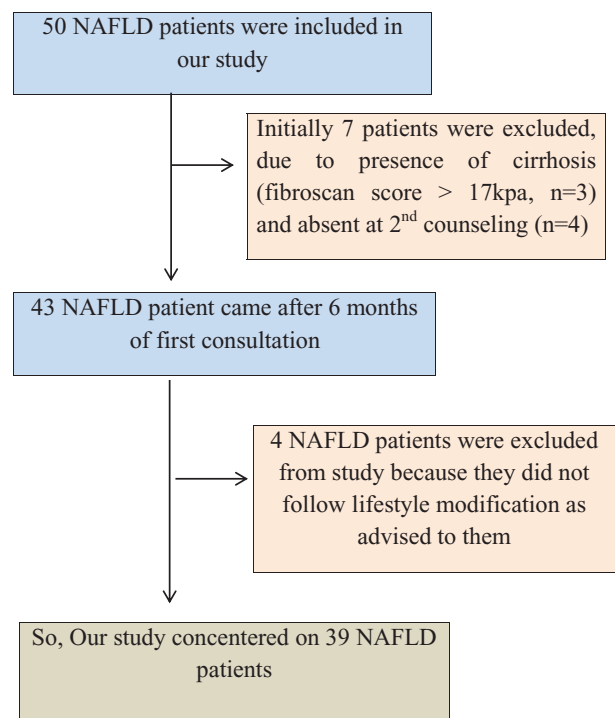


Figure 1. PRISMA flow diagram

follow the lifestyle modification as advised to them. Finally, our study concentrated on 39 patients (Figure 1).

Measurements and evaluation

Anthropometry measurements included weight in kilograms, height in meters, body mass index (BMI) and blood pressure. Cut-off points proposed by a WHO Expert Committee for the classification of overweight were used in this study [15]. Hypertension was diagnosed when a patient had received medicine for hypertension or had systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after taking a 5-minute rest [16].

Blood samples were collected after an overnight fast of >12 hours. Liver function tests included total bilirubin, direct and indirect bilirubin, ALT, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase and albumin. Other biochemical tests included fasting blood sugar, total cholesterol, serum fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR). Patients who used cholesterol-lowering medication or had a total serum cholesterol level ≥ 200 mg/dL were classified as having hypercholesterolemia [17]. HOMA-IR was calculated by Fasting insulin ($\mu\text{U}/\text{m}$) \times [Fasting glucose (mmol/L)/22.5]. A HOMA-IR value of ≥ 2.5 is taken as an indicator of insulin resistance (IR) in adults [18].

Fibroscan score was used to assess liver stiffness in our study. During Fibroscan, mild amplitude and low-frequency vibrations (50Hz) from ultrasound transducer probes are transmitted to the liver tissue, inducing an elastic shear wave that propagates through the underlying liver tissue. The velocity of the wave is directly related to the tissue stiffness. During liver-stiffness measurement, patients were in a supine position with the right arm in abduction. At least 10 valid measurements were obtained in one particular site from each participant. The liver-stiffness value was calculated; the success rate was >90% of all attempts and the interquartile range was <30% (Figure 2). A liver stiffness value of less than 5.6 kpa is considered as no fibrosis or mild fibrosis and a

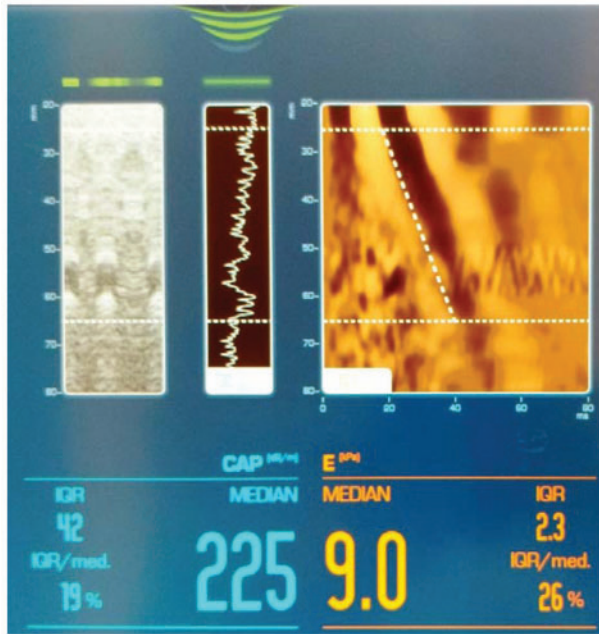


Figure 2. Fibroscan measurement

cut-off value of 17 kPa is considered to be optimal for discrimination of liver fibrosis from liver cirrhosis in NAFLD patients [19].

Fatty liver was diagnosed based on known standard criteria from trans-abdominal ultrasonography findings, including hepatorenal echo contrast, liver brightness and vascular blurring [20]. Trans-abdominal ultrasonography was performed by a single consultant radiologist.

Physical activity

In our study, physical exercise was assessed by self-reported questionnaires that included questions about duration, frequency and intensity of exercise. We advised to do regular, moderate physical activity, which is defined as doing physical exercise of at least moderate intensity more than three times per week, for at least 45 minutes each time (the University of California San Diego approach) for an uninterrupted duration of 6 months.

Physical activity of moderate intensity is defined as requiring a metabolic equivalent task (MET) score of 3.0–6.0 and a typical activity of moderate intensity is 'brisk' walking at 5.6 km/h on a flat surface requiring 3.8 MET [21]. Metabolic equivalent of

functional capacity: 3 MET, brisk walking; 4 MET, raking leaves, gardening and jogging; 5 MET, climbing one flight of stairs, dancing, bicycling, badminton and swimming; 6 MET, playing golf and carrying clubs [22].

Diet restriction

For diet restriction, patients had been sent to a dietician after the first consultation. Restriction of caloric intake to 25–30 kcal/kg/day of ideal body weight was advised to our study population [23]. Patients were advised to avoid saturated fats, simple carbohydrates, sweetened drinks and a 'fast food diet', and were monitored after 6 months using self-reported questionnaires.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) was used for statistical analysis. Data were expressed as means \pm standard error (SE). The results were analysed by paired samples t-test (Dependent t-test) with 95% confidence interval (CI). A probability value (*p*-value) below 0.05 was considered significant.

Results

Out of 39 study population, 27 participants (69.2%) were male and 12 (30.8%) were female. The mean age of our study population was 34.07 ± 0.99 years. The mean age of the male and female participants were 34.37 ± 1.23 years and 33.41 ± 1.69 years, respectively (Table 1).

Of 39 participants, 11 (28.2%) and 4 (10.3%) participants during their first consultation and second consultation were insulin-resistant, respectively, based on HOMA-IR values. Ten (25.6%) and 8 (20.5%) were hypertensive during their first consultation and second consultation, respectively. During the first visit, 19 participants (48.7%) and, during the second consultation, 10 (25.6%) participants had hypercholesterolemia.

The mean weight of our study population (79.99 ± 9.07 kg) improved after 6 months of lifestyle modification (74.57 ± 8.37 kg). During the first consultation, 5 (12.8%), 26 (66.7%) and 8 (20.5%) of our study populations had normal weight, overweight and obesity, respectively, while, at the time of the second consultation, 15 (38.5%), 22 (56.4%) and 2 (5.1%) participants had normal weight, overweight and obesity, respectively. After 6 months of lifestyle modification, five obese patients entered the overweight group and one obese patient entered the normal-weight group. In our study, 22 patients (56.41%) lost weight.

The mean BMI of the study population at the time of the first consultation was 27.53 ± 0.42 kg/m² but the mean BMI of the

Table 1. Demographic characters and clinical data of NAFLD patients before and after of 6 months lifestyle modification

Demographic character and clinical data	Before 6 months of lifestyle modification	After 6 months of lifestyle modification
Weight	79.99 ± 9.07 kg	74.57 ± 8.37 kg
Insulin resistance	11 (28.2%)	4 (10.3%)
HOMA-IR value	2.13 ± 0.09	1.74 ± 0.70
Hypertension	10 (25.6%)	8 (20.5%)
Hypercholesterolemia	19 (48.7%)	10 (25.6%)
Normal Weight	5 (12.8%)	15 (38.5%)
Overweight	26 (66.7%)	22 (56.4%)
Obesity	8 (20.5%)	2 (5.1%)
BMI (kg/m ²)	27.53 ± 0.42	25.63 ± 0.38
Fibroscan value (kPa)	8.31 ± 0.11	7.87 ± 0.12
ALT (U/L)	97.25 ± 2.62	66.69 ± 3.95

male participants ($26.80 \pm 0.44 \text{ kg/m}^2$) was lower than that of the female participants ($29.17 \pm 0.77 \text{ kg/m}^2$). During the follow-up visit after 6 months of lifestyle modification, the mean BMI of the study populations was $25.63 \pm 0.38 \text{ kg/m}^2$ but the BMI values of male and female participants were $25.17 \pm 0.53 \text{ kg/m}^2$ and $26.70 \pm 0.68 \text{ kg/m}^2$, respectively.

The mean ALT level of our study population had also significantly improved after 6 months of lifestyle modification (66.69 ± 3.95 vs $97.25 \pm 2.62 \text{ U/L}$, $p < 0.001$). It was also found that the mean Fibroscan value for liver stiffness had significantly improved after 6 months of lifestyle modification (7.87 ± 0.12 vs $8.31 \pm 0.11 \text{ kPa}$, $p = 0.009$) (Table 2). There was a positive correlation between Fibroscan values and BMI during the first consultation (Correlation coefficient value = 0.23, Figure 3).

Discussion

NAFLD is now considered to be one of the most common forms of chronic liver disease, with a prevalence ranging from 20–30% of adults and 5–17% in children [24,25]. So, early effective treatment of NAFLD is required to prevent further progression of liver disease to cirrhosis. It has been suggested that lifestyle modification, including moderate, intensive physical exercise and diet

restriction, should be the first line of defense for preventing progression to worsening states of liver damage in NAFLD [26].

Fibroscan detects liver-stiffness values noninvasively within a few minutes, thus achieving rapid quantification of hepatic fibrosis [27]. The main advantages of Fibroscan compared with other methods including liver biopsy used in the assessment of liver fibrosis are: it is a non-invasive, painless method; easy to perform at the bedside or in an outpatients' clinic; short time of examination; results are not modified with cardiac or respiratory movement; results are not influenced by associated comorbidities; no observer variability; fibrosis is estimated in a liver volume that exceeds 150–400 times those obtained by liver biopsy; no fasting, sedation or analgesia is required; thus, it is well suited to outpatient clinics as part of a standard appointment [28]. Our study also showed that, after 6 months of lifestyle modification, there was significant improvement in Fibroscan values ($p = 0.009$). Therefore, Fibroscan can be used to see the effectiveness of therapy for NAFLD patients and improvement of liver fibrosis during therapy.

ALT levels showed a significant positive correlation with both inflammation and fibrosis scores [29]. Elevated serum ALT levels may correlate with the severity of NAFLD. ALT is a reliable and sensitive marker of liver disease in NAFLD and elevated ALT activities may be the only clue to NAFLD, since there are no definitive blood

Table 2. Paired samples t-test to compare clinical data of NAFLD patients before and after 6 months of lifestyle modification

	Before lifestyle modification	After lifestyle modification	p-value
Weight, kg	79.99 ± 9.07	74.57 ± 8.37	0.046
HOMA-IR	2.13 ± 0.09	1.74 ± 0.70	0.024
Body mass index, kg/m^2	27.53 ± 0.42	25.63 ± 0.38	0.002
Fibroscan value, kPa	8.31 ± 0.11	7.87 ± 0.12	0.009
Alanine aminotransferase (U/L)	97.25 ± 2.62	66.69 ± 3.95	<0.001

NAFLD, non-alcoholic fatty liver disease; HOMA-IR, homeostatic model assessment of insulin resistance.

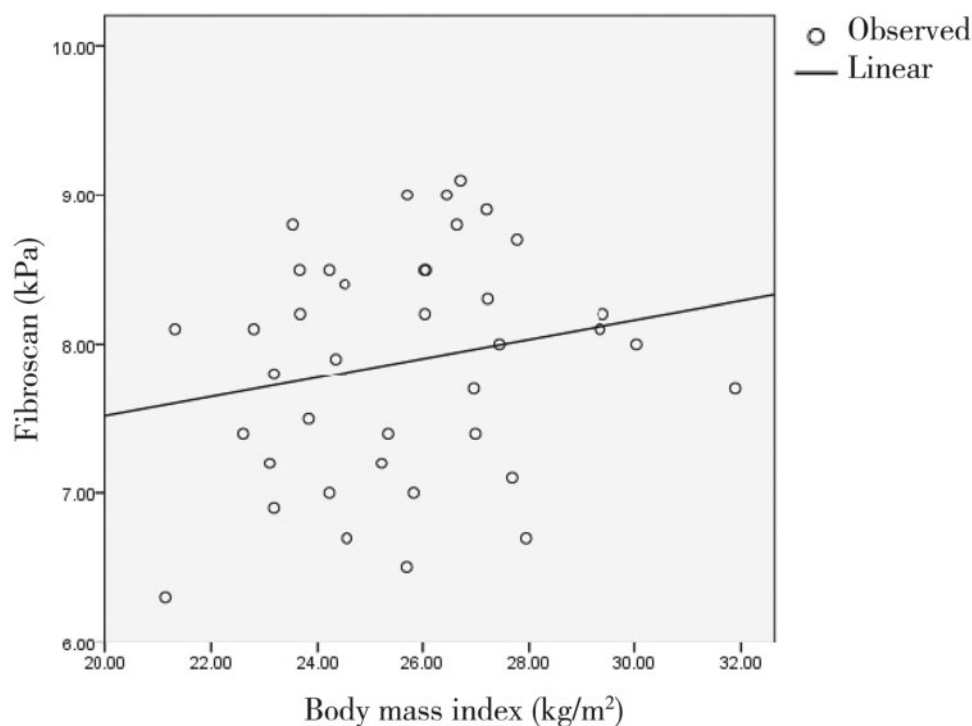


Figure 3. Correlation between body mass index and Fibroscan during first consultation

tests to confirm the diagnosis [30]. ALT may be the best indicator of hepatic injury due to NAFLD [31]. In our study, after 6 months of lifestyle modification, ALT levels improved significantly ($p < 0.001$). Hence, lifestyle modification helps to improve the ALT value, which is an indicator of hepatic inflammation in NAFLD.

Limitations of our study included small study populations and only a 6-month follow-up period. In addition, diet restriction and physical exercise were monitored after 6 months using self-reported questionnaires.

In conclusion, lifestyle modification including moderately intense physical exercise and diet restriction is an effective therapy in NAFLD patients. Apart from invasive techniques such as liver biopsy, Fibroscan as a non-invasive procedure that can be used to assess treatment response in NAFLD. ALT, the indicator of liver injury in NAFLD, is also improved by lifestyle modification.

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Conflict of interest statement: none declared.

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