# Low Sustainability of Weight Loss Among Patients with Non-alcoholic Fatty Liver Disease

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## ABSTRACT

**Background:** Weight loss, though difficult to attain and sustain over time, remains the cornerstone of non-alcoholic fatty liver disease (NAFLD) treatment. We aimed to describe weight changes among NAFLD patients.

**Methods:** This was a retrospective, cohort study of consecutively-identified NAFLD patients with >2 clinic visits from March2007–April2018. Weight changes from baseline were categorized into weight gain, weight loss, and no change. Baseline liver and metabolic biochemistries and non-invasive liver fibrosis tests were correlated with the final weight changes. Succeeding weight changes after the initial follow-up visits were used to determine sustainability of weight loss.

**Results:** Of the 240 patients included, 123 (51.2%), 93 (38.8%), and 24 (10%) had weight gain, weight loss, and no change, respectively. Only 12.5% had >5% weight loss. Duration of follow-up was significantly longer for patients with weight loss ($p<0.001$). None of the baseline demographic and laboratory data were associated with weight loss. Patients with weight loss also did not have significant changes to their biochemistries and non-invasive liver fibrosis tests compared to patients with weight gain/no change. Compared to patients with weight gain after the initial follow-up, where only 11.8% were able to lose weight on the final visit, 73.1% of patients who lost weight after the initial follow-up were able to sustain their weight loss on the final visit.

**Conclusions:** Weight loss is achieved in only a third of NAFLD patients. Although 73% of patients who lost weight initially were able to sustain it, patients who gained weight after the 1st follow-up were unlikely to lose weight on further follow-up.

**Key words:** Non-alcoholic fatty liver disease, weight loss, sustainability

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is associated with multiple metabolic disorders, including obesity, insulin resistance, type 2 diabetes mellitus, hypertension, and hyperlipidemia. An ultrasound finding of an echogenic liver in the absence of other causes of chronic liver injury is an acceptable diagnostic criteria for NAFLD [1]. Histologically, inflammatory injury to hepatocytes in a process initiated by fat deposition in patients with NAFLD has the potential to progress to fibrosis, cirrhosis, and hepatocellular carcinoma [1]. In some patients, liver cirrhosis and hepatocellular carcinoma may even be already present on first diagnosis of NAFLD [2]. Therefore, it is imperative to identify

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these patients in the early stages of the disease and institute treatment accordingly.

Lifestyle modification leading to weight loss remains the cornerstone of management of NAFLD. Multiple studies have shown that weight loss of ≥5-7% led to a greater reduction in non-alcoholic steatohepatitis (NASH) compared to those with lesser degree of weight loss [3-5]. In addition, a ≥10% weight loss led to more ideal results of both resolution of steatohepatitis and regression of fibrosis [3]. It is generally agreed that a >5% weight loss is needed in order to see objective histologic improvement in patients with NAFLD. However, weight reduction studies show that only around 60% adhere to the lifestyle intervention regimens [6]. Moreover, studies on lifestyle intervention for NAFLD have shown that only 30-38% of patients achieve weight reduction [3,7]. As if achieving weight reduction was not a high enough hurdle, maintaining the weight loss for those who do lose weight initially, appears even harder. A meta-analysis of weight loss intervention trials show that the mean weights of patients followed for at least a year slowly increased through the years after the initial weight loss during the first 6 months, although the weights did not increase above the baseline levels [8]. A longitudinal follow-up of NAFLD patients in the United States showed that even though 32% of overweight/obese patients lost >5% of their weight at some time during their usual clinic follow-up, only 25% maintained this favorable result over time [9]. Compounding on the difficulty in maintaining weight loss is that patients, especially those with poor motivation and social and emotional support, may go through cycles of "yo-yo" dieting with resultant weight cycling. In a study of close to 180,000 patients, DerSarkissian, et al demonstrated that 60% of their obese patients had cyclic patterns in their weight changes over 2 years and that those patients who lost the most weight initially, perhaps representing patients who are more motivated to lose weight, were more likely to maintain their weight loss over time [10].

Although there have been a number of studies looking at the effects of weight loss in NAFLD patients, very few have looked at the weight loss/gain patterns of these patients over time and its effects on liver enzymes and liver function tests. We therefore aimed to determine the proportion of NAFLD patients who lost weight versus those who maintained/gained weight during the first follow-up visit, and among those who lost weight initially, the probability of sustaining their weight loss at the last follow-up visit. We also aimed to determine the correlation of weight trends determined at last follow-up, namely: 1) weight gain/no change; 2) weight loss; 3) weight cycling, on liver and biochemical tests.

## SUBJECTS, MATERIALS AND METHODS

This was a retrospective, analytical, cohort study using data from a chart review of consecutive adult patients >18 years old with NAFLD seen in an outpatient hepatology clinic from March 2007 to April 2018. Patients were considered to have NAFLD if liver ultrasound demonstrated the presence of fatty liver, with no evidence of concomitant chronic liver disease such as autoimmune hepatitis and hepatitis B and C, no significant alcohol intake (>20 G/day for women and >40 G/day for men), and with no secondary causes of steatosis such as intake of drugs that may predispose to steatosis (amiodarone, estrogen, glucocorticoids, tamoxifen and valproic acid), those who underwent surgical procedures (i.e., gastroplexy, jejunoileal bypass, extensive small bowel resection, biliopancreatic diversion and small bowel diverticulosis). Patients with hepatocellular carcinoma and those with no follow-up visit after the initial consult were excluded.

At the initial clinic visit, demographic data, viral hepatitis B and C markers, liver biochemistries such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), albumin, and prothrombin time were determined. Other laboratory exams such as the fasting blood sugar (FBS), cholesterol, triglycerides, creatinine, blood uric acid (BUA), and platelet count were determined. At baseline and on succeeding follow-up visits, patients were advised to decrease their total caloric intake, especially carbohydrate intake, and to increase their physical activity through aerobic or resistance exercises at least three times a week at 30-60 minutes per session. No daily diaries or follow-up calls to check on their progress or adherence to the suggested lifestyle modifications were done. Follow-up visits were scheduled every 3-6 months thereafter with the same laboratory exams. The final weight change was derived from the difference between the weight on the final available clinic visit minus the baseline weight and was reported as either weight gain, weight loss or no change. Patients

with at least 2 clinic visits were included in this part of the analysis.

To determine the effects of weight trends on the baseline parameters, we included only patients who had at least 3 clinic visits for this part of the analysis. Weight trend was categorized as either: Weight gain – increase in weight at final visit compared to baseline with no weight decrease (compared to baseline) in between; Weight loss – decrease in weight at final visit compared to baseline with no weight increase (compared to baseline) in between; and Weight cycling – decrease/increase/no change in weight at final visit compared to baseline with either weight increase or decrease (compared to baseline) in between. We also determined the sustainability of weight loss based on the initial weight change during the first follow-up clinic visit.

The final weight change and weight trend categories were correlated with the changes in ALT, AST, and metabolic biochemistries, when available.

Statistical analysis was performed using SPSS version 22.0 software (IBM Corp, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviations and analyzed using the Kruskal-Wallis test, while categorical variables were presented as number (%) and analyzed using the Fisher's exact test. P-values of <0.05 were considered statistically significant.

The study was approved by the Institutional Review Board. All protocols and procedures used were conducted according to the Declaration of Helsinki. The data collected was handled by the researcher and confidentiality was applied in accordance to the Data Privacy Act of 2012. The database was in a password protected laptop available only to the investigators.

## RESULTS

Among the 663 patients diagnosed with fatty liver on ultrasound during the time period, 240 patients met inclusion criteria. At baseline, 185 (77.1%) patients were either overweight or obese while 55 (22.9%) were considered to have lean NAFLD. After a median of 13.4 months follow-up, 24 (10%) patients had no weight change, 123 (51.2%) gained weight, while 93 (38.8%) patients lost weight at the final clinic visit. Majority of patients who gained or lost weight had weight changes of less than 5% only and very few patients had gained or lost >10% of their weight from baseline. (Figure 1) The average weight gain for patients who gained weight was 5.9 ± 6.7% (4 ± 4.3kg) while patients who lost weight lost an average of 5.1 ± 4.6% (3.6 ± 3.3kg). Among the baseline parameters, only the presence of diabetes mellitus, number of clinic visits, and duration of

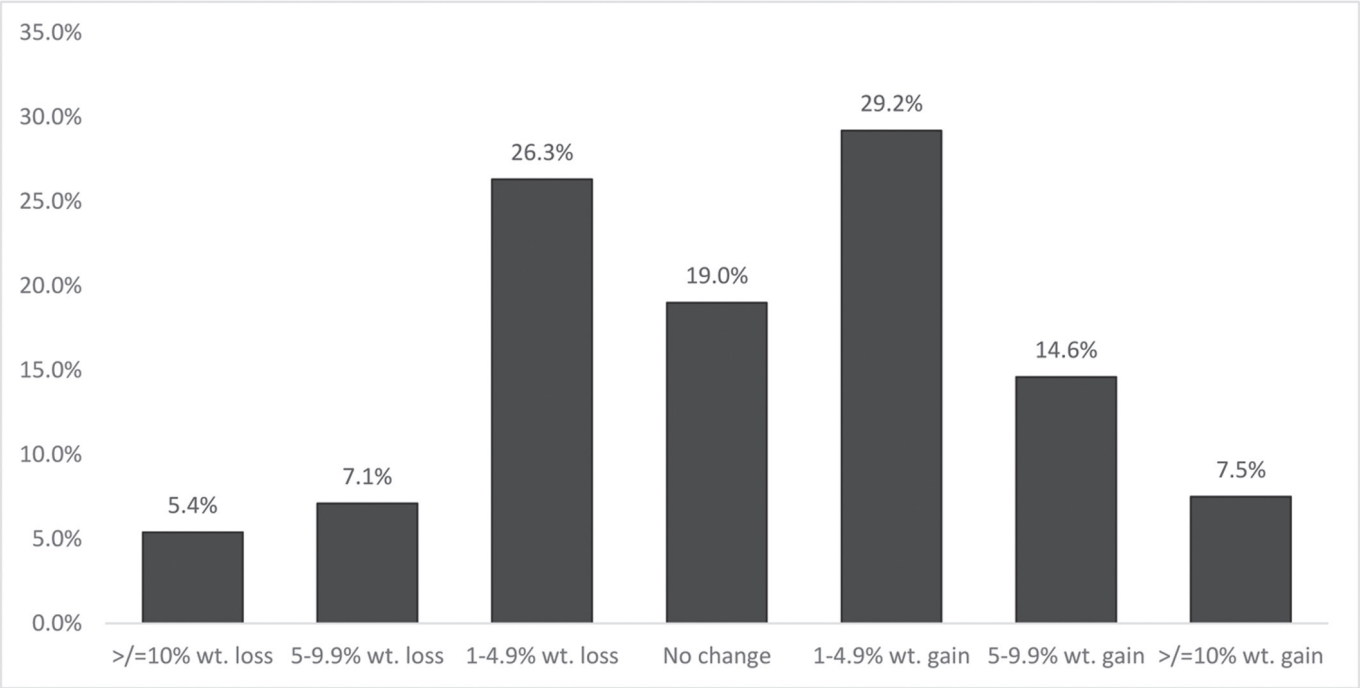


**Figure 1:** Weight changes of NAFLD patients at the end of follow-up

follow-up were significantly different between the three groups of patients, with diabetic patients more likely to have either weight gain or weight loss than no weight change, and patients with weight changes more likely to have more clinic visits compared to those who did not have weight changes. Patients who had weight loss were more likely to have longer duration of follow-up compared to patients with weight gain and no changes. Patients who were lean at baseline were not more likely to have weight loss compared to overweight/obese patients (Table 1).

At the last clinic visit, 47% and 44% of patients had a decrease in ALT and AST, respectively. Meanwhile, improvement in non-invasive scores for liver fibrosis were seen in 8% (APRI), 43% (FIB4) AND 4% (NFS) of patients. However, changes in the final weight did not significantly affect these markers, as well as other biochemical markers (Table 2). Subdividing patients who had weight loss

**Table 1.** Baseline characteristics according to weight changes among NAFLD patients at the end of follow-up

| | No change n=24 (10%) | Weight gain n=123 (51.2%) | Weight loss n=93 (38.8%) | p-value |
|---|---|---|---|---|
| Gender (M/F) | 10/14 | 67/56 | 50/43 | 0.505 |
| Age | 54.8 ± 11.1 | 50.8 ± 13.4 | 52.7 ± 15.9 | 0.058 |
| BMI: | | | | |
| Lean | 5 (9.1%) | 33 (60%) | 17 (30.9%) | 0.324 |
| Overweight/obese | 19 (10.3%) | 90 (48.6%) | 76 (41.1%) | |
| Alcohol intake (G/day) | 2.7 ± 8.5 | 3.1 ± 7.4 | 2.9 ± 6.6 | 0.961 |
| Diabetes mellitus | 14 (11.8%) | 51 (42.9%) | 54 (45.4%) | **0.036** |
| Hypertension | 17 (11.9%) | 74 (51.7%) | 52 (34.6%) | 0.407 |
| Cardiovascular disease | 5 (10%) | 19 (38%) | 26 (52%) | 0.081 |
| Metabolic syndrome | 16 (11%) | 69 (47.6%) | 60 (41.4) | 0.367 |
| ALT | 40.5 ± 21.9 | 51 ± 41.6 | 55.9 ± 42.2 | 0.094 |
| High ALT | 10 (8.6%) | 55 (47.4%) | 51 (44%) | 0.266 |
| AST | 30.6 ± 16 | 38.7 ± 23.8 | 39.3 ± 22.7 | 0.803 |
| Platelets | 235.4 ± 38.3 | 252.6 ± 61.9 | 256.3 ± 60.8 | 0.638 |
| Albumin | 4.4 ± 0.5 | 4.4 ± 0.5 | 4.4 ± 0.4 | 0.667 |
| INR | 1 ± 0.1 | 1 ± 0.1 | 1 ± 0.1 | 0.059 |
| FBS | 118 ± 28.8 | 119.2 ± 46 | 124.8 ± 42.3 | 0.057 |
| Cholesterol | 219.3 ± 32.9 | 204.9 ± 44.4 | 213.6 ± 49 | 0.321 |
| Triglycerides | 174 ± 74.9 | 159.2 ± 110 | 172.4 ± 129.5 | 0.092 |
| BUA | 6.2 ± 1.6 | 5.9 ± 1.8 | 6.2 ± 1.7 | 0.913 |
| Creatinine | 0.9 ± 0.3 | 0.9 ± 0.5 | 0.9 ± 0.2 | 0.184 |
| APRI: (n=234) | | | | |
| <0.5 | 19 (11.2%) | 87 (51.2%) | 64 (37.6%) | 0.628 |
| >0.5-1.5 | 3 (4.8%) | 32 (51.6%) | 27 (43.5%) | |
| >1.5 | 0 | 1 (50%) | 1 (50%) | |
| FIB-4: (n=234) | | | | |
| <1.45 | 16 (9.4%) | 86 (50.6%) | 68 (40%) | 0.850 |
| 1.45-3.25 | 6 (10.7%) | 30 (53.6%) | 20 (35.7%) | |
| >3.25 | 0 | 4 (50%) | 4 (50%) | |
| NFS: (n=234) | | | | |
| F0-F2 | 12 (8.8%) | 73 (53.7%) | 51 (37.5%) | 0.677 |
| Indeterminate | 9 (10.5%) | 43 (50%) | 34 (39.5%) | |
| F3-F4 | 1 (8.3%) | 4 (33.3%) | 7 (58.3%) | |
| Number of clinic visits | 3.2 ± 1.5 | 6.2 ± 5.9 | 5.8 ± 5 | **0.049** |
| Duration of follow-up (months) | 7.3 ± 9.1 | 31 ± 30.1 | 78.5 ± 53.9 | **0.035** |

**Table 2.** Improvements in biochemistries and non-invasive liver fibrosis tests according to weight changes among NAFLD patients

| | No change (n=24) | Weight gain (n=123) | Weight loss (n=93) | p-value |
|---|---|---|---|---|
| ALT decrease | 12 (50%) | 54 (43.9%) | 46 (49.5%) | 0.678 |
| AST decrease | 8 (33.3%) | 60 (48.8%) | 37 (39.8%) | 0.233 |
| FBS decrease (n=226) | 0 | 14 (12.2%) | 9 (10.1%) | 0.224 |
| Cholesterol decrease (n=227) | 0 | 14 (12.1%) | 4 (9%) | 0.206 |
| LDL decrease (n=225) | 0 | 13 (11.3%) | 8 (9.1%) | 0.247 |
| Triglycerides decrease (n=226) | 0 | 12 (10.4%) | 7 (7.9%) | 0.264 |
| Improvement in APRI | 3 (12.5%) | 7 (5.7%) | 6 (6.5%) | 0.471 |
| Improvement in FIB4 | 11 (45.8%) | 50 (40.7%) | 41 (44.4%) | 0.828 |
| Improvement in NFS | 2 (8.3%) | 4 (3.3%) | 4 (4.3%) | 0.521 |

**Table 3.** Improvements in biochemistries and non-invasive liver fibrosis tests according to degree of weight loss among NAFLD patients

| | No change/Weight gain (n=147) | <5% Weight loss (n=63) | ≥5% Weight loss (n=30) | p-value |
|---|---|---|---|---|
| ALT decrease | 66 (44.9%) | 32 (50.8%) | 14 (46.7%) | 0.735 |
| AST decrease | 68 (46.3%) | 25 (39.7%) | 12 (40%) | 0.615 |
| FBS decrease (n=226) | 14 (10.2%) | 5 (8.2%) | 4 (14.3%) | 0.677 |
| Cholesterol decrease | 14 (10.1%) | 4 (6.6%) | 4 (14.3%) | 0.499 |
| LDL decrease | 13 (9.5%) | 4 (6.6%) | 4 (14.3%) | 0.517 |
| Triglycerides decrease | 12 (8.8%) | 4 (6.6%) | 3 (10.7%) | 0.784 |
| Improvement in APRI (n=224) | 10 (6.8%) | 3 (4.8%) | 3 (10%) | 0.635 |
| Improvement in FIB4 | 61 (41.5%) | 28 (44.4%) | 13 (48.3%) | 0.920 |
| Improvement in NFS | 6 (4.1%) | 2 (3.2%) | 2 (6.7%) | 0.731 |

**Table 4.** Improvements in biochemistries and non-invasive liver fibrosis tests according to the weight trend among NAFLD patients

| | No change/Weight gain (n=45) | Weight loss (n=39) | Weight cycling (n=34) | p-value |
|---|---|---|---|---|
| ALT decrease | 20 (44.4%) | 17 (43.6%) | 18 (52.9%) | 0.679 |
| AST decrease | 23 (51.1%) | 19 (48.7%) | 17 (50%) | 0.976 |
| FBS decrease (n=109) | 6 (27.3%) | 6 (16.2%) | 10 (31.3%) | 0.177 |
| Cholesterol decrease (n=110) | 5 (12.2%) | 5 (13.5%) | 11 (34.4%) | **0.033** |
| LDL decrease (n=110) | 4 (9.8%) | 5 (13.5%) | 11 (36.7%) | **0.010** |
| Triglycerides decrease (n=110) | 3 (7.3%) | 6 (16.2%) | 9 (29%) | **0.049** |
| Improvement in APRI | 3 (6.7) | 4 (10.3%) | 1 (2.9%) | 0.463 |
| Improvement in FIB4 | 18 (40%) | 16 (41%) | 13 (38.2%) | 0.971 |
| Improvement in NFS | 1 (2.2%) | 2 (5.1%) | 1 (2.9%) | 0.753 |

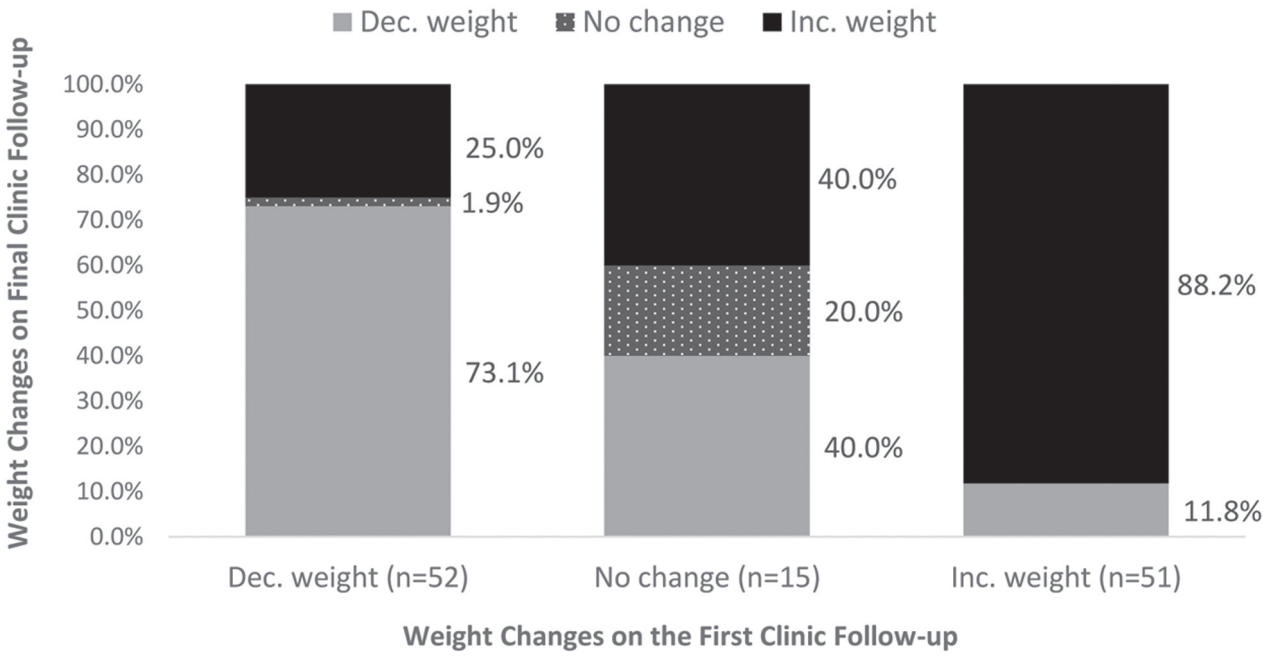


**Figure 2.** Weight changes at the end of follow-up according to the weight changes after the initial follow-up among NAFLD patients

into those who lost <5% and ≥5% likewise did not lead to differences in all the biochemical and non-invasive fibrosis markers (Table 3). In addition, sub-analysis of patients who were overweight/obese at baseline were not more likely to experience improvement in liver enzymes and non-invasive scores of liver fibrosis with weight loss, compared to lean patients. (p>0.05)

For patients who had at least 3 clinic visits, we were able to divide patients according to the following weight trends: No change/weight gain (38%); Weight loss (33%); and Weight cycling (29%). Except for a significantly greater decrease in cholesterol, LDL, and triglycerides in the Weight cycling group, there were no other significant differences in biochemical and non-invasive fibrosis score changes between the three groups (Table 4). For this same subgroup of patients, we determined that on the first follow-up clinic visit, 15 (12.7%) had no weight change, 51 (43.2%) had gained weight, and 52 (44.1%) had lost weight. At the final clinic visit, patients who had lost weight during the first follow-up visit were more likely (p<0.001) to maintain and still have weight loss (73%) compared to patients who did not have weight changes (40%) and patients with increased weight (11.8%). Conversely, patients who had gained weight at the initial visit were more likely to have increased weight (88.2%) at the final visit compared to patients who initially did not have weight change (40%) and patients who initially had weight loss (25%) (Figure 2).

## DISCUSSION

The present study shows that weight loss was achieved in 38.8% of NAFLD patients during routine clinical care, with no additional more extensive enforcement of the recommended lifestyle changes. However, majority (67.7%) of the patients with weight loss only had a mild loss of <5% of their baseline body weight, with patients having ≥5% weight loss accounting for only 12.5% of the overall population. Although our patient population was advised to lose weight by decreasing total caloric intake and increasing physical activity, a structured program to ensure that they follow this recommendation was not provided. This finding is in line with a randomized controlled trial of more intensive lifestyle modification to effect weight loss in NASH patients, where a weight loss of at least 4% can be achieved in 38% of the intensive intervention compared to only 19% for the less intensive group [7]. Similarly, a more intensive enforcement of the desired lifestyle changes resulted in a higher proportion of patients with >10% weight loss compared with the control group (40% vs. 0%) in one of the earliest randomized controlled trials of lifestyle intervention in NASH patients [11]. It is clear that trials comparing more

stringent lifestyle interventions versus less structured interventions/control groups result in a greater degree of weight loss. However, prospectively followed patients with less extensive lifestyle modifications, even outside the context of controlled trials, may lead to only slightly lesser degrees of weight loss [3,9]. Compared to retrospective data, prospectively following patients may give healthcare providers more opportunities and urgency to encourage weight loss. Furthermore, studies done in specialized centers may already have programs in place to maximize patients' chances of achieving weight loss [9].

We found that although there was no difference in the number of clinic visits between patients who lost and gained weight, patients who lost weight had a significantly longer duration of follow-up. This may be because patients who lose weight were likely more motivated and had a longer-lasting relationship with their healthcare provider, leading to better adherence to lifestyle change recommendations. While it is surprising to find that weight loss did not have a significant effect in improving the liver enzymes and biochemical parameters of patients, it may be because only a minority of our patients achieved >5% weight loss, which has been pegged as the minimum weight loss to achieve a reduction in hepatic steatosis in a meta-analysis [12]. However, weight loss of as little as 3% has been found to be associated with resolution of NAFLD in 41% [4]. It is therefore possible that histologic improvements may not always be reciprocated by improvements in serologic markers. The fact that close to 50% of our patients had improvements in their liver enzymes regardless of weight changes may be reflective of other variables that were not quantified in this study such as the level of physical activity. It has been found that exercise alone, regardless of weight loss, may reduce the amount of hepatic steatosis and serum free fatty acids [13].

We found that among patients with weight loss on the initial follow-up clinic visit, 73.1% were able to maintain their weight loss while 25% regained weight on further follow-up. This is consistent with another study which showed that 21% of their patients who had weight loss initially had regained weight on further follow-up [9]. A large study in obese patients showed that the ability to maintain weight loss may however be harder in non-specialized care settings, with 79% of patients unable to maintain their weight loss in 2 years [10]. One the possible reasons for weight regain is because following weight loss, there are physiologic compensatory changes that result in increased hunger and energy storage. Increases in orexigenic hormones such as ghrelin and decreases in anorexigenic hormones such as leptin and glucagon-like peptide-1 have been implicated in weight regain [14-15]. Furthermore, psychosocial factors [16], and the lack of supervised programs [6], especially during the maintenance phase, have been implicated in weight regain. This highlights the need for better programs and psychosocial support systems to keep our patients motivated to keep up with their lifestyle changes. In our study, patients who lost weight initially were more likely to have weight loss at the final visit compared to patients who gained weight initially (figure 2), implying that the weight change in the initial follow-up visit is a good indicator of patients' willingness and motivation to follow through with losing weight.

Our study has several limitations. The retrospective nature of the study prevents us from further exploring other factors that determines weight loss in patients with NAFLD. Although all patients were consistently advised to have lifestyle changes to achieve weight loss during each clinic visit, the lack of a structured program with regular accountability of the patients' adherence to the program may hinder the objective of achieving weight loss. Finally, paired liver biopsies to confirm histologic changes were not done and could have shed light on improvements in steatosis, inflammation and fibrosis that may otherwise not be deduced from the biochemistries. However, it is hard to convince patients to undergo liver biopsies for NAFLD outside of therapeutic trials.

## CONCLUSION

In summary, we have shown that 39% of NAFLD patients achieve weight loss during routine clinic follow-up visits. However, only 12.5% achieve ≥5% weight loss. Patients who lost weight on the initial visit were able to maintain their weight loss 73% of the time and are most likely to be more motivated to lose weight compared to patients who gained weight after the initial visit. Achieving weight loss in NAFLD patients is evidently difficult to achieve and will need a structured lifestyle change program and a multidisciplinary approach to tackle the psychosocial, genetic, behavioral and biochemical factors contributing to weight changes in NAFLD patients.

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