



Weight Loss After Bariatric Surgery Predicts an Improvement in the Non-alcoholic Fatty Liver Disease (NAFLD) Fibrosis Score

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Abstract

Purpose Non-alcoholic fatty liver disease (NAFLD) is present in up to 90% of bariatric surgery patients. Previous literature has demonstrated an improvement in liver steatosis and fibrosis in post-bariatric surgery patients. Our study aims to investigate if bariatric surgery results in an improvement in NAFLD fibrosis scores, and if this correlates with weight loss.

Methods A retrospective study was conducted on all patients who underwent bariatric surgery from 2010 to 2016 in our institution. Patients who had a redo bariatric surgery or concomitant gastric pathologies were excluded. Indications for bariatric surgery followed the Asia-Pacific Metabolic and Bariatric Surgery Society guidelines.

Results There were 192 patients in this study, with the majority being females ($n = 120$, 63%). Mean age was 42.7 ± 10.2 years old. Pre-operative mean weight and body mass index (BMI) were 113 ± 27.9 kg and 41.6 ± 7.98 kg/m² respectively. The mean pre-operative NAFLD fibrosis score was -1.27 . Six-month and 1-year follow-up post-surgery demonstrated a decrease in mean weight to 90.6 and 85.9 kg and a decrease in mean BMI to 33.8 and 31.6 kg/m². Mean NAFLD scores improved from -1.27 to -1.56 to -2.00 . The correlation between weight loss and NAFLD fibrosis score improvement was statistically significant at the first post-operative year (r -coefficient = 0.36, p value ≤ 0.001).

Conclusion Bariatric surgery results in weight reduction as well as an improvement in the NAFLD fibrosis score. The degree of weight loss predicts the extent of improvement in NAFLD fibrosis scores. More long-term studies need to be conducted to assess if this effect is permanent.

Keywords Bariatric surgery · Metabolic surgery · Weight loss · Non-alcoholic fatty liver disease · Liver fibrosis · NAFLD fibrosis score

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases globally and is the number one cause of chronic liver disease in the developed world. NAFLD has been shown to be prevalent in up to 75% of obese patients [1]. Specifically, studies on severely obese patients undergoing bariatric surgery have demonstrated NAFLD rates as high as 90%, as shown in a study by Sasaki et al. in 2014 [2]. Its more progressive subtype, non-alcoholic steatohepatitis (NASH), has accompanying inflammation and hepatocyte necro-apoptosis. NASH is present in 20–30% of NAFLD patients [3]

and is not only associated with liver cirrhosis but also with end-stage liver disease and mortality.

The gold standard for diagnosis of liver fibrosis in NAFLD or NASH patients is via a liver biopsy—which can be done either pre-, intra-, or post-operatively. However, the invasiveness of such a procedure has led to the development of alternative methods for detecting liver fibrosis [4]. The NAFLD fibrosis score was developed in 2007 by Angulo et al. [5] and accurately predicts advanced fibrosis with a positive predictive value (PPV) of 82%.

The first-line treatment for NAFLD, NASH and liver fibrosis is weight loss as well as the management of metabolic syndrome [1]. However, it is well known that weight loss achieved through lifestyle modification tends to be transient with high risk of relapse amongst patients [1]. Literature has shown that bariatric surgery helps to reduce the grade of hepatic steatosis, inflammation and fibrosis [2]. However, the limitation in this current body of literature is the heterogeneity regarding type of surgery, use of very low-calorie diet

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(VLCD) and study design. Further long-term studies will be needed before recommending bariatric surgery as a primary treatment for liver disease.

Our study aims to investigate if bariatric surgery results in an improvement in NAFLD fibrosis scores, and whether this improvement correlates with weight loss.

Materials and Methods

This was a single-centre retrospective study performed in a general hospital in Singapore. We included all patients who underwent bariatric surgery in our institution from January 2010 to December 2016, using a prospectively collected bariatric surgery database. Exclusion criteria were patients who had a redo bariatric surgery and those with co-existing gastric cancers or other pathologies requiring surgical intervention. Indications for bariatric surgery followed the guidelines of the Asia-Pacific Metabolic and Bariatric Surgery Society. All surgeries were performed by upper gastrointestinal surgical consultants with prior training in bariatric surgery. All patients were followed up for at least 1 year post-operatively.

Clinical Characteristics

Patient demographics, clinical characteristics, operative details and surgical outcomes were collected. Anthropometric measurements including height, weight and waist circumference were measured for all patients in the pre-operative period, as well as during their 6-month and 1-year post-operative clinic follow-up. Height and weight were measured using a standard wall-mounted stadiometer in the general surgery outpatient clinic. Waist circumference was measured at the umbilical level at minimal inspiration. Body mass index (BMI) was also calculated for all patients accordingly.

Biochemical Parameters

The NAFLD fibrosis score [5] was first developed by Angulo et al. in 2007 and is based on standard laboratory assessments including the presence of diabetes mellitus or impaired fasting glucose, platelet count ($\times 10^9/L$), albumin (g/dl), aspartate aminotransferase (AST, U/L) and alanine aminotransferase (ALT, U/L). Blood samples were collected in an outpatient clinical setting in the pre-operative period, as well as during post-operative follow-up at 6 months and 1 year respectively.

Statistical Analysis

Statistical analysis was performed using SPSS Version 21, using chi-square test or the Mann–Whitney test as appropriate. Pearson's correlation coefficient (r) was used to calculate the correlation between weight loss and improvement in NAFLD

fibrosis scores. P values of ≤ 0.05 were considered to be statistically significant.

Results

Patient Demographics and Clinical Characteristics

There were a total of 192 patients included in this study, of which the majority were females ($n = 120$, 63%). Mean age was 42.7 ± 10.2 years old. The majority were either Malay ($n = 77$, 40%) or Chinese ($n = 65$, 34%). Eighty-six (45%) patients had either impaired fasting glucose or diabetes mellitus, with a mean fasting glucose of 7.49 mmol/L and HbA1c of 8.07%. Pre-operative mean weight and BMI were 113 ± 27.9 kg and 41.6 ± 7.98 kg/m² respectively. Pre-operative waist circumference was 121 ± 15.9 cm. Patient demographics and clinical characteristics are further illustrated in Table 1.

Operative Details

Laparoscopic sleeve gastrectomy (LSG) was the most common bariatric operation performed ($n = 99$, 52%), followed by Roux-en-Y gastric bypass (RYGB) ($n = 87$, 45%), then gastric banding (LAGB) ($n = 6$, 3%).

Operative Outcomes

The mean pre-operative NAFLD fibrosis score was -1.27 ± 1.56 . According to the classification by Angulo et al., 53% of our patients had a low risk of advanced liver fibrosis, 40% of patients had an indeterminate score, while the remaining 7% had high risk of advanced liver fibrosis (Table 2). Six-month and 1-year follow-up demonstrated an overall decrease in mean weight from 113 to 90.6 (6-month mark) to 85.9 kg (1-year mark) and a decrease in mean BMI from 41.6 to 33.8 (6-month mark) to 31.6 kg/m² (1-year mark) as shown (Table 1).

There was also an improvement in mean NAFLD scores from -1.27 to -1.56 (6-month mark) to -2.00 (1-year mark). The percentages of patients who had high risk of advanced liver fibrosis also dropped across the post-operative follow-up period from 7 to 4% at 6 months to 2% at 1 year, with a corresponding rise in the number of patients who had intermediate- or low-risk scores (Table 2). Table 1 further demonstrates the post-operative change in the various parameters of the NAFLD fibrosis score. In particular, a statistically significant decrease ($p < 0.0001$) was noted in the following variables: the presence of IFG/DM, AST and ALT values. Correspondingly, there was no statistically significant change in the pre- and post-operative platelet and albumin values.

Table 1 Patient demographics and post-operative changes in anthropometric/biochemical measurements

| Patient demographics | | | | |
|---|---------------|---------------|---------------|----------------|
| Age (years) | 42.7 ± 10.2 | | | |
| Gender, no. (%) | | | | |
| Male | 72 (37) | | | |
| Female | 120 (63) | | | |
| Race, no. (%) | | | | |
| Chinese | 65 (34) | | | |
| Malay | 77 (40) | | | |
| Indian | 42 (22) | | | |
| Others | 8 (4) | | | |
| Clinical/laboratory values | Pre-operative | 6 months | 1 year | <i>p</i> value |
| Height (metres) | 1.65 ± 0.11 | | | |
| Weight (kilogrammes) | 113 ± 27.9 | 90.6 ± 22.0 | 85.9 ± 20.3 | < 0.0001 |
| Weight difference* (kilogrammes) | NA | − 22.4 ± 23.9 | − 27.1 ± 24.1 | NA |
| BMI (kilogrammes/m ²) | 41.6 ± 7.98 | 33.8 ± 6.71 | 31.6 ± 6.20 | < 0.0001 |
| BMI difference* (kilogrammes/m ²) | NA | − 7.8 ± 7.24 | − 10.0 ± 7.09 | NA |
| IFG/DM, no. (%) | 86 (45) | 28 (15) | 22 (11) | < 0.0001 |
| AST (units/litre) | 26.7 ± 13.9 | 20.5 ± 14.5 | 19.9 ± 8.02 | < 0.0001 |
| ALT (units/litre) | 35.5 ± 26.2 | 20.3 ± 34.5 | 20.6 ± 26.1 | < 0.0001 |
| Platelet (× 10 ⁹ /litre) | 281 ± 77.0 | 273 ± 72.6 | 264 ± 76.4 | 0.059 |
| Albumin (grammes/litre) | 42.4 ± 3.51 | 42.2 ± 3.45 | 42.1 ± 3.66 | 0.579 |
| NAFLD score | − 1.27 ± 1.56 | − 1.56 ± 1.58 | − 2.00 ± 1.43 | < 0.0001 |
| NAFLD difference | NA | − 0.29 ± 0.54 | − 0.73 ± 0.70 | NA |

All data are in mean ± 2SD unless otherwise stated

*Weight and BMI differences calculated from pre-operative weight and BMI respectively

Scatter plots (Diagram 1) were derived based on the weight differences as well as NAFLD fibrosis score differences at the 6-month and 1-year post-operative marks. Statistical analysis using the Pearson correlation coefficient demonstrated that the relationship between these two variables was statistically significant only at the first post-operative year, with a *r*-coefficient of 0.36 and *p* value of < 0.001. There was no statistically significant relationship between weight difference and NAFLD fibrosis score difference at the 6-month mark.

Table 3 also shows a comparison between the various bariatric surgical procedures. Patients were categorised into whether they underwent restrictive (LAGB and LSG) or bypass (RYGB) procedures and evaluated accordingly. There

was an improvement in their NAFLD fibrosis scores across the 6-month to 1-year post-operative period for all three groups. Patients who underwent RYGB had the greatest improvement in NAFLD scores when compared to those who underwent LSG or LAGB, and this result maintained at both the 6-month and 1-year post-operative marks. However, this difference was not statistically significant.

Discussion

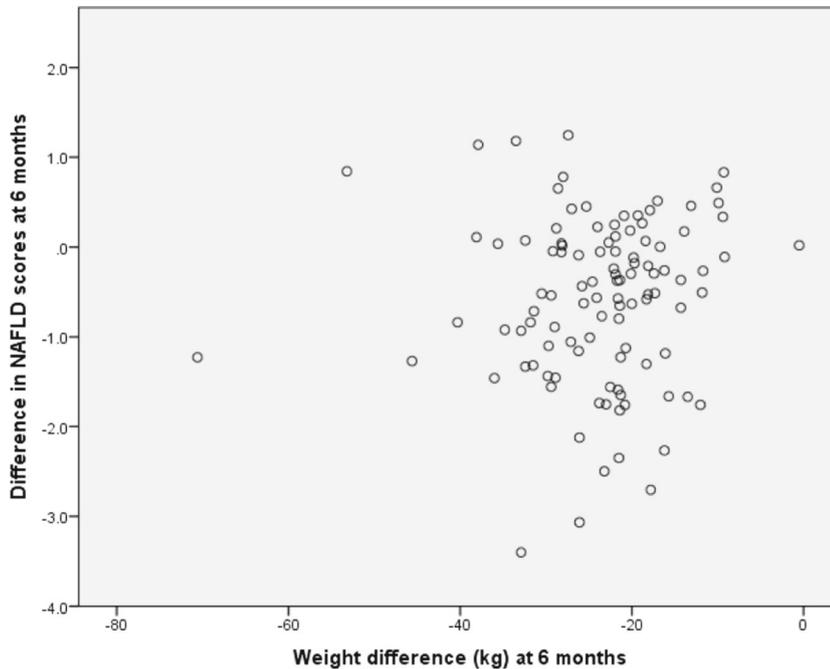
NAFLD is currently one of the most common causes of chronic liver diseases in developed countries, with a prevalence of up to 45% in a recent study from the USA [6]. NAFLD and its more progressive subtype, NASH, are associated with subsequent liver cirrhosis, end-stage liver disease and even mortality. Mortality rate amongst NAFLD patients is higher compared to the general population, at 13% during an average 7.6-year follow-up, with mortality causes mainly from malignancy, coronary heart disease and liver-related causes [7, 8]. Patients with more advanced liver fibrosis also have an increased rate of liver complications [8].

NAFLD, NASH and liver fibrosis are common in obese individuals, with recent literature demonstrating a prevalence

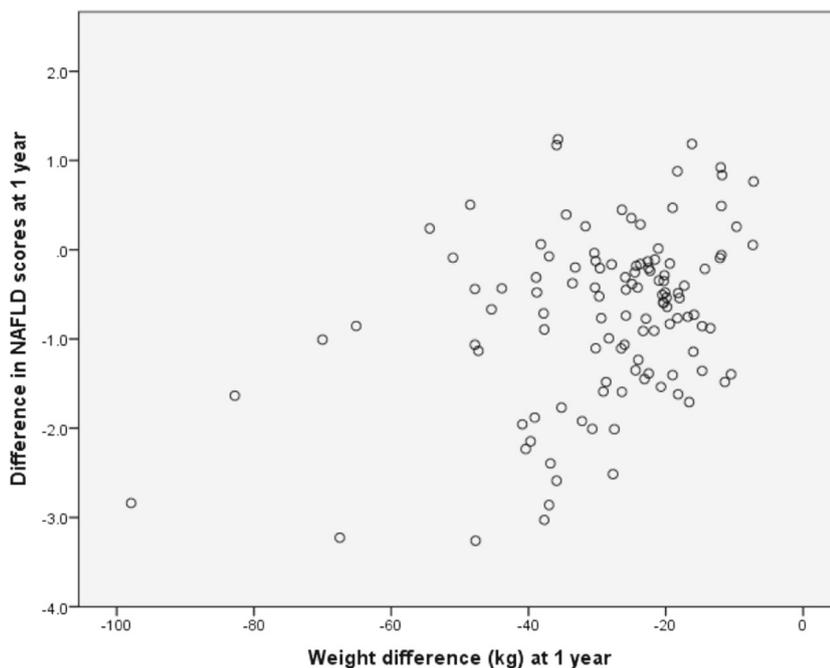
Table 2 NAFLD score grading

| NAFLD score | Pre-operative | 6 months | 1 year |
|------------------------------------|---------------|-----------|-----------|
| Low risk < − 1.455 | 102 (53%) | 110 (57%) | 123 (64%) |
| Intermediate risk − 1.455–0.675 | 77 (40%) | 75 (39%) | 65 (34%) |
| High risk > 0.675 | 13 (7%) | 7 (4%) | 4 (2%) |

All data are in mean ± 2SD unless otherwise stated

a 6-month post-operative period

Pearson r coefficient = 0.075
 p-value = 0.444

b 1-year post-operative period

Pearson r coefficient = 0.360
 p-value = <0.001

Diagram 1 Scatter plots comparing weight loss and improvement in NAFLD fibrosis scores. **a** 6-month post-operative period. **b** 1-year post-operative period

of up to 90% of NAFLD in bariatric surgery patients [2, 9]. Machado [9] has also documented the presence of histologically proven NASH in up to 24–98% of patients undergoing liver biopsy during bariatric surgery. There are currently many proposed theories for the pathophysiology of NAFLD and

liver fibrosis in obese patients, amongst which adipose tissue dysfunction and subsequent chronic low grade inflammation play a key role [10].

Liver biopsy is the current gold standard for the diagnosis and assessment of severity of liver fibrosis; however, it is an

Table 3 Difference in NAFLD scores amongst varying bariatric surgery procedures

| | 6 months | 1 year |
|------------------------------|--------------|--------------|
| Total (<i>n</i> = 192) | -0.29 ± 0.54 | -0.73 ± 0.70 |
| LSG + LAGB (<i>n</i> = 105) | -0.25 ± 0.48 | -0.69 ± 0.74 |
| RYGB (<i>n</i> = 87) | -0.33 ± 0.57 | -0.79 ± 0.66 |
| <i>p</i> value | 0.205 | 0.119 |

All data are in mean ± 2SD unless otherwise stated

invasive procedure with limitations such as sampling variability, expense and associated complications [11]. These limitations have led to the development of newer, simpler and less invasive methods of assessing liver fibrosis. The NAFLD fibrosis score was first described by Angulo et al. in 2007 [5] and is a simple non-invasive tool used for liver fibrosis assessment. It comprises a composite score of age, hyperglycaemia, body mass index, platelet count, albumin and aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio. In the 2007 paper by Angulo et al., routine demographic, clinical and laboratory values were analysed using multivariate modelling to predict the presence or absence of advanced fibrosis—and the above six variables were found to be independent indicators of advanced liver fibrosis. The area under the receiver operating characteristic curve for the score was 0.88 and 0.82 in the estimation and validation groups respectively. The NAFLD fibrosis score is the most studied score with external validation in multiple studies and results confirmed with a meta-analysis by Musso et al. [4]. Other studies have also shown that the NAFLD fibrosis score has an acceptable sensitivity, specificity and positive and negative predictive values for advanced liver fibrosis of 100%, 83%, 63% and 100%, respectively [12]. A higher NAFLD fibrosis score is also shown to be a significant predictor of mortality in NAFLD patients, with an odds ratio of 2.6 [13]. Hence, we adopted the NAFLD fibrosis score as a safer and more effective way to predict the severity of liver disease. The use of a validated non-invasive scoring system allowed us to assess our patient population at multiple time intervals without subjecting them to potential risks that may arise from multiple liver biopsies.

Bariatric surgery is currently considered the gold standard for weight loss treatment and reduction in obesity related comorbidities and is also an accepted treatment for NAFLD in obese patients [14]. The relationship between NAFLD and obesity is well established, although the exact pathophysiology is not known. Some authors propose that NAFLD is part of the metabolic syndrome, as NAFLD shares many pathophysiological characteristics with type 2 diabetes mellitus such as altered metabolism and adipocyte dysfunction [4]. Our study demonstrates that bariatric surgery results in weight loss as well as an improvement in the NAFLD fibrosis scores. This

improvement in the NAFLD fibrosis scores post-bariatric surgery is comparable to recent studies [1, 9, 10]. A meta-analysis by Mummadi et al. [15] also demonstrated improvement in liver steatosis, steatohepatitis and fibrosis in 91.6%, 81.3% and 65.5% of patients after bariatric surgery.

Conversely, rapid weight loss is known to increase the risk of liver fibrosis, with a weight loss of more than 1.6 kg a week resulting in a rapid reduction in hepatic fat and subsequent increase in visceral free fatty acids and proinflammatory cytokines [16]. Mathurin et al. performed a 5-year prospective study evaluating NASH in obese patients undergoing bariatric surgery, which showed a significant increase in mean liver fibrosis scores from 0.14 to 0.38 1 year after LAGB [17]. However, concerns about rapid weight loss resulting in worsening liver fibrosis are not reflected in our patient population. The improvement in NAFLD fibrosis scores in our patient population can be seen as early as the 6-month post-operative mark, lasting all the way until the 1-year post-operative period.

The correlation between weight loss and improvement in NAFLD fibrosis scores is significant only at the first post-operative year in our study. There was no significant correlation between weight loss and NAFLD fibrosis score improvement at the 6-month post-operative mark. This may be attributed to the fact that weight loss is most drastic in the immediate first 6 months post-surgery, whereas the improvement in the NAFLD fibrosis score is only prominent from the 1-year mark onwards. Literature has shown that BMI is an effective predictor of the severity of fatty liver disease, as compared to other serological markers. Abangah et al. [18] demonstrated that BMI and triglyceride levels had the greatest statistical correlation with severity of fatty liver disease on ultrasonography. Fassio et al. [19] also demonstrated that progress of liver fibrosis was significantly associated with obesity and BMI. With regard to post-bariatric surgery, a prospective study by Cazzo et al. [20] also demonstrated improvement in NAFLD fibrosis scores after RYGB, with resolution of advanced fibrosis significantly associated with percentage of excess weight loss and postsurgical BMI. This is in contrast to previous studies that demonstrate no significant correlation between improvement in NAFLD scores and the extent of weight loss [21].

With regard to the effect of the type of bariatric surgery on improvement on NAFLD fibrosis score, our study shows that there is no difference between the improvements in the NAFLD fibrosis scores amongst the various types of bariatric surgeries. However, patients who underwent RYGB had a consistently greater improvement in their NAFLD fibrosis scores across the 6-month to 1-year post-operative period, as compared to patients who underwent other forms of bariatric surgeries. A study by Nickel et al. also showed that RYGB had a statistically significant higher improvement in NAFLD fibrosis scores compared to LSG [21]. This may be postulated to be because of the additional effect of hormone alteration in

RYGB patients, which has a beneficial impact on insulin resistance and adipocyte dysfunction. Fischer et al. are currently conducting a multi-centre randomised, blinded trial studying the varying effects of LSG and RYGB on weight loss and improvement in NAFLD [22].

This study is a retrospective one, with a follow-up period of only 1 year. A longer study period and post-operative follow-up are needed to determine if the effects of bariatric surgery on NAFLD fibrosis scores are permanent. Given the current conflicting literature regarding the correlation of weight loss and NAFLD fibrosis score improvement, more prospective studies can be conducted for further evaluation.

Conclusion

In conclusion, our study demonstrates a correlation between the degree of weight loss and improvement in NAFLD fibrosis scores post-bariatric surgery. Significant correlation is noted only from the first year post-operative mark onwards. Degree of weight loss may be used as a surrogate marker to predict the extent of improvement in liver fibrosis scores after 1-year post-operative mark. However, whether bariatric surgery itself is an independent factor in the improvement in NAFLD fibrosis scores, regardless of the weight loss, remains to be seen. More studies will be needed to determine if there is a non-weight dependent factor in the improvement of the NAFLD fibrosis score.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent For this type of study, formal consent is not required.

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