Effect of bariatric surgery on fatty liver disease in obese patients: A prospective one year follow-up study

Daniel Toman[a,b], Petr Vavra[a,b], Petr Jelinek[a,b], Petr Ostruszka[a,b], Peter Ihnat[a,b], Ales Foltys[a,b], Anton Pelikan[a,b,c,d], Jan Roman[a,b]

Background. Non-alcoholic fatty liver disease (NAFLD), often associated with obesity and metabolic syndrome, manifests itself as steatosis, hepatic fibrosis, cirrhosis, or even end-stage liver disease. NAFLD causes inflammation, insulin resistance and cardiovascular complications. The current study aimed to evaluate the beneficial effects of bariatric surgery on biochemical parameters of hepatic functions in obese patients by comparing them before and one-year after the surgery.

Methods. A total of 72 morbidly obese patients underwent bariatric surgery between 2016 and 2018. The incidence of diabetes mellitus in this group was 29%, median body weight was 124.5 kg (109.0-140.0) and mean body mass index (BMI) was 44.38 ± 6.770 kg/m^2. The used surgical procedures included gastric bypass, sleeve gastrectomy, laparoscopic gastric plication, and single anastomosis duodeno-ileal bypass-sleeve gastrectomy. Biochemical parameters including ALT/AST ratio (AAR), NAFLD fibrosis score (NFS), hepatic fibrosis index (FIB-4) and Fatty Liver Index (FLI) were evaluated in all patients at the time of surgery and one year after the intervention.

Results. Significant improvement after the intervention was observed in 64 patients. A significant reduction in body weight (P<0.0001), waist circumference (P<0.0001), and body mass index (P<0.0001) were observed. NAFLD liver fibrosis index changed significantly (P<0.0001), suggesting a trend of improvement from advanced fibrosis towards stages 0-2. The FIB-4 fibrosis index indicated significant improvement (P=0.0136). Besides, a significant decline in hepatic steatosis (P<0.0001) was observed after bariatric surgery as compared to the pre-surgery fatty liver conditions.

Conclusion. Among the strategies to overcome NAFLD-associated impediments, bariatric surgery can be considered effective in reducing obesity and metabolic co-morbidities.

Trial Registration: ClinicalTrials.gov (NCT04569396)

Key words: NAFLD, bariatric surgery, obesity, liver fibrosis

Received: November 13, 2020; Revised: April 7, 2021; Accepted: April 7, 2021; Available online: April 19, 2021
https://doi.org/10.5507/bp.2021.021

[a]Department of Surgery, Faculty of Medicine, Ostrava University, Czech Republic
[b]Department of Surgery, University Hospital Ostrava, Czech Republic
[c]Department of Surgery, St. Mary's Hospital, Newport, Isle of Wight, United Kingdom
[d]Department of Health Care Sciences, Faculty of Humanities, Tomas Bata University Zlin, Czech Republic
Corresponding author: Daniel Toman, e-mail: daniel.toman1@gmail.com

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), as well as non-alcoholic steatohepatitis (NASH), are highly prevalent hepatic disorders, especially in the developed countries[1]. NAFLD is a spectrum of chronic liver diseases which range from steatosis to NASH and liver fibrosis, which in turn causes metabolic complications[2]. Risk factors include type 2 diabetes, obesity and hyperlipidemia[3]. Obese patients are in a chronic inflammatory state that correlates with insulin resistance (IR) as well as with elevation of both tumour necrosis factor-α (TNF-α) and monocyte chemotactic protein-1, which causes impairment of adipocyte insulin sensitivity[4]. Inflammation and activation of several immune pathways in obese patients affect hepatic lipid metabolism, leading to hepatic injury[5]. Hepatic steatosis is associated with increased production of interleukin-6 and other pro-inflammatory cytokines by hepatocytes and non-parenchymal cells, including Kupfer cells[6]. This overexpression of cytokines is likely to play a key role in the progression of NAFLD as well as of cardiovascular diseases. NAFLD, even without fibrosis, represents a nourishing environment for the development of hepatocellular carcinoma (HCC) through insulin resistance and steatosis, which leads to inflammation, increased adipokine action, oxidative stress and lipotoxicity, all of which support hepatocellular carcinogenesis[7]. In the general European population, the prevalence of NAFLD cases doubled over the last twenty years; similarly, an increase of 42.6-69.5% was observed in patients with Type 2 diabetes[8]. In the United States of America (USA), about six million individuals were reported to have NASH and 0.6 million to have NASH-induced liver cirrhosis[9,10]. Evidence suggests that obesity is a major contributing factor to developing NAFLD (ref.[2,3]). In 2005, the estimated global numbers of obese and overweight adults were 937 and 396 million, respectively[7]. According to 2008 reports, there were about 500 million obese adults and about 1.4 billion overweight individuals globally, which can gradually predispose them to Type 2 diabetes and

hepatic complications[11,12]. The number of overweight and obese individuals is projected to be 1.35 billion and 573 million by 2030 (ref.[9]). The management strategies include dietary control, weight loss, lifestyle modifications and use of drugs for reduction of insulin resistance and management of NAFLD-associated hepatic fibrosis[13,14]. Nevertheless, weight loss achieved by lifestyle modifications and drug therapy are very hard to maintain and the incidence of hepatic fibrosis among NAFLD patients is reported to have significantly increased in the last decades[15,16]. Hence, alternative approaches including bariatric surgery were adopted to manage obesity and NAFLD (ref.[17-19]).

Bariatric surgery is considered an important tool for the management of obesity-related complications and about 11.3 million bariatric surgeries annually are performed in USA alone[20]. These surgical interventions have significantly reduced mortality rates and improved patients' quality of life as a result of a significant decline in the body weight, insulin resistance and cardiovascular risks[21-23].

Studies suggest that about 87-94% of bariatric patients exhibit hepatic pathophysiology and that bariatric surgery is highly beneficial in reducing the severity of NAFLD (ref.[24,25]). Bariatric surgeries do not only exhibit beneficial outcomes in the form of weight loss but are also useful in normalizing metabolic alterations and other changes associated with NAFLD, such as blood lipids profile, insulin resistance, adipokines and inflammation[26]. Bariatric surgery is generally recommended for obese individuals with a BMI of 35-40 kg/m2 (ref.[27]). Bariatric surgery is preferred over other weight-reducing procedures for the management of NAFLD as it considerably improves biochemical and histological parameters of NAFLD. The presented study running from 2016 to 2019 was designed to prospectively investigate the effect of bariatric surgery in non-alcoholic obese individuals on liver biochemistry, BMI, NAFLD fibrosis score, FIB 4 index and FLI at a one-year follow-up.

METHODS

Study design and inclusion criteria

The current study is based on data from morbidly obese patients who qualified for bariatric surgery at the Department of Surgery, University Hospital Ostrava, Czech Republic, between 2016 and 2018. Patients >18 years of age, with BMI > 35-40 kg/m2 with hypertension and/or diabetes in whom conservative therapy failed to relieve the symptoms were included in the study. Exclusion criteria were: a history of excessive alcohol consumption, use of hepatotoxic drugs, infectious liver diseases (i.e. hepatitis A, B, C) and genetic hemochromatosis. A total of 72 patients (n=26 during 2016, n=26 during 2017 and n=20 during 2018) who qualified for bariatric surgery were included in the study. All patients signed informed consent for participation in the study.

Approval of the Ethics committee

The study was approved by the Ethics committee at the Department of Surgery, University Hospital Ostrava, Czech Republic.

Patient demographics

Patients' sex, age (years), weight (kg), height (cm) and associated co-morbidities such as diabetes and hypertension were recorded before surgery.

Biochemical Analysis

Biochemical parameters including triglyceride profile, platelet count, Gamma glutamyl-transferase (GGT), albumin concentration, alanine aminotransferase (ALT), aspartate aminotransferase (AST), as well as platelet count, triglycerides and blood glucose were determined using standard procedures[28,29]. BMI, a very useful tool for the prediction of various diseases including cardiovascular diseases and stroke[30-32], was also calculated.

Calculation of AAR

The ALT/AST Ratio known as AAR is an important indicator of liver diseases as well as of other diseases including muscular damage or other arterial occlusive disorders such as limb ischemia[33,34]. AAR was calculated for individual patients from their liver enzymes profile and data for all patients was presented as mean ± standard error of mean (SEM).

Estimation of NAFLD fibrosis score (NFS)

NFS was calculated following the standards set by the American and European Associations for the Study of Liver Disease[35-37]. This non-invasive serum index is based on several parameters including age, BMI, albumin, hyperglycaemia, platelet count and AST/ALT ratio[38-40]. The NFS score was calculated as:

-1.675 + 0.037 x Age (years) + 0.094 x BMI (kg/m^2) + 1.13 x IFG/diabetes score (i.e. yes = 1 & no = 0) + 0.99 x AST/ALT ratio - 0.013 x platelet count (x10^9/L) - 0.66 x albumin (g/dL) (ref.[41]),

where IFG stands for impaired fasting glycaemia.

Assessment of fibrosis using FIB-4 index

FIB-4 index is a non-invasive, highly specific and sensitive approach for prediction of hepatic fibrosis. FIB-4 values were determined for all patients included in the study using the previously reported standard formula[42,43]:

$$FLI = \frac{(e^{0.953 \times \log e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times \text{waist circumference} - 15.745)}}{1 + (e^{0.953 \times \log e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times \text{waist circumference} - 15.745)}} \times 100$$

$$FIB-4 = \frac{\text{Age of the Patients (years)} \times \text{AST[Unit per litter]}}{\text{Platelets count [per liter]} \times \left(\text{ALT}^{\frac{[\text{Unit per litter}]1}{2}}\right)}$$

Patient results were classified into groups F0 (indicating no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis) and F4 (liver cirrhosis).

Fatty Liver Index (FLI)

FLI is a useful approach for the calculation of liver steatosis and other fatty liver diseases. It is calculated us-

ing information such as waist circumference (Wci), triglycerides (TG), BMI, and GGT (ref.[31,44]).

Surgical interventions

To qualify for the bariatric surgery, the patients underwent extensive multi-disciplinary pre-operative evaluations. Patients were subjected to a specific dietary program before surgery as indicated in recent guidelines for bariatric surgery[45-47]. The most appropriate of the following procedures was used in the individual patients based on the patient condition: gastric bypass (Roux-en-Y), sleeve gastrectomy (LSG), Laparoscopic gastric plication (LGP) (ref.[48-51]).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and median (interquartile range, IQR) in case of normal and non-normal distribution, respectively. The Shapiro-Wilk test was used to test for normal distribution. The within-patient changes in clinical parameters (continuous or ordinal variables) from the baseline to one year after bariatric surgery were compared using the Wilcoxon matched-pairs signed-rank test for ordinal variables as well as for continuous variables where the change was non-normally distributed; for normally distributed continuous variables, the paired Student's t-test was used. The statistical testing was done at the two-tailed α level of 0.05. The data were analyzed using GraphPad Prism Version 8.0.2 (GraphPad Software, Inc., USA).

RESULTS

Patient demographics and biochemical analysis before surgery

A total of 72 severely or morbidly obese patients were referred for bariatric surgery between 2016 and 2018. Diabetes mellitus was present in 21 (29%) patients. The baseline characteristics of patients are shown in Table 1.

Post-surgical analysis of biochemical parameters

One year after the bariatric surgery, notable normalization of general health condition was observed in 64 patients (88%) while no significant change was detected in 8 patients (12%). In patients in whom the effect of bariatric surgery on NAFLD was positive, the improvement was confirmed by the clinical and biochemical characteristics (see Table 2). The changes were apparent from the significant decrease in the body weight (P<0.0001), waist circumference (P<0.0001), and body mass index (P<0.0001) as compared to that observed before bariatric surgery in the respective patients. From the biochemical results, a significant decrease in the platelet serum level (P=0.0240), and triglycerides (P<0.0001) was observed after surgery when compared to the corresponding paired values before surgery. However, no substantial change in the patients' biochemical characteristics of GGT, ALT, AST, and AAR was observed. A noticeable effect of bariatric surgery was observed in the extent of liver fibrosis as the NAFLD liver fibrosis index changed significantly

Table 1. Baseline characteristics of morbidly obese patients.

Characteristic	Before surgery (n = 72)
Age (years)	45.49 ± 11.18
Height (cm)	170.4 ± 8.93
Weight (kg)	124.5 (109.0-140.0)
Wci (cm)	128.3 ± 15.45
BMI (kg/m^2)	44.38 ± 6.77
Platelet count (×10^9/L)	274.4 ± 65.71
Triglycerides (mmol/L)	1.70 (1.29-2.05)
GGT (μkat/L)	0.44 (0.31-0.60)
GGT (IU/L)	26.35 (19.04-35.98)
Albumin (g/L)	41.24 ± 2.39
ALT (μkat/L)	0.44 (0.34-0.70)
ALT (IU/L)	25.58 (20.51-41.92)
AST (μkat/L)	0.40 (0.33-0.56)
AST (IU/L)	23.95 (19.61-35.03)
AAR	0.86 (0.67-1.13)
NAFLD	-0.88 (-1.7-0.19)
FIB-4	0.76 (0.61-1.21)
FLI	96.00 (83.50-99.00)

Values expressed as mean ± SD or median (IQR)

(P<0.0001), thereby showing a trend from advanced fibrosis towards stages 0-2. The reduction in the liver fibrosis was also apparent from the FIB-4 fibrosis index, which showed a significant improvement (P=0.0136) and a reduction in the fibrotic severity. A significant decrease in the non-invasive fatty liver index (P<0.0001) was observed after the bariatric surgery compared to the pre-surgery fatty liver conditions, indicating an improvement in the status and in the degree of hepatic steatosis.

NAFLD fibrosis score, fibrosis FIB-4 index and other analyses

To ascertain the relation of bariatric surgery to the change in liver fibrosis and steatosis, the 64 patients were assigned (based on the results of the NAFLD fibrosis scoring system) to cohorts of fibrosis stages F0-F2 (< −1.455 as Cohort 1) and F3-F4 (> 0.675 as Cohort 2), using the cut-off values for the exclusion or presence of advanced fibrosis based on the pre-surgery baseline NAFLD liver fibrosis scoring system (see Table 3). In the Cohort 1 [n = 23 (36%)], a significant decrease in the body weight (P<0.0001), waist circumference (P<0.0001) and body mass index (P<0.0001) was observed one year after the bariatric surgery compared to the pre-surgery values. The pre- and post-surgery paired analysis also revealed a significant reduction in the level of triglycerides (P=0.0037), while no significant changes were observed in the remaining investigated biochemical parameters. A notable improvement in the hepatic fibrotic reversibility was apparent from the significant change in the NAFLD fibrosis index (P=0.0149) and the liver rejuvenation was further confirmed by the significant decrease in the steatosis index (P=0.0031). In the Cohort 2 [n=11 (17%)], a similar improvement in the clinical condition

Table 2. Paired value analysis of changes in clinical, biochemical, and fibrosis indices characteristics in morbidly obese patients before and 1 year after the bariatric surgery.

Characteristics	Before surgery	1 year after surgery	*P*
Weight (kg)	124.0 (109.0-137.8)	90.00 (83.25-102.5)	< 0.0001[a]
Wci (cm)	125.5 (115.0-138.0)	102.0 (96.00-110.0)	< 0.0001[a]
BMI (kg/m^2)	43.24 (38.58-48.75)	31.00 (29.00-34.75)	< 0.0001[a]
Platelets (×10^9/L)	276.0 ± 63.33	263.9 ± 58.55	0.0240[b]
Triglycerides (mmol/L)	1.70 (1.26-2.04)	1.40 (1.20-1.76)	< 0.0001[a]
GGT (μkat/L)	0.44 (0.31-0.61)	0.44 (0.33-0.60)	0.1639[a]
GGT (IU/L)	26.35 (18.67-36.85)	25.00 (19.00-37.50)	0.2188[a]
Albumin (g/L)	41.29 ± 2.301	41.30 ± 2.052	0.9801[b]
ALT (μkat/L)	0.42 (0.34-0.70)	0.46 (0.34-0.60)	0.1720[a]
ALT (IU/L)	25.15 (20.36-42.36)	27.50 (21.00-36.75)	0.1262[a]
AST (μkat/L)	0.41 (0.35-0.58)	0.41 (0.33-0.54)	0.5788[a]
AST (IU/L)	25.00 (20.96-35.78)	25.00 (21.00-31.50)	0.6265[a]
AAR	0.87 (0.66-1.13)	0.90 (0.79-1.05)	0.3824[a]
NAFLD	-0.900(-1.90-0.19)	-1.66 (-2.39–0.40)	< 0.0001[a]
FIB-4	0.77 (0.61-1.20)	0.85 (0.65-1.17)	0.0136[a]
FLI	96.00 (83.50-99.00)	74.00 (50.00-87.00)	< 0.0001[a]

Values expressed as median (IQR) or mean ± SD, n = 64
[a]Wilcoxon matched-pairs signed-rank test
[b]Paired Student's *t*-test

Table 3. Paired value analysis of changes in clinical and biochemical characteristics of morbidly obese patients before and 1 year after bariatric surgery in the cohorts of NAFLD liver fibrosis patients.

Characteristics	NAFLD fibrosis score = < −1.455 (F0-F2)			NAFLD fibrosis score = > 0.675 (F3-F4)		
	Before surgery	1 Year after surgery	*P*	Before surgery	1 Year after surgery	*P*
Weight (kg)	123.4 ± 16.55	92.39 ± 12.85	< 0.0001[a]	151.8 ± 22.79	114.5 ± 27.25	< 0.0001[a]
Wci (cm)	126.2 ± 14.46	105.0 ± 10.56	< 0.0001[a]	142.5 ± 16.57	116.5 ± 19.85	< 0.0001[a]
BMI (kg/m^2)	43.85 ± 6.30	32.61 ± 4.717	< 0.0001[a]	49.62 ± 7.664	37.27 ± 9.758	< 0.0001[a]
Platelets (×10^9/L)	285.3 ± 45.86	279.6 ± 48.21	0.4234[a]	233.0 ± 71.95	215.2 ± 47.67	0.2043[a]
Triglycerides (mmol/L)	1.80 (1.20-2.19)	1.60 (1.20-1.80)	0.0037[b]	2.07 ± 0.49	1.46 ± 0.39	0.0010[a]
GGT (μkat/L)	0.46 ± 0.20	0.45 ± 0.19	0.7180[a]	0.53 ± 0.21	0.50 ± 0.16	0.3463[a]
GGT (IU/L)	28.16 ± 12.55	26.61 ± 11.51	0.6098[a]	31.75 ± 12.54	30.55 ± 9.66	0.5162[a]
Albumin (g/L)	41.05 ± 2.514	40.74 ± 1.912	0.5799[a]	41.75 ± 2.113	41.36 ± 1.629	0.6375[a]
ALT (μkat/L)	0.54 ± 0.37	0.47 ± 0.16	0.3389[a]	0.34 (0.25-0.84)	0.45 (0.33-0.60)	0.3652[b]
ALT (IU/L)	31.93 ± 22.19	28.17 ± 9.796	0.3776[a]	20.36 (15.00-50.30)	25.00 (20.00-36.00)	0.4492[b]
AST (μkat/L)	0.40 (0.30-0.54)	0.41 (0.33-0.50)	0.8797[b]	0.66 ± 0.44	0.50 ± 0.24	0.2277[a]
AST (IU/L)	25.00 (19.00-34.13)	24.00 (19.00-30.00)	0.7940[b]	39.33 ± 26.44	30.09 ± 15.07	0.2452[a]
AAR	0.98 ± 0.37	0.95 ± 0.22	0.6301[a]	1.57 ± 1.62	0.97 ± 0.16	0.2424[a]
NAFLD	-0.870 (-1.02–0.27)	-1.71 (-2.19–0.80)	0.0149[b]	1.70 (0.98- 2.32)	0.25 (-0.61- 1.07)	0.0029[b]
FLI	88.43 ± 10.26	72.09 ± 21.29	0.0031[a]	98.00 (96.00-100.0)	87.00 (73.00-95.00)	0.0098[b]

Values expressed as mean ± SD or median (IQR), *n* = 23 (cohort 1) and 11 (cohort 2)
[a]Paired Student's *t*-test; [b]Wilcoxon matched-pairs signed-rank test

was apparent from the significant decrease in the 1-year post-surgery levels of body weight (P<0.0001), waist circumference (P<0.0001), body mass index (P<0.0001), and the serum level of triglycerides (P=0.0010) compared to the pre-surgery baseline measurements. The bariatric surgery also induced a prominent improvement in this cohort of patients with advanced liver fibrosis, recording a significant improvement in the NAFLD fibrosis index (P=0.0029) after one year, indicating an attenuation of hepato-steatosis as revealed by the significant reduction in the fatty liver index (P=0.0098) compared to the pre-surgery baseline paired controls.

The FIB-4 liver fibrosis index was used in combination with the NAFLD scoring system. Among the 64 bariatric surgery patients, 56 (87%) patients belonged to the cohort of FIB-4 fibrosis stages F0-F1 (FIB-4 index < 1.30), see Table 4, while no patient with advanced fibrosis (≥ F3 = > 2.67) was present in our group. In the FIB-4 F0-F1 cohort of patients, a marked improvement of the morbidity was observed, manifesting itself as a significant decrease in the

Table 4. Paired value analysis of basic changes in clinical and biochemical characteristics of morbidly obese patients before and 1 year after bariatric surgery in the FIB-4 liver fibrosis patients cohort.

Characteristics	FIB-4 fibrosis score = < 1.30 (F0-F1)		
	Before surgery	1 year after surgery	*P*
Weight (kg)	122.0 (108.0-133.0)	90.00 (81.00-100.0)	< 0.0001[a]
Wci (cm)	124.0 (114.0-137.0)	100.0 (96.00-108.0)	< 0.0001[a]
BMI (kg/m^2)	42.96 (37.24-48.00)	31.00 (29.00-34.00)	< 0.0001[a]
Platelets (×10^9/L)	281.1 ± 60.01	269.7 ± 58.20	0.0441[b]
Triglycerides (mmol/L)	1.70 (1.20-2.00)	1.40 (1.20-1.71)	< 0.0001[a]
GGT (μkat/L)	0.43 (0.31-0.60)	0.44 (0.31-0.57)	0.1423[a]
GGT (IU/L)	25.75 (18.56-36.00)	25.00 (19.00-34.00)	0.1636[a]
Albumin (g/L)	41.26 ± 2.319	41.45 ± 1.874	0.5414[b]
ALT (μkat/L)	0.42 (0.34-0.71)	0.46 (0.34-0.66)	0.2287[a]
ALT (IU/L)	25.00 (20.36-42.51)	28.00 (20.00-38.00)	0.1636[a]
AST (μkat/L)	0.40 (0.31-0.54)	0.41 (0.33-0.55)	0.6270[a]
AST (IU/L)	23.95 (19.00-32.00)	25.00 (21.00-32.00)	0.5989[a]
AAR	0.88 ± 0.32	0.94 ± 0.20	0.0691[b]
FIB-4	0.72 (0.60-1.01)	0.83 (0.61-1.10)	0.0007[a]
FLI	95.00 (83.00-99.00)	68.00 (48.00-84.00)	< 0.0001[a]

Values expressed as median (IQR) or mean ± SD, n = 55
[a]Wilcoxon matched-pairs signed-rank test
[b]Paired Student's *t*-test

body weight (*P*<0.0001), waist circumference (*P*<0.0001) and the body mass index (*P*<0.0001) when compared to the individual patients' baseline characteristics. The analysis of the clinically relevant serum biochemical analysis in these patients 1 year after the bariatric surgery showed a significant decrease in the platelet count (*P*=0.0441) and the level of triglycerides (*P*<0.0001). The non-invasive FIB-4 scoring system also further validated the beneficial effects of the bariatric surgery on the reduction of the obesity-associated morbidities and on the enhancement of the overall patient's quality of life. This was substantiated by the significant improvement in the FIB-4 liver fibrosis index (*P*=0.0007) and a change in the severity of steatosis as apparent from the significant decrease in the index of fatty liver conditions (*P*<0.0001) as compared to the parameters of the pre-surgery baseline paired controls in this FIB-4 fibrotic patients' cohort.

DISCUSSION

We set out to assess the outcomes of patients who had undergone bariatric surgery one year after the procedure. Our assessment registered successful outcomes in 88% of patients one year after the surgery as measured by a 10% excess weight loss (EWL), a decrease in FLI, or both.

Using the BMI and lipid levels as our proxy for the metabolic syndrome[52], we found an overall improvement rate of 88% one year after the surgery. Panagioutou et al. 2018 illustrated resolution of dyslipidemia in >95% of patients undergoing bariatric surgery 2 years following surgery and a 95% reduction in the prevalence of the metabolic syndrome five years following surgery. Although the exact mechanisms through which bariatric surgery leads to the resolution of NAFLD is unknown, it is assumed to lead to changes in gut hormones, inflammatory conditions, insulin sensitivity, weight loss and dyslipidaemia[53]. Our results, which were restricted only to patients with severe fibrosis or advanced cirrhosis, showed a change in the proportion of patients with advanced fibrosis (F3-F4). This is in accordance with results of prior studies, in which bariatric surgery has been shown to be capable of reversing even cirrhosis[54]. Similarly, our results are also in accordance with those reported by Nostdet et al (2016) who have shown that in 80% of patients, fibrosis scores were either improved or unchanged after the surgery[55]. It is also worth mentioning that our results are in agreement with those reported by Nosdet et al. even though in our study, we used a non-invasive indicator of liver damage while Nosdet et al. used liver biopsy. This further corroborates the validity of the non-invasive approach chosen in our study.

Various studies have examined the predictors of success or failure of the surgery. At present, however, there is no consensus on EWL value considered as success; the same can be said about standardization of the follow-up time[56]. In our study, a total of 8 (12%) patients did not show improvement, i.e, their triglyceride levels remained >2.3 mmol/L and/or there was less than 10% change in body weight one year after the surgery. Those who did not show improvements had slightly higher baseline weights, waist circumference, triglyceride levels and liver function tests (Table 5).

Younger age was previously reported to be a significant predictor of weight loss at 12 months following the surgery for patients who underwent Endoscopic Sleeve Gastroplasty[57]. Similarly, a higher body fat percentage has been shown to predict weight loss following surgery[58]. On the other hand, our results showed that a higher proportion of patients with higher triglycerides and anthropo-

Table 5. Comparison of patients who had improvements in weight and metabolic derangements one year following bariatric surgery at the University Hospital Ostrava, Czech Republic, 2016-2018.

Patient characteristics at baseline	Patients who improved (n=64)	Patients who did not improve (n=8)
Median age in years (IQR)	47 (38-45)	44 (38-53)
Gender		
Female	50 (78%)	6 (75%)
Male	14 (22%)	2 (25%)
median weight kg (IQR)	125 (110-143)	129 (118-133)
median waist circumference cm (IQR)	126 (117-136)	136 (127-136)
BMI category kg/m^2		
30.0-39.9	16 (25%)	2 (25%)
≥40	48 (75%)	6 (75%)
Median Triglycerides mmol/L		
<1.7	32 (50%)	0 (0)
1.7-2.2	27 (42%)	2 (25%)
2.3-5.6	5 (8%)	4 (50%)
≥5.7	0 (0)	2 (25%)
FLI		
<60	0 (0%)	0 (0%)
≥60	64 (100%)	8 (100%)
median albumin g/dL (range)	4.20 (3.60-4.70)	4.00 (3.50-4.30)
Median AST IU (range)	23.95 (3.59-108.0)	34.13 (26.95-36.00)
Median ALT IU (range)	25.00 (11.0-113.7)	41.32 (17.96-50.30)
Median GGT IU (range)	25.75 (11.38-68.0)	30.00 (26.95-44.31)
AAR ratio		
<1.0	42 (66%)	4 (50%)
1.0-1.9	20 (31%)	4 (50%)
≥2.0	2 (3%)	0 (0%)
NAFLD Score		
F0-F2	23 (36%)	0 (0%)
Indeterminate	30 (47%)	6 (78%)
F3-F4	11 (17%)	2 (22%)
FIB-4 Index		
<-1.45	56 (87%)	8 (100%)
1.45-3.25	8 (13%)	0 (0%)
>3.25	0 (0%)	0 (0%)
Median Platelet count ×10^9/L (range)	257 (131.0-434.0)	283 (227.0-357.0)
Type of surgery		
Laparoscopic gastric bypass	8 (12%)	3 (37%)
LSG	53 (93%)	3 (37%)
Laparoscopic gastric plication	3 (5%)	2 (26%)
DM		
Present	15 (23%)	6 (75%)
Absent	49 (77%)	2 (25%)
Year of Surgery		
2016	20 (77%)	6 (23%)
2017	25 (96%)	1 (4%)
2018	19 (95%)	1 (5%)

morphic measurements, i.e., values positively correlated with body fat percentage, were found among patients who did not improve. In this, our results are similar rather to other studies[59,60]. In another paper, ALT and AST have been shown to predict successful weight loss one year after the surgery[61,62].

There are three types of bariatric surgery procedures: (i) restrictive procedures such as sleeve gastrectomy or gastric plication that reduce the size of the stomach so that less food can be consumed, (ii) malabsorptive, i.e. biliopancreatic diversion that bypasses a segment of the small bowel so that less food is absorbed and (iii) a hybrid procedure, i.e., the Roux-en-Y gastric bypass[53]. Our results illustrated better outcomes in patients who underwent laparoscopic sleeve gastrectomy (LSG). This is accordance with conclusions by Fobi et al.[51] that LSG negates the need for further intervention and periodic blood testing to identify and treat deficiencies, resulting in substantial

weight loss and resolution of comorbidities up to 3-5 years follow-up. Initial weight loss from the sleeve gastrectomy alone was in their study found to be very good (50-60% excess weight loss) at one year without the need for further intervention. The LSG provides additional advantages; namely, no anastomoses (connections between the bowel parts) are created and it's possible to convert it later to either the gastric bypass or lap band if needed.

Our study comes with some limitations. A shorter follow-up period did not allow us to assess long-term morbidity and mortality rates following surgery as well as other effects on weight loss[64]. We did not perform liver biopsy or imaging procedures for evaluation of the liver condition of individual patients, i.e. methods that are most commonly used for definitive diagnosis of NAFLD (ref.[65]). However, the surrogate non-invasive markers used in our study were shown to provide results of sufficient reliability for diagnosis and follow-up[66].

NFS scores of < -1.455 indicated a fibrosis score of F0-F2, NFS scores of -1.455 – 0.675 indicated an indeterminate fibrosis score, and NFS scores of > 0.675 correlated with a fibrosis score of F3-F4. Patients' results were classified into groups F0 indicating no fibrosis, F1 (mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis) and F4 (liver cirrhosis)

CONCLUSION

A prospective study in morbidly obese patients showed that one year following the bariatric surgery, a significant improvement in morbidity-associated clinical conditions was detected in 88% of patients. The patients showed a marked reduction in the body weight, waist circumference, and body mass index, as well as a decrease in the serum level of triglycerides. Using the validated NAFLD-FIB-4 non-invasive scoring system that avoids the need for invasive liver biopsy, it was observed that bariatric surgery bestowed a significant decrease in fibrosis in a majority of patients, along with a reduction in steatosis. It can be concluded that bariatric surgery-induced weight loss may lead to a marked improvement in several factors involved in the regulation of inflammation and fibrogenesis in patients with NAFLD and may therefore substantially safeguard the patients from the development of cirrhosis and hepatocellular carcinoma.

ABBREVIATIONS

AAR, ALT/AST ratio; ALT, Alanine amino-transferases; AST, Aspartate amino-transferases; BMI, Body mass index; EWL, Excess weight loss; FIB-4, Hepatic fibrosis index; FLI, Fatty liver index; GGT, Gamma glutamyl-transferase; IFG, Impaired fasting glycaemia; IQR, Median interquartile range; IR, Insulin resistance; LGP, Laparoscopic gastric plication; LSG, Laparoscopic sleeve gastrectomy; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NFS – NAFLD, fibrosis score; SADI-S, Single anastomosis duodeno-ileal bypass-sleeve gastrectomy; SD, Standard deviation; SEM, Standard error of mean; TG, Triglycerides.

Acknowledgement: This manuscript was supported by the University of Ostrava in The Czech Republic under the grant number SGS03/LF/2018.

Author contributions: PI, DT: devised the main conceptual ideas and outline of the work; PV, PI: conceived the study and were in charge of overall direction and planning; AP: helped supervise the project; AF, PO: contributed to the interpretation of the results; DT, PO, JR: processed the experimental data, performed the analysis, drafted the manuscript and designed the figures; DT: took the lead in writing the manuscript with input from all authors; All authors provided critical feedback and helped shape the research, analysis and contributed to the final manuscript.

Conflict of interest statement: None declared.

REFERENCES

1. Greenfield V, Cheung O, Sanyal AJ. Recent advances in nonalcholic fatty liver disease. Curr Opin Gastroenterol 2008;24(3):320-7.
2. Dixon JB, Bhathal PS, O'brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121(1):91-100.
3. Angulo P: Nonalcoholic fatty liver disease. N Engl J Med 2002; 346(16):1221-31.
4. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003;112:1821-30
5. Bertola A, Bonnafous S, Anty R, Patouraux S, Saint-Paul MC, Iannelli A, Gugenheim J, Barr J, Mato JM, Le Marchand-Brustel Y, Tran A, Gual P. Hepatic expression patterns of inflammatory and immune response genes associated with obesity and NASH in morbidly obese patients. PloSOne 2010;5:e13577.
6. Day CP. From fat to inflammation. Gastroenterology 2006;130(1):207-10.
7. Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H, Karin M. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 2010;140(2):197-208.
8. Blachier M, Leleu H, Peck-Radosavljevic M, Valla D-C, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013;58(3):593-608.
9. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology 2009;49(1):306-17.
10. Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology 2002;36(6):1349-54.
11. Kelly T, Yang W, Chen C-S, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes 2008;32(9):1431-37.
12. Organization WH. Obesity and overweight (Fact sheet N 311) http:// www. who. int/mediacentre/factsheets/fs311/en. In.: Accessed; 2015.
13. Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. Gut 2007;56(12):1760-69.
14. Wong VW-S, Wong GL-H, Choi PC-L, Chan AW-H, Li MK-P, Chan H-Y, Chim AM-L, Yu J, Sung JJ-Y, Chan HL-Y. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut 2010;59(7):969-74.
15. Puterbaugh J. The emperor's tailors: the failure of the medical weight loss paradigm and its causal role in the obesity of America: I can easier teach twenty what were good to be done than to be one

of the twenty to follow mine own teaching. The brain may devise laws for the blood, but a hot temper leaps o'er a colddecree. Portia, Merchant of Venice. Diabetes, Obe Metab 2009;11(6):557-70.
16. Fassio E, Álvarez E, Domínguez N, Landeira G, Longo C. Natural history of nonalcoholic steathepatitis: a longitudinal study of repeat liver biopsies. Hepatology 2004;40(4):820-6.
17. Aguilar-Olivos NE, Almeda-Valdes P, Aguilar-Salinas CA, Uribe M, Méndez-Sánchez N. The role of bariatric surgery in the management of nonalcoholic fatty liver disease and metabolic syndrome. Metabolism 2016;65(8):1196-207.
18. Angulo P. NAFLD, obesity, and bariatric surgery. Gastroenterology 2006;130(6):1848-52.
19. Shaffer EA. Bariatric surgery: a promising solution for nonalcoholic steatohepatitis in the very obese. J Clin Gastroenterol 2006;40:S44-S50.
20. Livingston EH. The incidence of bariatric surgery has plateaued in the US. Am J Surg 2010;200(3):378-85.
21. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. Jama 2004;292(14):1724-37.
22. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, LaMonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357(8):753-61.
23. Pontiroli AE, Morabito A. Long-term prevention of mortality in morbid obesity through bariatric surgery. a systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. Ann Surg 2011;253(3):484-7.
24. Reha JL, Lee S, Hofmann LJ. Prevalence and predictors of nonalcoholic steatohepatitis in obese patients undergoing bariatric surgery: a Department of Defense experience. Am Surg 2014;80(6):595-9.
25. Weiner R. Surgical treatment of non-alcoholic steatohepatitis and non-alcoholic fatty liver disease. Dig Dis 2010;28(1):274-9.
26. Sasaki A, Nitta H, Otsuka K, Umemura A, Baba S, Obuchi T, Wakabayashi G. Bariatric surgery and non-alcoholic Fatty liver disease: current and potential future treatments. Front Endocrinol 2014;5:164.
27. Panel NIoHCD. Gastrointestinal surgery for severe obesity. Ann Intern Med 1991,115:956-61.
28. Sallie R, Michael Tredger J, Williams R. Drugs and the liver part 1: Testing liver function. Biopharm Drug Dispos 1991;12(4):251-9.
29. Cazzo E, Jimenez LS, Pareja JC, Chaim EA. Effect of Roux-en-Y gastric bypass on nonalcoholic fatty liver disease evaluated through NAFLD fibrosis score: a prospective study. Obes Surg 2015;25(6):982-5.
30. Obese H. Body Mass Index (BMI). Obes Res 1998;6(2):51S-209S.
31. Huang X, Xu M, Chen Y, Peng K, Huang Y, Wang P, Ding L, Lin L, Xu Y, Chen Y. Validation of the fatty liver index for nonalcoholic fatty liver disease in middle-aged and elderly Chinese. Medicine 2015;94(40):e1682. doi: 10.1097/MD.0000000000001682
32. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. Arch Intern Med 2002;162(22):2557-62.
33. Botros M, Sikaris KA. The de ritis ratio: the test of time. Clin Biochem Rev 2013;34(3):117.
34. Rief P, Pichler M, Raggam R, Hafner F, Gerger A, Eller P, Brodmann M, Gary T. The AST/ALT (De-Ritis) ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. Medicine 2016;95(24):e3843.
35. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55(6):2005-23.
36. Castera L, Chan H, Arrese M. European Associatio n for Study of Liver; Asociacion Latinoamericana para el Estudio de l Higado. EASL-ALEH clinical practice guidelines: non-invasive test s for evaluation of liver disease severity and prognosis. J Hepatol 2015;63(1):237-64.
37. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45(4):846-54.
38. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011;43(8):617-49.
39. LIVER CCOA. Chronic liver Disease. Essentials of Family Medicine 2008;341.
40. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso MDC, Sala M, Brú C, Rodés J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999;29(1):62-7.
41. Cheah MC, McCullough AJ, Goh GB-B. Current modalities of fibrosis assessment in non-alcoholic fatty liver disease. J Clin Transl Hepatol 2017;5(3):261.
42. Hussain Shaikh F, Zeb S, Aziz Siddiqui K, Aamir Ghori M, Sadik Memon M, Zaki M. Fib-4 index: diagnostic validity for predicting hepatic fibrosis in south east asian patients of chronic hepatitis c virus (HCV) genotype 3 infection. Prof Med J 2017;24(10):1501-9.
43. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ, Network NCR. Use of the FIB4 index for non-invasive evaluation of fibrosis in nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7(10):1104.
44. Castiglione A, Bedogni G, Miglioli L, Crocè L, Masutti E, Passalacqua M, Bellentani S. 676 The fatty liver index: A simple and accurate predictor of hepatic steatosis. J Hepatol 2006,44:S249-S50.
45. Fried M, Yumuk V, Oppert J, Scopinaro N, Torres A, Weiner R, Yashkov Y, Frühbeck G. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg 2014;24(1):42-55.
46. Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Spitz AF, Apovian CM, Livingston EH, Brolin R, Sarwer DB. AACE/TOS/ASMBS Guidelines. Obesity 2009;17(S1):S3-72.
47. Thorell A, MacCormick A, Awad S, Reynolds N, Roulin D, Demartines N, Vignaud M, Alvarez A, Singh P, Lobo D. Guidelines for perioperative care in bariatric surgery: enhanced recovery after surgery (ERAS) society recommendations. World J Surg 2016; 40(9):2065-83.
48. Sánchez-Pernaute A, Herrera MAR, Pérez-Aguirre ME, Talavera P, Cabrerizo L, Matía P, Díez-Valladares L, Barabash A, Martín-Antona E, García-Botella A. Single anastomosis duodeno–ileal bypass with sleeve gastrectomy (SADI-S). One to three-year follow-up. Obes Surg 2010;20(12):1720-26.
49. Brethauer SA, Harris JL, Kroh M, Schauer PR. Laparoscopic gastric plication for treatment of severe obesity. Surg Obes Relat Dis 2011;7(1):15-22.
50. Melissas J, Koukouraki S, Askoxylakis J, Stathaki M, Daskalakis M, Perisinakis K, Karkavitsas N. Sleeve gastrectomy-a restrictive procedure? Obes Surg 2007;17(1):57.
51. Fobi MA, Lee H, Holness R, Cabinda D. Gastric bypass operation for obesity. World J Surg 1998;22(9):925-35.
52. Williams T. Metabolic Syndrome: Nonalcoholic Fatty Liver Disease. FP Essent. 2015;435:24-9.
53. Hafeez S, Ahmed MH. Bariatric Surgery as Potential Treatment for Nonalcoholic Fatty Liver Disease: A Future Treatment by Choice or by Chance? J Obes 2013;2013:839275. doi:10.1155/2013/839275
54. Kral JG, Thung SN, Biron S, Hould F-S, Lebel S, Marceau S, Simard S, Marceau P. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. Surgery 2004;135(1):48-58. doi:10.1016/j.surg.2003.10.003
55. Nostedt JJ, Switzer NJ, Gill RS, Dang J, Birch DW, de Gara C, Bailey RJ, Karmali S. The Effect of Bariatric Surgery on the Spectrum of Fatty Liver Disease. Can J Gastroenterol Hepatol 2016;2016:2059245. doi:10.1155/2016/2059245
56. Panagiotou OA, Markozannes G, Kowalski R, Gazula A, Di M, Bond DS, Ryder BA, Adam GP, Trikalinos TA. AHRQ Technology Assessments. Short- and Long-Term Outcomes after Bariatric Surgery in the Medicare Population. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018. Jan 7. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544890/
57. Sharaiha RZ, Kumta NA, Saumoy M, Desai AP, Sarkisian AM, Benevenuto A, Tyberg A, Kumar R, Igel L, Verna EC, Schwartz R, Frissora C, Shukla A, Aronne LJ, Kahaleh M. Endoscopic Sleeve Gastroplasty Significantly Reduces Body Mass Index and Metabolic Complications in Obese Patients. Clin Gastroenterol Hepatol 2017;15(4):504-10. doi:10.1016/j.cgh.2016.12.012
58. Doležalova-Kormanova K, Buchwald JN, Skochova D, Pichlerova D, McGlennon TW, Fried M. Five-Year Outcomes: Laparoscopic Greater Curvature Plication for Treatment of Morbid Obesity. Obes Surg 2017;27(11):2818-28. doi:10.1007/s11695-017-2709-3

59. Sohn YB, Kim SJ, Park SW, Kim S-H, Cho S-Y, Lee SH, Yoo KH, Sung KW, Chung JH, Koo HH, Jin DK. The metabolic syndrome and body composition in childhood cancer survivors. Korean J Pediatr 2011;54(6):253-9. doi:10.3345/kjp.2011.54.6.253
60. Paniagua L, Lohsoonthorn V, Lertmaharit S, Jiamjarasrangsi W, Williams MA. Comparison of waist circumference, body mass index, percent body fat and other measure of adiposity in identifying cardiovascular disease risks among Thai adults. Obes Res Clin Pract 2008;2(3):215-23. doi:10.1016/j.orcp.2008.05.003
61. Lee YC, Lee WJ, Lin YC, Liew PL, Lee CK, Lin SC, Lee TS. Obesity and the decision tree: predictors of sustained weight loss after bariatric surgery. Hepatogastroenterology 2009;56(96):1745-9.
62. Kahramanoğlu Aksoy E, Göktaş Z, Albuz Ö, Akpınar MY, Öztürk D, Buluş H, Uzman M. Effects of sleeve gastrectomy on liver enzymes, non-alcoholic fatty liver disease-related fibrosis and steatosis scores in morbidly obese patients: first year follow-up. J Lab Med 2019;43(2):115-22. doi:10.1515/labmed-2018-0181
63. Cottam S, Cottam D, Cottam A. Sleeve Gastrectomy Weight Loss and the Preoperative and Postoperative Predictors: a Systematic Review. Obes Surg 2019;29(4):1388-96. doi: 10.1007/s11695-018-03666-7
64. Courcoulas AP, Yanovski SZ, Bonds D, Eggerman TL, Horlick M, Staten MA, Staten MA. Long-term Outcomes of Bariatric Surgery: A National Institutes of Health Symposium. JAMA Surg 2014;149(12):1323-9. doi:10.1001/jamasurg.2014.2440
65. Mayo Clinic. Triglycerides: Why do they matter?2020 [accessed 12th January 2021]. Available from: https://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/triglycerides/art-20048186#:~:text=A%20simple%20blood%20test%20can,2.3%20to%205.6%20mmol%2FL.
66. Chalasani N, Abdelmalek MF, Loomba R, Kowdley KV, McCullough AJ, Dasarathy S, Neuschwander-Tetri BA, Terrault N, Ferguson B, Shringarpure R, Shapiro D, Sanyal AJ. Relationship between three commonly used non-invasive fibrosis biomarkers and improvement in fibrosis stage in patients with non-alcoholic steatohepatitis. Liver Int 2019;39(5):924-32. doi:10.1111/liv.13974