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Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis

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Conflict of interest: all the authors GL, RC, L NW, VG, GB, HV, NM, AL, EL, VR, SD, FP, PM declare no conflict of interest related to the present study.

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Abstract:

Background & Aims: Studies are needed to determine the long-term effects of bariatric surgery for patients with nonalcoholic steatohepatitis (NASH). We evaluated sequential liver biopsies, collected the time of bariatric surgery and 1 and 5 years later, to assess the long-term effects of bariatric surgery in patients with NASH.

Methods: We performed a prospective study of 180 severely obese patients with biopsy-proven NASH, defined by the NASH clinical research network histologic scores. The patients underwent bariatric surgery at a single center in France and were followed for 5 years. We obtained liver biopsies from 125 of 169 patients (76%) having reached 1 year and 64 of 94 patients (68%) having reached 5 years after surgery. The primary endpoint was the resolution of NASH without worsening of fibrosis at 5 years. Secondary endpoints were improvement in fibrosis (reduction of ≥ 1 stage) at 5 years and regression of fibrosis and NASH at 1 and 5 years.

Results: At 5 years after bariatric surgery, NASH was resolved, without worsening fibrosis, in biopsies from 84% of patients (n=64; 95% CI, 73.1–92.2). Fibrosis decreased, compared with baseline, in biopsies from 70.2% of patients (95% CI, 56.6–81.6). Fibrosis disappeared from biopsies from 56% of all patients (95% CI, 42.4–69.3) and from biopsies from 45.5% of patients with baseline bridging fibrosis. Persistence of NASH was associated with no decrease in fibrosis and less weight loss (reduction in body mass index of $6.3 \text{ kg/m}^2 \pm 4.1$ in patients with persistent NASH vs reduction of $13.4 \text{ kg/m}^2 \pm 7.4$; $P=.017$ with resolution of NASH). Resolution of NASH was observed at 1 year after bariatric surgery in biopsies from 84% of patients, with no significant recurrence between 1 and 5 years ($P=.17$). Fibrosis began to decrease by 1 year after surgery and continued to decrease until 5 years ($P<.001$).

Conclusions: In a long-term follow-up of patients with NASH who underwent bariatric surgery, we observed resolution of NASH in liver biopsies from 84% of patients 5 years later. The reduction of fibrosis is progressive, beginning during the first year and continuing through 5 years.

KEY WORDS: RYGB, gastric bypass, sleeve gastrectomy, gastric banding

Introduction

The global threat of obesity and the metabolic syndrome explain the growing public health burden of NAFLD worldwide. In the past 10 years, NAFLD has become the second cause of hepatocellular carcinoma and the third cause of decompensated cirrhosis on the transplant list in the USA ¹.

Non-alcoholic steatohepatitis (NASH) represents the severe and inflammatory phenotype of NAFLD and has the highest risk of disease-progression to cirrhosis ². Thus, experts recommend targeting therapeutic developments in NASH patients to reduce the risks of morbidity and mortality ³.

Sustained weight loss through lifestyle changes including diet and physical activity is the first step of therapeutic management according to international NASH guidelines ^{4,5}. Indeed, weight loss enhances liver and peripheral insulin sensitivity, reduces oxidative stress, and improves the lipid profile. Weight loss of at least 7 to 10% is necessary for the regression of NASH ^{6,7}. However, only 10% of patients reach this objective with lifestyle therapy at 1 year and less than half maintain the weight loss 5 years later ⁸.

Thus, there are an increasing number of clinical trials evaluating novel molecules that focus on the multiple pathways involved in the pathogenesis of NASH. However, despite positive results in phase II and III studies, for the moment, no drugs have been approved for this disease.

Parallel to pharmaceutical development, bariatric surgery is an attractive option in severely obese patients. Bariatric surgery induces long-term weight loss (15%–25%) and remission of diabetes while also reducing long-term mortality, cardiovascular events, and cancer ⁹⁻¹⁵. Bariatric surgery results in a significant short term improvement in steatosis which is closely connected with the progression of insulin resistance ¹⁶. Bariatric surgery induces the resolution of NASH in approximately 80% of cases at 1 year but the long-term impact is still

unclear because there are no large studies in NASH patients¹⁷. The only available long-term results come from studies in patients with mild NAFLD lesions showing a sustained decrease in liver fat and probable improvement in necro-inflammatory features¹⁸.

In addition to the resolution of NASH, medical agencies and expert panels consider a decrease in the extent of fibrosis to be a key endpoint for the reduction of liver mortality and morbidity³. The effect of bariatric surgery on the progression of fibrosis is a subject of debate. Indeed, the worsening of fibrosis is a major concern since a report on the development of cirrhosis 5 years after surgery in a historical study of ileojejunum bypass, a procedure that is no longer used¹⁹. More recently, a short-term decrease in fibrosis was observed in NASH patients¹⁷. Although the largest prospective cohort study of mild NAFLD patients reported a risk of the worsening of fibrosis at 5 years, this study is frequently misinterpreted¹⁸. First, the worsening of fibrosis at 5 years was slight and the fibrosis score of 95% of patients 5 years later was \leq F1. Also, most patients (more than 90%) did not have NASH. Obviously, the low percentage of extensive fibrosis at baseline in this study prevented the risk of significant worsening and the lack of baseline NASH makes it impossible to draw any firm conclusions. Thus, new long-term prospective data in a population of NASH patients with fibrosis are clearly needed.

Based on this, we performed a prospective study with long-term follow-up to analyze the evolution of NASH and fibrosis including consecutive liver biopsies at 1 and 5 years.

Methods

Outcomes

The primary outcome of our study was the resolution of NASH with no worsening of fibrosis 5 years after surgery. The secondary outcomes were: a) improvement in fibrosis (reduction of ≥ 1 stage) at 5 years, b) progression of NASH and fibrosis compared to baseline, at 1 and 5 years. Fibrosis stage 1a, 1b and 1c were considered to be stage 1 for the statistical analysis. Other secondary outcomes included changes from baseline to 5 years in serum aminotransferase, g-glutamyl transpeptidase, serum triglycerides, total cholesterol, fasting blood glucose concentrations, anthropometric measures (weight, body mass index). Insuline resistance (IR) was assessed with the quantitative insulin sensitivity check index (QUICKI) that was calculated as follows: QUICKI: $1/(\log \text{ fasting insulin})(\log \text{ fasting plasma glucose})$. The IR index is equal to $1/\text{QUICKI}$.

Patients

Between 1994 and June 2017, severely or morbidly obese patients were referred to our bariatric surgery unit for evaluation for bariatric surgery. Patients who fulfilled the following criteria for bariatric surgery were prospectively included in the Lille Bariatric Cohort on the day of the surgical procedure. Patients were: 1) 18 years or older at the time of evaluation and fulfilled the criteria for bariatric surgery according to French national guidelines; 2) had been morbidly (BMI >40) or severely obese (BMI >35) with at least one comorbidity factor (eg, arterial hypertension or diabetes mellitus) for at least 5 years and were resistant to medical treatment; 3) had no medical or psychological contraindications to bariatric surgery; 4) had French health insurance coverage; 5) did not drink excessively, defined as an average daily consumption of alcohol of 20 g/d for women and 30 g/d for men, and had no history of excessive drinking for a period longer than 2 years at any time in the past 20 years; 6) had no

history of long-term consumption of hepatotoxic drugs and; 7) screened negative for chronic liver disease.

In June 2017, the Lille Bariatric Cohort included 2616 patients. We excluded 11 patients for a history of excessive alcohol consumption before or after bariatric surgery, 2 who had hepatitis B and 64 other patients who did not have a baseline liver biopsy. Two of the excluded patients for past history of alcohol consumption died of alcoholic hepatitis or alcohol-related complications. Patients with potential confusing bias as hepatotoxin (i.e. tamoxifen use for breast cancer) did not performed follow-up liver biopsy. Among the cohort, 189 patients had a pathology-based NASH diagnosis and 9 patients were excluded from analysis due to the poor quality of the liver biopsy (sample size of < 6 portal triads or length < 8 mm). Thus, 180 patients with NASH were included and prospectively followed for 5 years after baseline (see flow chart in Figure 1).

Informed written consent was obtained from all patients and the study was performed in accordance with the Declaration of Helsinki. The ethics committee approved the cohort and was supported by grants by the government and the French Ministry of Health (PHRC). After legal revision, new approval was obtained in 2006 (no. CP06/49; NCT01129297).

Surgical procedures

The indication for bariatric surgery was confirmed after an extensive preoperative multidisciplinary evaluation according to current French guidelines. All patients followed a nutritional program before surgery. This program began with a multidisciplinary evaluation (nutritionist, psychologist, dietician and therapeutic education nurse) to adapt pre-operative care according to patient profile. In addition, all patients were required to undergo outpatient follow-up and to participate in a therapeutic education program for a period of 6 to 12 months before surgery. At the end of this program, a multidisciplinary evaluation was again carried out to validate and schedule the surgery.

The type of surgery was then chosen by the patient after s/he received comprehensive information about the various available surgical procedures, their specific risks and expected results. From 1994 to 2001, only biliointestinal bypass and gastric banding were proposed. After 2001, gastric bypass was performed. Starting in 2004, biliointestinal bypass was no longer performed and was replaced by gastric bypass. The second bariatric procedure included an adjustable gastric band inserted by laparoscopy (Lap-Band System; INAMED Health, Santa Barbara, CA, USA). The third procedure was Roux-en-Y gastric bypass, which involved partitioning the upper stomach to create a small gastric pouch, and gastrojejunostomy to re-establish gastrointestinal continuity. The final procedure consisted of sleeve gastrectomy and has been performed since 2006. Over the study period, the rate of gastric bypass was stable. One year after the introduction of sleeve gastrectomy, the use of gastric banding was gradually replaced and reduced from 33% to 10% of the surgical procedures while sleeve gastrectomy increased from 5% to 17%.

Histological analysis

Liver biopsies were systematically planned during the surgical procedure and were performed in 2552 cases (97.6%), but not in 64 cases for miscellaneous reasons. A histological assessment was planned approximately 1 year and 5 years after surgery. To avoid artifacts related to prolonged exposure of the liver, liver needle biopsy was performed during the first part of the surgical procedure after trocar insertion and abdominal exploration, within 10 minutes after pneumo-peritoneum installation. The Hepafix needle biopsy system was used until 2010 and the MONOPTY needle biopsy system (16G, ref: 121620; C. R. Bard, Tempe AZ, USA) thereafter. Biopsies were routinely stained with H&E saffron, red Sirius, and Perl's staining. Steatosis was quantified by the percentage of hepatocytes containing fat droplets (amount of steatosis). The pathologists (E.L., V.G., B.B. and D.B.) first diagnosed NASH,

then determined the NAS and graded the severity of necroinflammatory activity using the Brunt score^{20,21} which is defined by a 3-step scale: mild (grade 1), moderate (grade 2) and severe (grade 3). The NAS score, defined as the unweighted sum of scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2), ranging from 0 to 8, was also evaluated for the histological follow-up of NASH after bariatric surgery^{22,23}. As the Brunt and NAS scores were developed and published in 1999 and in 2005, respectively, all liver biopsies performed before 2005 were reviewed and graded retrospectively^{17,18}. After 2005, all biopsies were graded prospectively with these 2 scores, and results were standardized in a report. Pathologists were blinded to clinical and biological data. Liver fibrosis was assessed semi-quantitatively using the Kleiner fibrosis score (defined as follows: F0, normal; F1 stage is divided into 3 subclasses: 1a, mild pericellular fibrosis in zone 3, 1b, moderate pericellular fibrosis in zone 3, and 1c, portal fibrosis; F2, perivenular and pericellular fibrosis confined to zones 2 and 3, with or without portal or periportal fibrosis; F3, bridging or extensive fibrosis with architectural distortion and no clear-cut cirrhosis; and F4, cirrhosis)²³. For inclusion in the histological analysis of consecutive liver biopsies, liver samples had to be at least 8 mm long or contain at least 6 portal triads.

Statistical Analysis

Continuous variables are expressed as means \pm SD in case of normal distributions, or medians (interquartile range [IQR]) otherwise. Normality was examined using histograms and the Shapiro-Wilk test. Ordinal (semi-quantitative scores) and non-ordinal categorical variables were expressed as numbers (percentage). The semi-quantitative NAS score ranging from 0 to 8 was also described using medians (IQR). Patient characteristics before bariatric surgery (baseline) were described according to the presence of bridging fibrosis (Brunt/Kleiner F3) or cirrhosis (F4) without statistical comparisons. We studied within-patient

changes in metabolic, biological, and histologic parameters (all continuous or ordinal variables) from baseline to 5 years, from baseline to 1 year and from 1 to 5 years after bariatric surgery using the Wilcoxon signed rank tests for ordinal variables or continuous variables when the change was not normal, or using the paired Student-t test otherwise. We calculated the rate (with a 95% confidence interval [CI]) of improvement, defined as a decrease ≥ 1 point (grade) compared to the baseline value for each semi-quantitative score. We compared the rate of disappearance of NASH between patients with mild vs moderate or severe NASH at baseline using the Fisher's exact test. The exploratory analysis compared the baseline characteristics (BMI, biological and histologic parameters) of patients with persistent and non-persistent NASH 5 years after surgery using the Mann-Whitney U test for ordinal variables and continuous variables with a non-normal distribution, or the Student t-test otherwise. The 5-year changes in BMI, in NAS and the progression of fibrosis were compared using an analysis of covariance adjusted for baseline values. Statistical testing was performed at the 2-tailed a level of .05. Data were analyzed using NCSS 9 software (Kaysville, UT, USA).

Results

Cohort subjects

A total of 180 of the patients enrolled in the Lille bariatric cohort at analysis presented with liver biopsy-proven NASH at surgery (figure 1). This NASH cohort mainly included women, mean age 46.7 years old, with a median fibrosis score of 2 (IQR, 1-3). Patient characteristics are shown in Table 1. The main surgical procedure was gastric bypass (66.1%) (supplementary table 4).

During the 5-year follow-up, 3 patients died from non-liver related causes including 2 deaths from surgical complications within the first month after surgery and 1 from cardiac dysfunction 4 years after surgery.

A histological evaluation was performed in 74% (125/169) of patients at the 1-year follow-up and 68% (64 out of 94) at the 5-year follow-up. The main reason the histological evaluation was not available in most cases was biopsy refusal (Figure 1). Patients without liver biopsy after bariatric surgery were not significantly different from those with a histological follow-up except for a lower BMI at 1 year (supplementary Tables 1-3). Baseline fibrosis did not influence the probability of undergoing histological reevaluation at 5 years (66% in F3/F4 patients vs. 70% in F0-F2 patients, $p=.65$).

Primary Outcome: Resolution of NASH without worsening of fibrosis from baseline to 5 years

The resolution of NASH with no worsening of fibrosis occurred in 84.4 % ($n=64$, 95% IC: 73.1-92.2) of cases 5 years after bariatric surgery ($p<.001$) (Figure 2). Improvement was observed in all the histological components of NASH (Table 2). The NAS decreased from a median of 5 (IQR, 4-5) to 1 (IQR, 0-2), $p<.001$. The NAS improved by at least 2 points in 90.6% ($n=64$, 95% CI: 80.7.2-96.5) of patients. Hepatocellular ballooning improved in 87.5%

(n=64, 95% CI: 76.8-94.4) and lobular inflammation in 59.4% (n=64, 95% CI: 46.4-71.5) of cases. Resolution of NASH at 5 years was not influenced by the baseline severity of NASH (84% in moderate and severe vs. 85% in mild NASH, p=.9) or fibrosis (83.3% in F3-F4 vs. 86.3 % in <F3, p=.9).

Five years after surgery, the BMI was reduced by 5% or less in 11.3% of patients, by between 5 and 10% in 27.4% of patients and by more than 10% in 61.3% . The extent of weight loss influenced the rate of resolution of NASH without the worsening of fibrosis at 5 years (primary outcome) (Graph abstract figure). The median BMI loss in the cohort was 12 kg/m² which was significantly associated with NASH resolution without the worsening of fibrosis at 5 years. Indeed, patients with a BMI loss ≥ 12 kg/m² had a higher probability of achieving the primary endpoint than those with BMI loss < 12 kg/m²: 93 vs. 73%, p<.0001.

In a subgroup analysis comparing gastric banding to gastric bypass, gastric bypass was significantly more effective in achieving the primary endpoint p=.03. (comparison detailed in supplementary files: Tables 8 & 9)

Secondary outcomes

Evolution of fibrosis at 5 years

Fibrosis improved at 5 years in 70.2% (n=57, 95% CI: 56.6-81.6) of the patients with baseline fibrosis (\geq F1). The median fibrosis score decreased from a baseline of 1.5 (IQR, 1-3) to 0 (IQR, 0-1) at 5 years, p<.001 (Table 2.). Detailed data on the regression of fibrosis are provided in Table 2 and Figure 3. Moreover, 68.2% (n=22, 95% CI: 45.1-86.1) of patients with \geq F3 fibrosis at baseline had <F3 fibrosis at 5 years.

The disappearance of fibrosis (defined as F0 score) in patients with baseline fibrosis (F \geq 1) was observed in 56.1% (n=57, 95% CI: 42.4-69.3) of patients at 5 years. Patients with a

fibrosis score \leq F3 at baseline were more likely to present with the disappearance of fibrosis than those with F3-F4 at baseline: 62.9% (n=35, 95% CI: 44.9-78.5) vs. 45.5% (n=22, 95% CI: 24.4-67.8) (p=.07), respectively. Details of the evolution of fibrosis according to baseline fibrosis (F0 to F4) are provided in Table 3.

We performed a supplementary analysis to study the progression of the non-invasive (APRI) score from baseline to 5 years in a larger population (n=86/94, 91% of the cohort at 5 years). Our analysis showed that the APRI score was significantly reduced from baseline to 5 years and improved from 0.28 [0.20-0.43] to 0.17 [0.13-0.26] p<.001 (n=86). Furthermore, patients without resolution of NASH had higher APRI scores than those without NASH: APRI 0.35 [0.17-0.63] vs. 0.16 [0.12-0.22] p=.014.”

Evolution according to the resolution or persistence of NASH at 5 years

Patients with persistent NASH and/or a worsening of fibrosis had a less favourable response to bariatric surgery with less weight loss after adjustment for baseline BMI than those without NASH (BMI: $-6.3 \text{ kg/m}^2 \pm 4.1$ vs. $-13.4 \text{ kg/m}^2 \pm 7.4$, p=.017, respectively) and thus a higher BMI at 5 years ($40.9 \text{ kg/m}^2 \pm 10.7$ vs. $35.3 \text{ kg/m}^2 \pm 7.1$ p=.03, respectively) (Table 4.). Patients with persistent NASH had more severe histological lesions at 5 years than those without NASH: median fibrosis 2 (IQR, 1.3-3) vs. 0 (IQR, 0-1), p<.001, median NAS 4 (IQR, 3.5-5.5) vs. 1 (IQR, 0-2), p<0.001 and steatosis 60% (IQR, 30-75) vs. 5% (IQR, 1-20), p<.001, respectively (Table 4.).

The disappearance of NASH alone, without taking into consideration the worsening of fibrosis, was associated with an improvement in fibrosis: - 1 (IQR, 0; -2) vs. 0 (IQR, 0; 2), p=.019) (adjusted with baseline fibrosis).

Patients with persistent NASH had more biological abnormalities: AST 43 IU/L [33-63] vs. 20 IU/L (IQR, 17-24), ALT 46 IU/L (IQR, 33-52) vs. 18 IU/L (IQR, 17-25) and γ GT

72 IU/L (IQR,25-146) vs. 18 IU/L (IQR, 12-28) ($p < 0.01$ for all), insulin resistance (1/QUICKI) 3.5 (IQR, 3.1-4.1) vs. 2.9 (IQR, 2.7-3.1) $p = .01$ (Table 4).

Evolution of histological features during the 5 years of follow-up.

One year after surgery, NASH resolved in 84% ($n = 125$, 95% CI: 76.4-89.9) of cases, ($n = 125$, $p < .001$). The Brunt necroinflammation severity scale improved (supplementary Table 5) ($p < .001$). Median fibrosis was significantly reduced: 2 (IQR, 1-3) vs. 1 (IQR, 0-2), $p < .001$. All the histological features of NASH improved including hepatocellular ballooning, lobular inflammation and steatosis (as shown in supplementary Table 5 and supplementary Figure 1).

There was no difference in the resolution of NASH ($p = .17$) between the 1- and 5-year follow-up (see Supplementary Figure 1).

Unlike the necroinflammatory process, fibrosis continued to improve between the 1- and 5-year follow-up ($p < .001$) with a decrease that began at 1 year ($p < .001$) (supplementary Tables 5 and 6).

Evolution of clinical and biological features during the 5 years of follow-up

Clinical and biological parameters except for total bilirubin, albumin, LDL cholesterol, prothrombin time and platelets improved within the first year. These improvements were maintained at the 5-year follow-up (Table 2. and supplementary tables 5, 6). The degree of weight loss influenced the metabolic response after surgery. A BMI loss of more than 10% was associated with greater improvement in the metabolic outcome. (Supplementary Table 7). Weight regain is a main issue after bariatric surgery. However, the

small sample size of our cohort made it impossible to analyze its impact on the persistence of NASH at 5 years.

Discussion

In this long-term prospective study with consecutive liver biopsies, bariatric surgery was shown to induce the resolution of NASH without worsening of fibrosis in 84% of patients at 5 years. Long-term resolution of NASH led to the regression of fibrosis in 70% of cases. The resolution of NASH occurred within the first year and was maintained over the 5-year period, while fibrosis began to improve within 1 year and continued throughout the 5-year follow-up.

With a 80% success rate for the resolution of NASH without worsening of fibrosis, bariatric surgery could be considered as a therapeutic option for morbidly obese patients. Most patients improved within 1 year after treatment. Very few recurrences were observed between 1 and 5 years. An absolute change in liver fat content, lobular inflammation and hepatocellular ballooning was observed in most cases as well as a decrease of 2 points or more in the NAS score. The long-term benefits, suggest the notion of disease remission. NASH remission should be considered in relation to the remission of diabetes and the metabolic syndrome which have already been described after bariatric surgery. Thus, effects of bariatric surgery go beyond NASH and provide a global metabolic benefit. As shown for refractory diabetes, bariatric surgery should be evaluated in NASH patients with mild obesity (BMI <35 kg/m²) and advanced fibrosis.

Fibrosis is the most reliable predictor of liver related mortality. Its improvement is an important endpoint (recommended by FDA) in clinical trials³. In our study, improvement of fibrosis (70% of cases at 5 years) was gradual and regular, beginning in the first year and continuing throughout the 5 years of follow-up. In patients with baseline bridging fibrosis (\geq F3), fibrosis improved and even disappeared at 5 years in 68% and 45% of cases, respectively. The pathophysiological mechanism of fibrolysis continues long after suppression of the necro-inflammatory process. Such phenomenon has also been described

after viral suppression in hepatitis B and C. These data support the notion that bariatric surgery could reduce liver related mortality. Broad cohort studies are still required to evaluate survival and to clarify the causes of worsening fibrosis especially in patients with baseline F3/F4 fibrosis.

Twenty percent of patients were non-responders to surgery and had persistent NASH at 5 years. NASH was already present in most of them at 1 year, suggesting that the persistent disease at 5 years was more likely due to an early phenomenon rather than recurrent disease during follow-up. Low weight loss and less improvement in insulin resistance were associated with failing to reach the primary endpoint. Identifying predictive factors of success/failure as early as possible seems necessary to propose alternative therapeutic strategies. Concerning the choice of surgical procedures, no recommendations can be given as the study was not planned to compare their efficacy (sample size and the study design were not adapted). This question is still a main issue and requires further studies.

Long term data on the histological effects of medical or surgical treatment on NASH are lacking. The prospective design of our study with sequential liver biopsies limits bias. Moreover, although a certain number of patients did not have biopsies the absence of significant differences between patients with or without liver biopsy strongly supports the hypothesis that biopsy refusal did not result in bias. Secondly, 68% of patients had available liver biopsies, a high rate compared to previous studies showing the long term regression of fibrosis in patients treated for HBV ²⁴. In addition, the identical histological results observed at 1 year in the present study and those in our previous study in a smaller cohort suggest that our data are robust ¹⁷.

Prevalence of NASH varies widely among studies, and our prevalence may seem to be low ^{25, 26}. It is possible that biopsies may have been mainly performed in patients with suspected liver injury in some studies without a systematic liver biopsy protocol. Finally, our

selection process may have decreased the prevalence of NASH at bariatric surgery because patients have been required to follow a strict nutritional medical program since 2006. Exclusion of patients who did not complete the program could have influenced the prevalence of NASH.

Furthermore, the length of the liver biopsy could be considered a limitation because certain experts recommend a length of 2-3 cm. However, we used a conservative approach to biopsies and requested that they be at least 8 mm long, which is longer than the minimal length proposed by expert guidelines. Needle biopsy was used to ensure good quality liver biopsies thus avoiding the risk of inflammation associated with wedge biopsy. Thus, although the length of liver biopsy may not be optimal and might be considered a limitation to the study, the quality of liver biopsy was correct. Regarding noninvasive assessment of fibrosis, results with the APRI score must be analyzed by considering its limits. Only future studies with an adapted study design could confirm or not the interest of this test in this setting. Up to now, liver biopsy remains the only validated method to assess fibrosis evolution after bariatric surgery.

The benefits of bariatric surgery on liver histology must be weighed against the risk and safety of surgery. Our study did not have the power and was not designed to perform a safety analysis, and these studies are urgently needed. Thus, bariatric surgery cannot be considered first line therapy due to the surgical risk¹⁰. It explains the differences between American and European guidelines on NAFLD^{4,5}, with the former considering the data to be too premature to recommend bariatric surgery, whereas the latter suggest that it can be proposed to highly selected patients.

In conclusion, this prospective 5-year follow-up of obese NASH patients showed that the beneficial effects of bariatric surgery on the resolution of NASH were durable and led to a sustained reduction in fibrosis over five years.

Figures legends:

Graphical abstract

A. Evolution of NASH 5 years after bariatric surgery according to BMI loss. The numerical data have been provided but the statistical analysis was not performed on the 3 categories due to the limited sample size because 2 of cells in the 2 x 2 table had less than 5 cases. Thus, we combined BMI loss in the 0-5 & 5-10 kg/m² groups into 1 group and performed a Chi square test by comparing BMI ≤10 kg/m² (i.e. group 0-5 & group 5-10 kg/m²) to BMI loss > 10 kg/m². (Fisher's exact test p=.03).

B. Histogram representing the fibrosis distribution according to Brunt Fibrosis score at baseline, 1 year, and 5 years. (Are represented only patients with available biopsies at each time points.) Statistical analysis: Paired Wilcoxon sign rank test.

C. Upper panel (A) Evolution of NASH and Nafld features, H&E (Hematoxylin and Eosin) staining (x 400).A.1. liver biopsy at baseline; A.2. liver biopsy at 1 year after surgery; A.3. liver biopsy at 5 years after surgery.

Lower panel (B), evolution of fibrosis, SR (sirius red) staining (x 25). B.1 liver biopsy at baseline, B.2. liver biopsy at 1 year after biopsy; B.3. liver biopsy at 5 years.

Figure 1.

Title: Flow Chart study

Figure 2.

Title: Resolution of NASH without worsening of fibrosis, 5 years after bariatric surgery.

Histogram shows the rate of NASH resolution without worsening of fibrosis, 5 years after bariatric surgery. (N=64 patients). Paired biopsy analysis. Statistical analysis: Paired Wilcoxon sign rank test. Diagnosis and resolution of NASH was defined by the pathologist.

Figure 3

Title: Evolution of fibrosis after surgery

A. **Evolution of fibrosis after surgery:** Histogram representing the fibrosis distribution according to Brunt Fibrosis score at baseline, 1 year, and 5 years. (Are represented only patients with available biopsies at each time points.) Statistical analysis: Paired Wilcoxon sign rank test

B. Resolution of fibrosis after surgery: Histogram representing the rate of fibrosis resolution at 5 years. Fibrosis resolution is defined by a F0 fibrosis score of Brunt scale on liver histology at 5 years.

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Lille bariatric cohort
2616 patients treated between 1994 and June 2017
Followed prospectively

11 Patients excluded for history of alcohol consumption (>30g/day for men and 20g/day for women)

64/2616 (2.4%) Patients without liver biopsy at baseline

2 patients excluded for HBV

2350 patients without biopsy proven NASH

189 patients with NASH

9 patients excluded due to insufficient sample size of liver biopsy

180 patients biopsy-proven NASH at time of surgery

- 2 patients died of surgical complications
- 2 gastric banding ablation due to incoercible vomiting
- 1 patient followed in another center
- 3 patients were lost of follow-up

3 patients did not reach 1 year follow-up at time of analysis

125/169 (74%) patients with liver biopsy at 1 year
44*/169 without liver biopsy.

- 1 patient died of cardiac decompensation before 5 years evaluation.
- 1 gastric band ablation after band migration
- 1 patient with follow-up in another medical center
- 6 patients were lost of follow-up

66 patients did not reach 5 years follow-up at time of analysis

64/94 (68%) patients with liver biopsy at 5 years
30**/94 patients without liver biopsy.

***patients without liver biopsy at 1 year:**

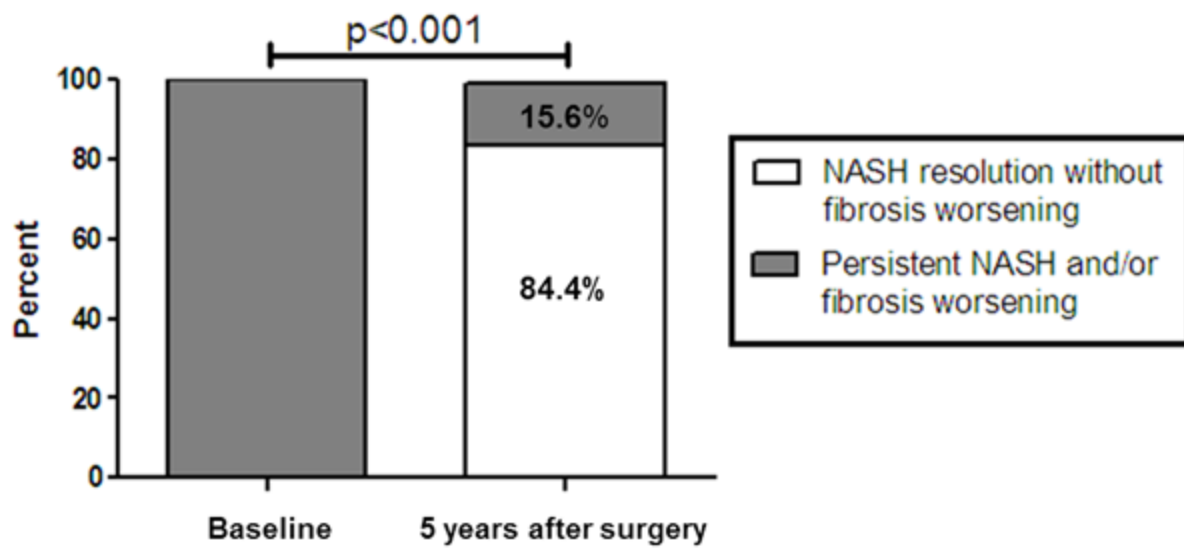
- 29 refused liver biopsy
- 8 medical contra-indications(#)
- 2 estimated unnecessary by practitioner
- 1 forgotten to be schedule by practitioner
- 4 miscellaneous reasons

****patients without liver biopsy at 5 years:**

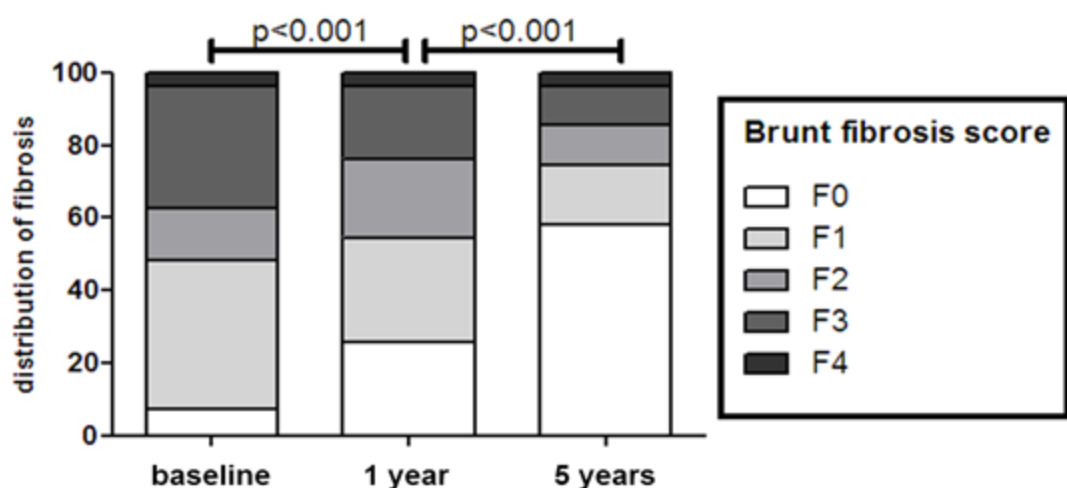
- 11 medical contra-indication (§)
- 19 patients refused liver biopsy

2 pregnancy, 1 psychiatric decompensation, 1 antiplatelets treatment, 2 surgical complications, 1 cancer, 1 gastric ulcer.
§ 1 pulmonary embolism, 1 cardiac decompensation, 1 myocardial infarction, 1 psychiatric decompensation, 3 surgical, 3 anticoagulation therapy, 1 breast cancer.

Primary Outcome



A Evolution of fibrosis after surgery



B Resolution of fibrosis at 5

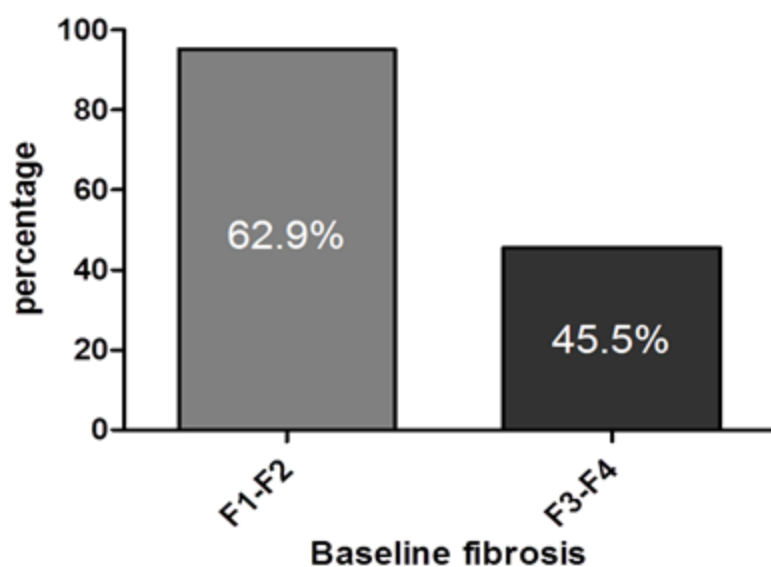


Table 1. Characteristics of the cohort

Characteristics	Fibrosis (Kleiner)			
	Overall (180)	<F3 (n=118)**	≥F3 (n=58)**	F4 (n=9)
Women, n (%)	116 (66)	77 (65)	39 (67)	6 (66)
Age, y, mean ± SD	46.7 ± 10.6	46.1 ± 10.5	47.5 ± 10.8	50.9 ± 5.8
BMI, kg/m ² , mean ± SD	48.1 ± 7.9	48.2 ± 7.7	48.3 ± 6.9	46 ± 6.5
BMI at age, kg/m ² , of 20	29.5 ± 7.4	30.1 ± 8.3	29 ± 6.6	29.6 ± 4.4
Diabetes, n (%)	128 (71)	77 (65)	48 (83)	7 (78)
Arterial Hypertension, n (%)	137 (76)	87 (74)	47 (81)	6 (66)
Biological features				
HDL cholesterol, mmol/L, median (IQR)	1.1 [0.9-1.2]	1.0 [0.9-1.3]	1.1 [0.9-1.2]	1.0 [0.8-1.2]
LDL cholesterol, mmol/L, median (IQR)	3 [2.2-3.4]	3 [2.4-3.4]	2.8 [2.1-3.7]	2.8 [1.3-4.1]
Triglycerides, mmol/L median (IQR)	1.8 [1.3-2.5]	1.8 [1.3-2.4]	1.8 [1.3-2.6]	2 [1.2-2.6]
Total cholesterol, mmol/L, median (IQR)	5 [4.2-5.6]	5 [4.3-5.5]	4.6 [4.2-5.8]	4.8 [3.2-6.2]
AST, IU/L, median (IQR)	36 [28-49]	34 [27-41]	49 [32-61]	49 [33-62]
ALT, IU/L, median (IQR)	45 [33-62]	42 [32-56]	51 [36-68]	45 [34-58]
GGT, IU/L, median (IQR)	56 [39-96]	50 [34-76]	82 [37-135]	106 [50-170]
bilirubin, mg/dL, median (IQR)	4 [3-6]	4 [3-6]	4.9 [3.7-6]	4.5 [3.7-6.5]
Fasting glucose, mg/dL, median (IQR)	136[102-191]	124[100-178]	152[112-221]	167[124-213]
Insulin resistance index*, median (IQR)	3.5 [3.3-3.7]	3.4 [3.2-3.6]	3.6 [3.4-3.9]	3.7 [3.3-4.0]
HBA1c (%), median (IQR)	7.3 [6-8.9]	6.9 [5.9-8.9]	7.7 [6.3-8.9]	7.9 [6.5-8.6]
Albumin, g/L, mean ± SD	42.8 ± 2.9	43 ± 2.9	42 ± 2.9	41.6 ± 1.8
Platelets, G/L, mean ± SD	258 ± 63	253 ± 60	252 ± 71	218 ± 62
PT, %, mean ± SD	96 ± 5.5	97 ± 5.4	94 ± 5.6	96.5 ± 5.4
Histological features				
biopsy length, mm, median (IQR)	14 [10-16]	14 [10-17]	13.5 [10-15]	13.5 [10-17]
portal triads, median (IQR)	9 [7-10]	9 [7-10]	9 [7-11]	7 [6-8]
NAS score, mean ± SD	5 [4-5]	5 [4-5]	5 [4.8-6]	5 [4.5-6]
Steatosis, %, median (IQR)	60 [40-75]	60 [40-75]	60 [39-80]	50 [30-75]
Steatosis > 60% (%)	102 (56.7%)	68 (58)	32 (55)	4 (44)
Brunt, n (%)				
1	121 (67)	93 (79)	26 (45)	1 (11)
2	46 (26)	23 (19)	21 (36)	5 (56)
3	13 (7)	2 (2)	11 (19)	3 (33)
Ballooning, n (%)				
0	4 (2.2)			
1	114 (63.3)			
2	62 (34.5)			
Lobular inflammation, n (%)				
0	9 (5)			
1	119 (66.1)			
2	48 (26.7)			
3	4 (2.2)			
Fibrosis (Kleiner), **n (%)				
0	30 (17)			
1a/1b/1c/1 [total]	22/15/14/2 [53] (30)			
2	35 (20)			
3	49 (28)			
4	9 (5)			

*: insulin resistance was obtained with the formula (1/QUICKI)

** : 4 liver biopsies had insufficient quality to properly quantify fibrosis.

Table 2. Evolution of clinical, biological and histological features between baseline and 5 years after bariatric surgery

Characteristics	Paired values analysis		
	Before surgery	5 Year after surgery	P value
BMI, kg/m², mean ± SD	48.1 ± 6.9	36.1 ± 7.8	<.001
Biological characteristics			
HDL cholesterol, <i>mmol/L</i> , mean ± SD	1.1 [0.9-1.3]	1.3 [1.2-1.5]	<.001 ^a
LDL cholesterol, <i>mmol/L</i> , mean ± SD	2.7 [2.2-3.4]	2.8 [2.4-3.4]	.36 ^a
Triglycerides, <i>mmol/L</i> median (IQR)	1.6 [1.3-2.4]	1.1 [0.7-1.6]	<.001 ^b
Total cholesterol, <i>mmol/L</i> , median (IQR)	4.9 [4.1-5.4]	4.6 [4.1-5.3]	.64 ^b
AST, <i>IU/L</i> , median (IQR)	36 [27-50]	21 [18-26]	<.001 ^b
ALT, <i>IU/L</i> , median (IQR)	47 [36-65]	19 [13-30]	<.001 ^b
GGT, <i>IU/L</i> , median (IQR)	50 [38-77]	20 [13-39]	<.001 ^b
bilirubin, <i>mg/dL</i> , median(IQR)	0.5 [0.4-0.6]	0.5 [0.4-0.6]	.86 ^b
Fasting blood glucose, <i>mg/dL</i> , median (IQR)	132 [92-192]	105 [89-123]	<.001 ^b
Insulin resistance Index, median (IQR)*	3.4 [3.3-3.6]	2.9 [2.7-3.1]	<.001 ^b
HbA1c, median (IQR)	7.5 [6-8.8]	5.9 [5.5-6.5]	<.001 ^b
Albumin, <i>g/L</i> , mean ± SD	42.9 ± 2.7	42.5 ± 3.6	.41 ^a
Platelets, <i>G/L</i> , mean ± SD	249 ± 63	241 ± 57	.19 ^a
PT,%, mean ± SD	95.8 ± 6.0	95.1 ± 6.6	.37 ^a
Histologic characteristics			
Steatosis, median(IQR)	60 [50-74]	6 (1-20)	<.001 ^b
Brunt, n(%)			<.001 ^b
0	0	58	
1	43	3	
2	15	2	
3	6	1	
Ballooning, *n (%)			<.001 ^b
0	3	55	
1	36	6	
2	25	3	
Lobular inflammation, *n (%)			<.001 ^b
0	5	38	
1	45	23	
2	13	3	
3	1	0	
Fibrosis (Kleiner), *n (%)			.001 ^b
0	7	39	
1a/1b/1c/1 [total]	12/5/7/1 [25]	3/2/5 [10]	
2	10	6	
3	19	7	
4	3	2	

HDL, high-density lipoprotein; LDL, low-density lipoprotein. AST aspartate aminotransferase, ALT alanine aminotransferase, GGT Gamma-glutamyl transpeptidase. BMI body mass index, HbA1c : glycated hemoglobin.

^a Paired Student t test. ^b Wilcoxon signed rank test.

Paired histologic characteristics could be evaluated for 64 patients between baseline and 5 year after surgery.

Insulin resistance index was obtained with the formula (1/QUICKI index)

Table 3. Evolution of Fibrosis from baseline to 5 years after bariatric surgery.

Brunt fibrosis score at baseline	Brunt fibrosis score, 5 years after bariatric surgery.					Total
	0	1	2	3	4	
0	7	0	0	0	0	7
1	14	6	3	2	0	25
2	8	1	1	0	0	10
3	10	3	2	3	1	19
4	0	0	0	2	1	3
Total	39	10	6	7	2	64

Table 4. Comparison of patients with resolution of NASH without worsening of fibrosis (meeting primary outcome) to those with persistent NASH and/or worsening of fibrosis at 5 years

Characteristics of patients at 5 years	Resolution of NASH Without worsening of fibrosis	Persistence of NASH And/or worsening of fibrosis	P value
Baseline BMI kg/m ² , mean ± SD	49.3 ± 7.0	47.7 ± 7.9	.86
BMI at 5 years, kg/m ² , mean ± SD	35.3 ± 7.1	40.9 ± 10.7	.028 ^a
Evolution of BMI, mean ± SD	-13.4 ± 7.4	- 6.3 ± 4.1	.017 ^a
Histological characteristics			
Brunt Fibrosis score, median [IQR]	0 [0-1]	2 [2-3]	<.001 ^b
Brunt fibrosis evolution, median [IQR]	-1 [0; -2]	1 [0-1.3]	.003 ^b
NAS, median [IQR]	1 [0-2]	4 [3.5-5.5]	<.001 ^b
NAS evolution, median [IQR]	-4 [-5; -2]	0 [-2; 0]	.005 ^b
steatosis, %, median [IQR]	5 [1-10]	60 [30-75]	<.001 ^b
Biological characteristics			
Fasting glucose mg/dL, median [IQR]	104 [89-117]	128 [85-165]	.17 ^b
HbA1c, % median [IQR]	5.8 [5.5-6.4]	6.8 [5.5-7.5]	.21 ^b
Insulin resistance index, median [IQR]	2.9 [2.7-3.1]	3.5 [3.1-4.1]	.001 ^b
AST; IU/L, median [IQR]	20 [17-24]	43 [33-63]	<.001 ^b
ALT IU/L, median [IQR]	18 [17-25]	46 [33-52]	.010 ^b
GGT IU/L, median [IQR]	18 [12-28]	72 [25-146]	<.001 ^b
Total Bilirubin md/dL, median [IQR]	0.5 [0.4-0.5]	0.7 [0.4-1]	.10 ^b
LDL cholesterol mmol/L median [IQR]	2.7 [2.4-3.2]	3.3 [2.2-5.0]	.46 ^b
HDL cholesterol mmol/L median [IQR]	1.4 [1.2-1.5]	1.3 [1.0-1.6]	.58 ^b
Triglycerides mmol/L median [IQR]	1 [0.7-1.6]	1.6 [1.3-2.2]	.037 ^b
Albumin, g/L, mean ± SD	42 ± 3	44 ± 4	.51 ^a
Platelets, G/L, mean ± SD	248 ± 51	233 ± 76	.48 ^a
PT, %, mean ± SD	96 ± 7	90 ± 12	.12 ^a

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

AST aspartate aminotransferase, ALT alanine aminotransferase,

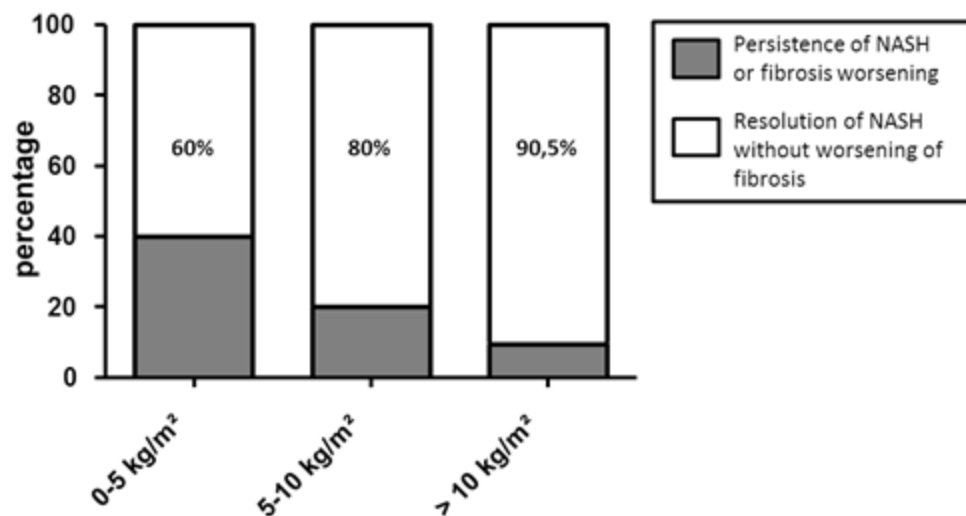
GGT Gamma-glutamyl transpeptidase. BMI body mass index,

HbA1c : glycated hemoglobin, PT, Prothrombin Time.

^a Paired Student t test.

^b Wilcoxon signed rank test.

NASH resolution according to weight loss



Fibrosis evolution after surgery

