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Bariatric surgery is associated with reduction in non-alcoholic steatohepatitis and hepatocellular carcinoma: A propensity matched analysis

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ABSTRACT

Introduction: Obesity is a risk factor for non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). Bariatric surgery can provide durable weight-loss, but little is known about the later development of NASH and HCC after surgery.

Methods: Bariatric surgery (n = 3,410) and obese controls (n = 46,873) from an institutional data repository were propensity score matched 1:1 by demographics, comorbidities, BMI, and socioeconomic factors. Comparisons were made through paired univariate analysis and conditional logistic regression.

Results: Total of 4,112 patients were well matched with no significant baseline differences except initial BMI (49.0 vs 48.2, $p = 0.04$). Bariatric group demonstrated fewer new-onset NASH (6 0.0% vs 10.3%, $p < 0.0001$) and HCC (0.05% vs 0.34%, $p = 0.03$) over a median follow-up of 7.1 years. After risk-adjustment, bariatric surgery was independently associated with reduced development of NASH (OR 0.52, $p < 0.0001$).

Conclusions: Bariatric surgery is associated with reduced incidence of NASH and HCC in this large propensity matched cohort. This further supports the use of bariatric surgery for morbidly obese patients to ameliorate NASH cirrhosis and development of HCC.

Introduction

Incidences of non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC) are increasing throughout the United States.[1,2] A large contributing factor may be the rise of obese adults, as this trend is increasingly affecting adolescents, as well. The progression of NASH from non-alcoholic fatty liver disease (NAFLD) occurs in approximately 10–25% of patients[3] and can lead to significant risks in liver-related mortality due to the development of hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). It is projected that more than 10% weight loss is needed in order to improve NASH,[4] however, weight loss modification through lifestyle changes alone account for only 3–5% total body weight loss on average and does not provide durable weight loss over time.[5] Two first-line medications (Vitamin E and pioglitazone) have been used to augment this effect,[6] however there are concerns due their association with other cancers and morality risk, also in their lack of improving hepatic fibrosis.[7] Additionally, the effectiveness of these medications was only studied in non-diabetic patients which leaves limited options for the greater proportion of obese patients that are also diabetic.

Bariatric surgery has shown to provide sustained weight loss throughout the course of a patient's lifetime,[8] and most patients who are candidates for bariatric surgery have some degree of NAFLD.[6] Previous studies have shown that bariatric surgery not only improves steatosis in NASH, but may also improve hepatic fibrosis even in patients who may have other metabolic diseases including diabetes mellitus type II (DM2).[5,7,9,10] However, this was not a consistent finding since a few studies also showed worsening hepatic fibrosis over time.[5,7,9–11] It is due to this concern that despite guidelines suggesting the benefit of bariatric surgery in reducing the progression to NASH, there is still no definitive recommendation on its routine use.[6,11] This may, in part, have contributed to the overall decrease in the number of bariatric

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surgery procedures performed in patients with NAFLD from 2004-2012.[12] Clearly more evidence is needed to further understand this association.

There is a lack of case-controlled studies in the literature highlighting the effect of bariatric surgery on NASH[5,7] and the few studies on bariatric surgery and HCC only analyzed its prevalence in a bariatric population and did not address the development of new HCC after bariatric surgery.[13,14] Most studies also have relatively short follow up times as little as one month to only five years.[5,14] We hypothesized that performing case-matching through propensity score analysis of all patients who received bariatric surgery with long-term follow up will be able to better elucidate the risk of developing NASH and HCC after bariatric surgery.

Materials and methods

Patients

All adult patients who underwent bariatric surgery (including RYGB, sleeve gastrectomy, and adjustable gastric banding) for morbid obesity ($n = 3,410$) at a single academic institution between 1985 and 2015 were identified retrospectively from a prospectively maintained database.[15] To identify an appropriate control group, an institutional clinical data repository (CDR) of all routine outpatient visits from the same academic institution was queried to identify a non-operative cohort of 46,873 morbidly obese patients who did not undergo bariatric surgery. Propensity-matched groups were then generated to facilitate adjusted comparisons between the operative and non-operative cohorts. The Institutional Review Board of the University of Virginia approved this study (#17132) with waiver of consent due to its retrospective nature.

Data collection

Patient demographics, BMI, relevant comorbidities (diabetes mellitus, hypertension, gastroesophageal reflux disease, congestive heart failure/coronary artery disease, current tobacco and alcohol use), and insurance status were captured through the CDR for all patients. Patients were excluded if they were less than 18 years old, prisoners, or had incomplete medical records. These baseline characteristics were collected at the time of initial diagnosis of morbid obesity (BMI $>40\ kg/m^2$) that were entered into the electronic medical record for non-operative control patients, and at the time of the preoperative appointment for the patients who received bariatric surgery. Diagnoses of NASH and HCC were identified by ICD codes through the CDR for both operative and non-operative patients before and after the time of bariatric surgery or diagnosis of obesity in the control group. New diagnoses of NASH or HCC were captured even if patients were treated at outside institutions through the inclusion of ICD codes upon follow up visits. For all patients with a diagnosis of HCC, tumor characteristics were collected, as available, via review of the electronic medical record including pathology reports, laboratory results, and radiologic imaging even from outside institutions, if applicable.

Statistical analyses

Patients were matched 1:1 with all model variables chosen a priori, including demographics (age, initial BMI, race), history of NASH or HCC, relevant comorbidities (DM2, hypertension, gastroesophageal reflux disease (GERD), congestive heart failure/coronary artery disease), relevant preoperative substance use (alcohol/tobacco), and time of follow up. Adequacy of the match was assessed by balance metrics, including standardized mean difference and histograms of propensity scores.[16]

The primary outcome of interest was the overall incidence of NASH or HCC between the operative and non-operative groups. Secondary outcomes included differences in tumor characteristics among patients diagnosed with HCC. Complete tumor characteristics were not available for all patients. Univariate analyses were performed using Chi-square or Fisher's exact tests for categorical variables and Wilcoxon rank-sum test for continuous variables to assess for statistical differences in demographics, outcomes, and tumor characteristics between the operative and non-operative patients. Within the propensity matched cohort, multivariate logistic regression was used to assess the association between bariatric surgery and the incidence of NASH. Variables in the model were selected a priori based on clinical risk factors for NASH, and performance of the model was assessed by calculating area under the curve. Statistical significance was defined with the standard, two-sided alpha value of <0.05. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 3,410 patients who received bariatric surgery were evaluated and compared with 45,750 obese control patients who did not receive bariatric surgery from the same institutional data repository. Both patient groups varied in all demographic factors, and in almost all baseline comorbidities evaluated (Supplemental Table 1).

Propensity case-matching resulted in the inclusion of 2,057 bariatric surgery patients and 2,055 control patients (Table 1). The two groups were well matched in all baseline characteristics except for initial BMI (Table 1, Supplemental Figure 1) with histograms of matched propensity scores shown in Supplemental Figure 2. The clinical implications for a median difference in BMI of $0.6\ kg/m^2$ is likely minimal. Both BMIs (47 vs $46.4\ kg/m^2$) would still be within the same extreme obesity class III designation. After propensity score matching, there were no differences in the baseline prevalence of NASH (279 vs 256, $p = 0.29$), DM2 (432 vs 460, $p = 0.28$), viral hepatitis (102 vs 104, $p = 0.88$), GERD (958 vs 971, $p = 0.66$), and alcohol use (34 vs 39, $p = 0.55$) between the bariatric surgery group and control group.

Of the 2,057 patients in the matched bariatric surgery group, 121 (5.9%) received sleeve gastrectomy, 1,617 (79%) received RYBG, 275 (13%) received laparoscopic gastric banding, and 44 (2%) received other bariatric procedures. The median follow-up time was 7.1 years after bariatric surgery or after the initial obese diagnosis in the control group.

Patients in the bariatric surgery group developed lower incidences of NASH (123 (6%) vs 212 (10%), $p < 0.0001$) compared to the propensity-matched control group. This was highly significant even when both groups were matched on demographics, related comorbidities, tobacco use, and the initial BMI just prior to surgery or with the obese diagnosis in the control group as highlighted in Table 1. Lower incidences of NASH were present in the bariatric surgery group compared to the matched control group during the duration of follow up as shown in Fig. 1. Bariatric surgery patients also progressed to decreased incidences of HCC (1 (0.05%) vs 7 (0.3%), $p = 0.03$) as only one patient was found to have HCC in the matched bariatric surgery group. Further statistical analysis on the differences of tumor characteristics were not performed due to the low number of cases of HCC in both groups.

After risk adjustment using conditional logistic regression which included clinical variables associated with obesity and NASH, bariatric surgery was found to be independently and highly associated with a decreased incidence of NASH by 48% (OR 0.52, 95% CI 0.40–0.68, $p < 0.0001$, Table 2). The same analysis also found viral hepatitis to have a negatively association with NASH (OR 0.23, 95%

Table 1
Comparison of baseline characteristics of the propensity-matched bariatric surgical and non-surgical groups.

	No Bariatric Surgery n = 2,055	Bariatric Surgery n = 2,057	*p* value
Age (years)	43 (21)	42 (15)	0.83
Female	1738 (85)	1709 (83)	0.19
White	1764 (86)	1780 (86)	0.52
Initial BMI (kg/m^2)	46.4 (16)	47 (9)	0.04
Government insurance	835 (41)	790 (38)	0.14
DM Type II	460 (22)	432 (21)	0.28
Viral Hepatitis	104 (5)	102 (5)	0.88
NASH	256 (12)	279 (14)	0.29
Hypertension	782 (38)	790 (38)	0.82
GERD	971 (47)	958 (47)	0.66
Current alcohol use	39 (2)	34 (2)	0.55
Current smoker	556 (27)	550 (27)	0.82
CHF/CAD	91 (4)	97 (5)	0.66
COPD	59 (3)	52 (2)	0.5
OSA	129 (6)	137 (7)	0.62
Degenerative Joint Disorder	376 (18)	413 (20)	0.15

Categorical variables listed as N (%) and continuous variables listed as median (IQR).
BMI = Body mass index; DM Type II = Diabetes mellitus type II; NASH = Non-alcoholic steatohepatitis; GERD = Gastroesophageal reflux disease; CHF = Congestive heart failure; CAD = Coronary artery disease; COPD = Chronic obstructive pulmonary disease; OSA = Obstructive sleep apnea; HCC = Hepatocellular carcinoma.

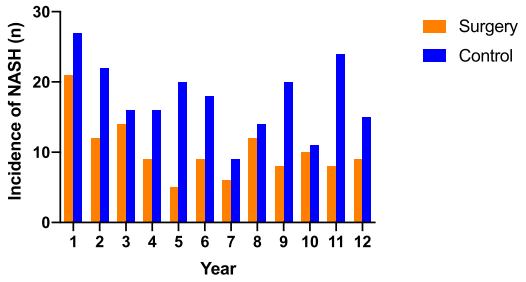

Fig. 1. Distribution of the Incidence of NASH in the Bariatric Surgery Group Compared to the Non-surgical Control Group Over Time.
Number of new NASH cases (n). Year is number of follow up years after bariatric surgery or obese diagnosis in the control group. NASH = Non-alcoholic steatohepatitis.

Table 2
Conditional logistic regression for risk of developing new non-alcoholic steatohepatitis after bariatric surgery (NASH). DM2 = Diabetes mellitus Type II; GERD = Gastroesophageal reflux disease.

Risk factors	Odds Ratio	95% CI		*p* value
Bariatric Surgery	0.52	0.40	0.68	<0.0001
Viral Hepatitis	0.23	0.12	0.48	<0.0001
DM Type 2	0.70	0.45	1.08	0.11
Female	0.70	0.40	1.2	0.21
White	1.55	0.85	2.82	0.15
Federal Insurance	1.35	0.92	1.98	0.13
Hypertension	0.85	0.54	1.33	0.47
Cardiac Disease	0.35	0.13	0.91	0.03
GERD	0.48	0.33	0.72	0.0003
Tobacco	1.28	0.85	1.95	0.24
Alcohol	0.85	0.31	2.38	0.76

CI 0.12–0.48, $p < 0.0001$) that was highly statistically significant. All viral subtypes of hepatitis were included in the analysis, and so it is unclear how many hepatitis patients had the Hepatitis C subtype compared to other subtypes that are less associated with NASH.

Discussion

Bariatric surgery was associated with fewer cases of NASH by 48% through risk-adjusted analysis compared to propensity score matched controls in this large cohort of patients with extended follow up. Through case-controlled propensity score matching, we found bariatric patients had decreased incidences of both NASH and HCC even when cases were matched on demographics and comorbidity risk factors such as DM2, GERD, alcohol and tobacco use. The one bariatric patient with HCC had a questionable diagnosis suggestive of HCC, but based on final histopathology, had other possible etiologies that also included cholangiocarcinoma and distant metastasis. Therefore, it is possible that the bariatric surgery group ultimately had no new cases of HCC during follow up. This aligns with a recent nationwide database study that showed decreased prevalence rates of HCC in bariatric surgery patients who were also propensity-matched with obese controls.[13]

Currently, NASH is the second leading cause of HCC requiring liver transplantation.[17,18] The increasing prevalence of NASH is predicted to overcome viral hepatitis as the leading cause of HCC since the advent of antiviral therapies have become more curative.[6] Our results showed bariatric surgery patients had a decreased probability of new NASH diagnoses after surgery compared to obese controls. Other meta-analyses involving liver pathology of post-bariatric surgery patients also found similar results[5,7,9,10]. One large meta-analyses which included 32 studies found bariatric surgery led to complete resolution of hepatic steatosis, inflammation, and balloon degeneration in the majority of patients, with significant decreases in NASH compared to baseline.[9] Another meta-analysis also found an overall decrease in the incidences of NASH after subgroup analysis even with different types of bariatric surgery procedures.[10] Unfortunately, we were not able to make a similar analysis due to the distribution of NASH and HCC among the different bariatric procedures in our database. Despite multiple studies showing overall positive findings in a majority of patients, a small group of patients also developed new or worsening hepatic fibrosis.[5,7,9–11,19] The cause for this discrepancy is still not well understood and may not be accounted for the different types of bariatric surgery alone. The risk of worsening or developing hepatic fibrosis is important to the safety and efficacy of bariatric surgery on patients with NASH cirrhosis. Previous studies show increased mortality risk after bariatric surgery in patients with NASH cirrhosis[20,21]. This largely contributes to why bariatric surgery is still not an established recommendation for NAFLD or NASH[6,11]. Future studies are needed to establish risk stratification for patients with NAFLD or NASH prior to bariatric surgery in order to identify patients more or less likely to develop and progress to NASH cirrhosis after surgery.

There are multiple theories regarding the pathogenesis of liver disease in obese patients that are related to metabolic syndrome

and insulin resistance. The increased release of free fatty acids and diacylglycerol from adipocytes, as well the secretion of pro-inflammatory cytokines such as TNF-alpha, IL-6, and leptin, can lead to a chronic inflammatory state that stimulate hepatic cell proliferation while also inhibiting apoptosis.[22] Higher leptin levels have also been implicated in the angiogenesis of HCC.[22] Since the risk factors of both HCC and NASH include obesity, it is unclear if the long-term weight loss resulting from bariatric surgery, or the weight loss itself, is associated with this decreased risk.

This study is limited by the retrospective design; however, the use of propensity matching accounted for important baseline characteristics in both groups, including initial BMI and comorbidities common in patients with morbid obesity. Unfortunately, we are unable to provide information regarding the matched interval weight loss of both the surgical and non-surgical groups for the duration of follow up since this was not consistently and accurately recorded in the retrospective review. Also, attempting to accurately report BMI at the time of new NASH or HCC diagnosis is highly susceptible to error, particularly in patients treated at outside institutions. In addition, we were surprised to find viral hepatitis was also a highly significant risk factor in our logistic regression analysis. It may be the thorough preoperative evaluation prior to bariatric surgery captured greater numbers of patient with baseline viral hepatitis compared to the control patients, and so had decreased incidences of new cases during the extended follow up period.

If bariatric surgery can improve the progression of NASH while also decreasing incidences of NASH and even possibly HCC, then there is no need to avoid bariatric surgery in patients with morbid obesity and NAFLD. We would not only be prohibiting the definitive weight loss option for these patients, but also prohibiting the harmful, obesity-related outcomes which would ultimately result in decreased quality of life and higher overall costs of their care.

Conclusion

Propensity match analysis of a large cohort of bariatric surgery patients compared with obese non surgery controls revealed patients who had undergone bariatric surgery had fewer new cases of NASH and HCC during with extended follow up. Further risk adjustment also showed bariatric surgery was associated with fewer cases of NASH by 48%. These results highlight the importance of bariatric surgery offering more than a procedure for sustained weight loss, but also in its potential to further abate obesity-related comorbidities, as well.

Conflicts of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.09.006.

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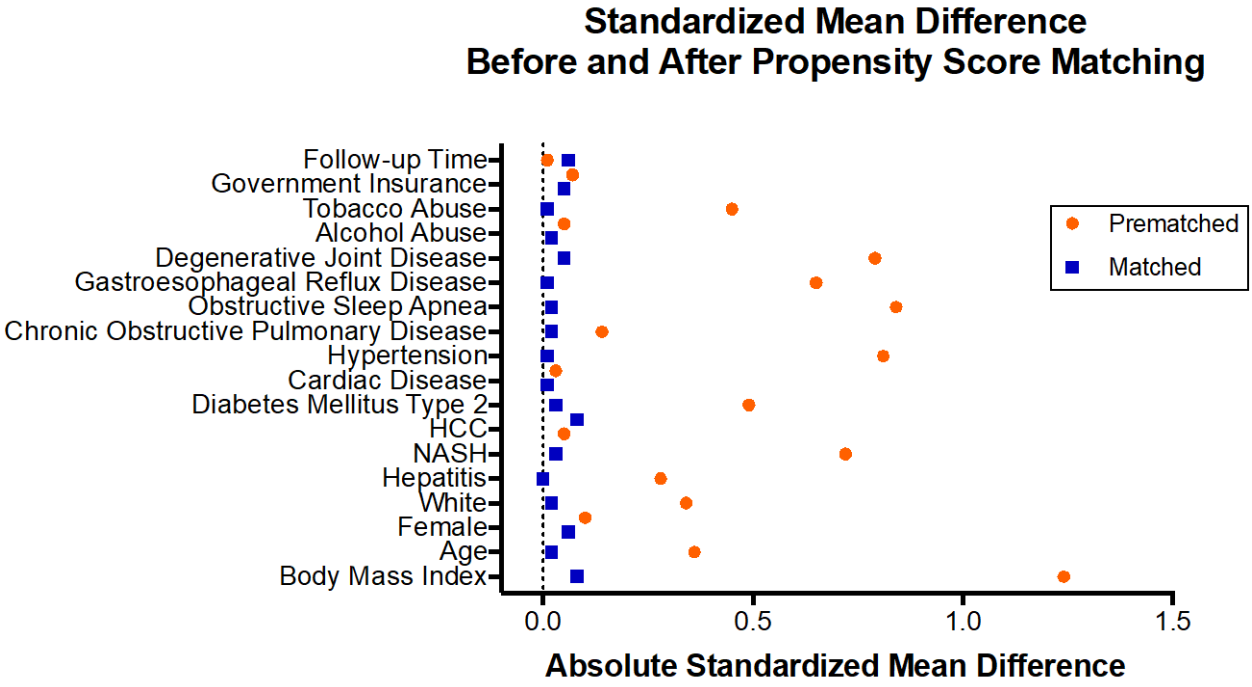
Supplemental Table 1. Baseline Characteristics Between All Bariatric Surgical Patients and Non-surgical Controls.

	No Bariatric Surgery n = 45,750	**Bariatric Surgery** n = 3,410	***p* value**
Age (years)	49 (23)	43 (16)	<0.0001
Female	30076 (66)	2768 (81)	<0.0001
White	34517 (75)	3008 (88)	<0.0001
Initial BMI (kg/m^2)	38.6 (7)	49 (12)	<0.0001
Government insurance	15961 (35)	1299 (38)	0.0002
DM Type II	4499 (10)	982 (29)	<0.0001
Hepatitis	1069 (2)	291 (8)	<0.0001
NASH	1003 (2)	867 (25)	<0.0001
Hypertension	7179 (16)	1741 (51)	<0.0001
GERD	11003 (24)	1846 (54)	<0.0001
Current alcohol use	1093 (2)	58 (2)	0.01
Current smoker	6008 (13)	1073 (31)	<0.0001
CHF/CAD	1834 (4)	158 (5)	0.07
COPD	611 (1)	116 (3)	<0.0001
OSA	234 (0.5)	934 (27)	<0.0001
Degenerative Joint Disorder	1652 (4)	1082 (32)	<0.0001
New NASH	3308 (7)	205 (6)	0.008
New HCC	210 (0.5)	12 (0.3)	0.37

Categorical variables listed as N (%) and continuous variables listed as median (IQR).
BMI = Body mass index; DM Type II = Diabetes mellitus type II; NASH = Non-alcoholic steatohepatitis; GERD = Gastroesophageal reflux disease; CHF = Congestive heart failure; CAD = Coronary artery disease; COPD = Chronic obstructive pulmonary disease; OSA = Obstructive sleep apnea; HCC = Hepatocellular carcinoma

Supplemental Figure 1: Balance assessment before and after propensity score matching showing the absolute standardized mean difference.



Supplemental Figure 2. Distribution of propensity scores **A.** before matching and **B.** after matching