

Bariatric Metabolic Surgery Reduced Liver Enzyme Levels in Patients with Non-Alcohol Fatty Liver Disease

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ABSTRACT

Introduction. Approximately 93.3 million Americans are obese (BMI > 30 kg/m²) and 51% have non-alcoholic fatty liver disease (NAFLD). Progression of NAFLD can lead to non-alcoholic steatohepatitis (NASH), which is the leading cause of liver transplant in the United States. This study analyzed liver enzyme levels following bariatric metabolic surgery in NAFLD patients up to one-year post-surgical intervention.

Methods. A retrospective analysis of adults with NAFLD who underwent bariatric metabolic surgery from 2009 to 2016 was conducted. The primary outcomes were transaminase levels following surgery. Secondary outcomes included levels of blood glucose and lipids.

Results. A total of 130 participants consisting of 80% Caucasian females with an average BMI of 47.5 kg/m² participated in the study. Reductions were noted in ALT (57.6% decrease) and AST (47.7% decrease) at one-year post-surgical intervention. Significant reductions also were noted in levels of blood glucose (22.34%; $p < 0.0001$), HbA1c (1.11% change; $p < 0.0001$), LDL (19.75%; $p = 0.0046$), total cholesterol (10.12%; $p = 0.0153$), and triglycerides (37.21%; $p < 0.0001$) with an increase in HDL levels (17.22%; $p = 0.0007$). Significant correlations were noted at six months between levels of alkaline phosphatase and both ALT ($p = 0.0101$) and AST ($p = 0.0009$), as well as an additional correlation trending toward significance between ALT and alkaline phosphatase at one year ($p = 0.0547$). When separated by obesity class, participants with class II obesity experienced improved outcomes compared to participants with class III obesity.

Conclusions. Bariatric metabolic surgery was associated with a reduction in liver enzyme levels in NAFLD. These findings suggested that bariatric metabolic surgery is a viable treatment option for participants with NAFLD. *Kans J Med* 2021;14:209-214

INTRODUCTION

The prevalence of obesity in the United States has increased to 93.3 million, with 85% of individuals with class III obesity (Body Mass Index [BMI] 40-59.9 kg/m²) estimated to have hepatic steatosis, 40% of whom also have steatohepatitis.¹ Bariatric metabolic surgery is associated with reduced obesity related morbidity and mortality and improvements in metabolic markers of disease; yet, its impact as a treatment option for

patients with Non-Alcoholic Fatty Liver Disease (NAFLD) has not been well defined.^{2,3}

Patients with NAFLD are at a significantly increased risk of cardiovascular disease, type 2 diabetes mellitus, and chronic kidney disease.^{2,4,5} Patients with NAFLD may progress to Non-Alcoholic Steatohepatitis (NASH), which results in a three-fold increased risk of cardiovascular mortality; a seven-fold increased risk of developing hepatocellular carcinoma (HCC); and a six-fold increased risk of liver associated mortality. NASH has surpassed viral hepatitis as the second leading indication for liver transplant in the United States, with only 10% of transplant candidates with NAFLD or NASH receiving liver transplants yearly.⁶

Despite the success of bariatric metabolic surgery in obesity treatment, and the significant association between obesity and NAFLD, weight loss using diet and exercise remains the standard of care. Total body weight loss of 3 - 5% may reduce hepatic steatosis, but losses greater than 10% are necessary to prevent liver fibrosis. Unfortunately, only 10% of patients who attempt weight loss using diet and exercise alone achieve this goal.^{7,8} Furthermore, randomized clinical trials for patients with NAFLD using weight loss alone has not decreased mortality, nor has it reduced cardiovascular events, which remain the number one cause of death for patients with NAFLD.⁹ Additionally, use of pharmacologic therapy for weight loss in NAFLD is not superior to surgical intervention and there are currently no Food and Drug Administration (FDA) approved medications specifically used to treat NAFLD in the United States.¹⁰

Bariatric metabolic surgery can improve management of comorbid medical conditions. A single-center randomized control trial comparing remission of type II diabetes mellitus in patients with obesity, with diabetes mellitus defined by fasting glucose less than 100 mg/dL and HbA1c lower than 6.5% in the absence of pharmacotherapy at two years, using treatment with medical therapy versus bariatric metabolic surgery found that none of the patients treated with medical therapy alone achieved remission after two years, while 75% in the gastric-bypass group and 95% in the biliopancreatic-diversion group achieved remission.¹¹ Surgical patients not only experienced greater weight reduction when compared to patients using diet and exercise alone, but also had decreased rates of complications from diabetes including myocardial infarction (7%), retinopathy (7%), nephropathy (7%), and neuropathy (13%) when compared to patients using diet and exercise for weight loss.

A mortality benefit has been observed in patients undergoing bariatric metabolic surgery, with a reduced mortality rate of 2.51 per one thousand person-years in surgical candidates versus nonsurgical candidates.¹² A 0.76 decrease in overall mortality and 0.46 reduction in cardiovascular mortality at 16 years was observed post-intervention in patients with NAFLD who underwent bariatric metabolic surgery compared to control groups, along with an increased likelihood of resolution of type II diabetes, hypertension, and reduction in the use of anti-hypertensive medications.^{13,14} Additionally, 60.4% of gastric bypass patients and 22.7% with gastric banding experienced remission of hyperlipidemia following bariatric metabolic surgery in a three-year study focusing specifically on hyperlipidemia treatment.¹⁴ Bariatric metabolic surgery for NAFLD patients specifically showed promising

effects in liver-related pathologic changes. A review of the current literature showed that a 9.75% to 36.5% reduction in BMI was associated with complete resolution of hepatic steatosis, ballooning, and fibrosis in 66% of patients across multiple studies.¹⁵

The objective of this study was to evaluate the effect of bariatric metabolic surgery on liver enzyme levels in participants with diagnosed NAFLD prior to bariatric metabolic surgery. Secondary analysis included the association of bariatric metabolic surgery with type II diabetes mellitus and hyperlipidemia. The effects of bariatric metabolic surgery were separated by obesity class to determine the impact of the intervention at all stages of obesity progression. Lastly, adverse effects on bone health and cholestatic disease were analyzed, as these markers have not been studied extensively in patients with NAFLD.

METHODS

Research Participants. Study participants included individuals ages 18 years and older who completed bariatric metabolic surgery from January 1, 2009 through April 1, 2016 at a Midwest hospital. Participants were included in the study if they had a diagnosis of NAFLD with elevations in transaminase levels at baseline, an absence of known chronic liver disease, no significant alcohol consumption, and demonstration of hepatic steatosis by imaging or liver biopsy. Participants were excluded if they were diagnosed previously with hepatitis B, hepatitis C, hepatocellular carcinoma, liver cirrhosis, alcohol abuse, substance abuse, pregnancy, any eating disorder or aberrant eating behavior, or severe liver disease defined by those awaiting liver transplant, renal failure defined by patients on dialysis or awaiting kidney transplant, active malignancy, Cushing's syndrome, bacterial endocarditis, osteomyelitis, or tuberculosis. All participants enrolled met the inclusion and exclusion criteria and were followed clinically for eight weeks prior to surgery and up to one-year post-surgical intervention. The study was approved by the local Institutional Review Board and by the university's Human Subjects Committee.

Data Collection. This study was a retrospective chart review of patients with a clinical diagnosis of NAFLD prior to completion of bariatric metabolic surgery. Data abstracted included the following demographics: age, race, ethnicity, gender, height, weight, date of birth, BMI, and date of surgery. Biometric variables included serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), systolic and diastolic blood pressures, levels of hemoglobin A1c (HbA1c), fasting plasma glucose, lipids including total cholesterol, triglycerides, low density lipoprotein (LDL), and high density lipoprotein (HDL), alkaline phosphatase, total bilirubin, albumin, total protein, and creatinine. Other variables included medication use (anti-hypertensive, anti-diabetic, and cholesterol lowering medications) and associated comorbidities (obstructive sleep apnea, dyslipidemia, hypertension, hyperlipidemia, and diabetes mellitus). All biometric variables were collected at four discrete time points: at the time of bariatric metabolic surgery, and three months, six months, and one-year post-surgical intervention. Blood pressures were measured to the nearest 2 mmHg using an aneroid sphygmomanometer. Heights were measured without shoes to the nearest 0.125 inch. Verified body weights were measured to the nearest 0.1 pound (0.045 kg) with clothing and no shoes at baseline. BMI was calculated by kilograms divided by current height in meters

squared. All patient data were deidentified and entered into a secure data processing website, REDCap®.¹⁶

Statistical Analysis. Data were analyzed using SAS version 9.4 (SAS Int. Inc., Cary, NC). Frequencies, proportions, means, and standard deviations were generated. Shapiro-Wilks tests were conducted to check variables for their distribution. As normality assumptions for variables and differences in time point measurements (between baseline and three months, three months and six months, and six months and twelve months) were rejected, the natural logarithm transformation was applied to the outcome variables.

For longitudinal data and to characterize the trajectories for individual units, random coefficient multilevel models were conducted to analyze the data and model parameters. Schwarz's Bayesian information criterion was considered for selecting the appropriate covariance structure between repeated measurements. Bonferroni adjusted least squared means of groups were used for pairwise comparisons.

Independent t-tests were applied to compare the mean difference between participants with diabetes and hypertension, and one-way ANOVA was used to compare the mean difference between BMI. A Tukey test was carried out for the pairwise comparisons of BMI. Moreover, linear single and multiple regression models and correlation analyses were conducted to reveal further associations between dependent and independent variables. All statistical tests at $p \leq 0.05$ were considered significant.

RESULTS

A total of 130 participants met the inclusion and exclusion criteria for the study. The majority were Caucasian (80%, $n = 104$) and female (79.2%, $n = 103$; Table 1). Additionally, 9.2% ($n = 10$) of participants were Hispanic or Latino. Average baseline BMI was $47.50 \text{ kg/m}^2 \pm 7.71$ with 18.2% ($n = 23$) having class II obesity (BMI $35.0\text{-}39.9 \text{ kg/m}^2$) and 82.3% ($n = 107$) having class III obesity (Table 1). Average age was 49.37 ± 12.17 years (range 24 to 75; Table 1).

Table 1. Baseline demographic data from study participants.

| Gender | Percentage |
|----------------------------------|------------|
| Male | 20.8 |
| Female | 79.2 |
| Ethnicity | |
| Caucasian | 80 |
| Hispanic | 9.2 |
| American Indian or Alaska Native | 1.5 |
| Asian or Pacific Islander | 0.8 |
| Other | 8.5 |
| Obesity class | |
| Class II | 18.2 |
| Class III | 82.3 |

At baseline, participants were diagnosed with the following comorbidities: hypertension (81%, n = 106), type II diabetes mellitus (45%, n = 59), and hyperlipidemia (83%, n = 108). A total of 71% (n = 93) were taking at least one antihypertensive medication and 45% (n = 59) used at least one medication to treat type II diabetes mellitus.

Average liver enzyme levels were reduced markedly at one-year post-surgical intervention. ALT was reduced by 57% (28.58) and AST was reduced by 47% (24.21) at one-year post-intervention (Figure 1). Negative correlations were noted between both ALT and AST levels with alkaline phosphatase levels at six months (correlation coefficient of 0.35, p = 0.0101 with AST; correlation coefficient of 0.27, p = 0.0009 with ALT) and at one year between alkaline phosphatase and ALT (correlation coefficient of 0.21, p = 0.0547).

Statistically significant correlations were noted at one-year post-intervention between levels of ALT and total cholesterol (correlation coefficient of 0.30, p = 0.0311), triglycerides (correlation coefficient of 0.34, p = 0.0108), and LDL (correlation coefficient of 0.35, p = 0.0126).

Secondary outcome measures, including fasting blood sugar, HbA1c, total cholesterol, triglycerides, LDL, HDL, cholesterol, and systolic and diastolic blood pressures also showed improvement (Table 2). Fasting plasma glucose decreased on average by 36.09 mg/dL at one year (p < 0.0001) and HbA1c decreased from 6.59% at baseline to 5.49% at one year (p < 0.0001) following surgery (100-125 mg/dL fasting glucose; HbA1c 6.5% mmol/L; Table 2). Lipid levels improved at one-year post surgery, with cholesterol decreasing on average by 17 mg/dL (p = 0.0153), LDL decreasing by 24 mg/dL (p = 0.0046), and triglycerides decreasing by 68 mg/dL (p < 0.0001). The HDL level increased by 9 mg/dL at one year (p = 0.0007).

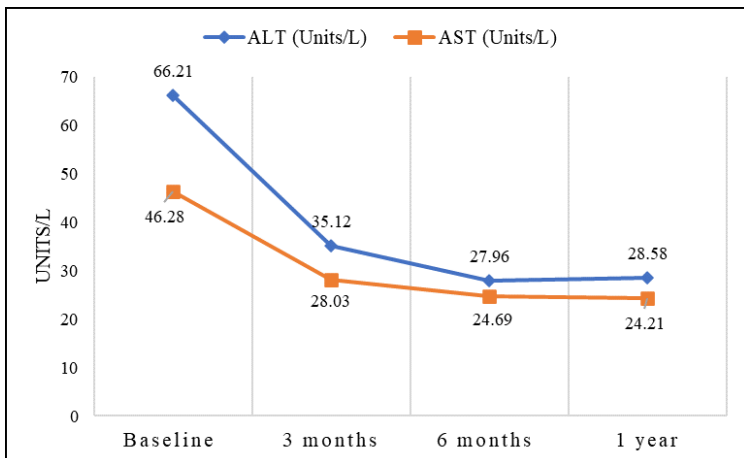


Figure 1. Transaminase level averages one-year post-surgical intervention.

Table 2. Laboratory values were measured at four different time points.

| Survey item | Baseline* | 3 months | 6 months | 1 year |
|---------------------------------------|-----------|----------|----------|--------|
| ALT (0-35 units/L) | 66.21 | 35.12 | 27.96 | 28.58 |
| AST (0-35 units/L) | 46.28 | 28.03 | 24.69 | 24.21 |
| Glucose, fasting (70-100 mg/dL) | 131.81 | 102.09 | 99.8 | 94.82 |
| HbA1c | 6.59% | 5.93% | 5.62% | 5.49% |
| Total cholesterol (<239 mg/dL) | 187.89 | 167.89 | 164.79 | 170.94 |
| Triglycerides (<199 mg/dL) | 182.9 | 145.44 | 120.5 | 114.86 |
| HDL (<40 mg/dL) | 44.46 | 39.98 | 43.92 | 53 |
| LDL (<129 mg/dL) | 120.2 | | | 96.47 |
| Alkaline phosphatase (26-104 units/L) | 83.2 | 84.8 | 87.16 | 86.73 |
| Total bilirubin (0.2-1.2 mg/dL) | 0.51 | 0.57 | 0.61 | 0.61 |

*Baseline corresponds with the laboratory values observed at time of bariatric metabolic surgery.

At one-year post-surgical intervention, significant differences were noted in the change in transaminase levels when comparing by obesity class (Figure 2). Patients with class II obesity had lower average transaminase levels at one year with ALT at 33.03 (u/L) and AST at 26.99 (u/L), in contrast with patients with class III obesity who had an average ALT of 67.64 (u/L) and AST of 47.36 (u/L; Table 3). Participants with class II obesity also had statistically significant positive correlations between levels of ALT and glucose (correlation coefficient of 0.13; p = 0.00332), HbA1c (correlation coefficient of 0.22; p = 0.0109), and triglycerides (correlation coefficient of 0.17; p = 0.0321). Additionally, in participants with class II obesity, both ALT (correlation coefficient of 0.17, p = 0.0011) and AST (correlation coefficient of 0.19, p = 0.0034) levels were correlated with a rise in alkaline phosphatase levels from 83.2 (u/L) at baseline to 86.73 (u/L) at one year.

All participants in this study, regardless of obesity class, experienced increases in alkaline phosphatase and total bilirubin levels at one-year post-surgical intervention (Table 3). The mean alkaline phosphatase level was increased by 3.53 mg/dL with a peak level of 87.16 mg/dL (Figure 3), and total bilirubin levels increased by 0.11 u/L at one year.

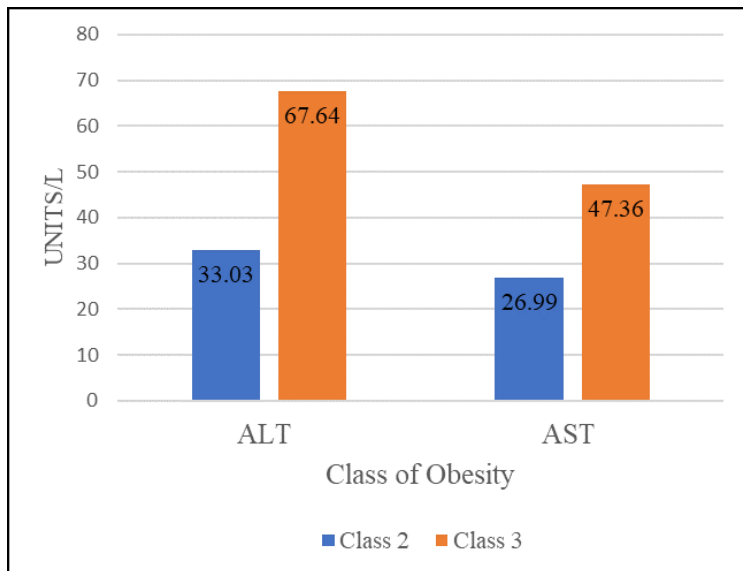


Figure 2. Transaminases based on obesity class.

Table 3. The average measurements for primary and secondary outcomes for patients with Class II and Class III obesity taken at one year.

| Obesity class | Average |
|----------------------|---------|
| Class II | |
| ALT | 33.03 |
| AST | 26.99 |
| Glucose | 100.76 |
| HbA1c | 5.80 |
| Triglycerides | 134.46 |
| Total cholesterol | 172.86 |
| Alkaline phosphatase | 86.39 |
| Class III | |
| ALT | 67.64 |
| AST | 47.36 |
| Glucose | 134.33 |
| HbA1c | 6.60 |
| Triglycerides | 182.16 |
| Total cholesterol | 184.47 |
| Alkaline phosphatase | 81.99 |

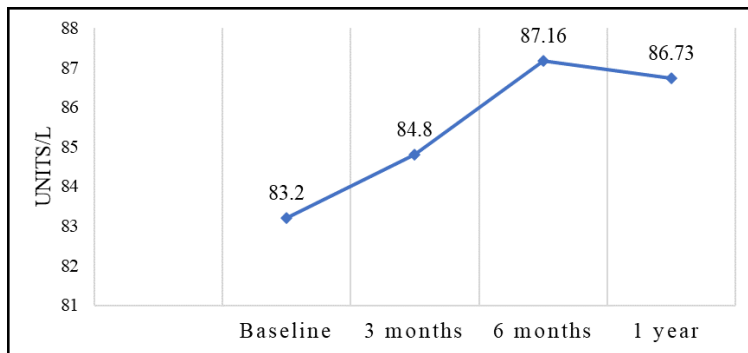


Figure 3. Alkaline phosphatase levels (units/L) were analyzed throughout this study.

DISCUSSION

Results obtained from this study showed that bariatric metabolic surgery was associated with significantly reduced liver enzyme levels in participants with NAFLD up to one-year post-surgical intervention with ALT reduced by 37.64 u/L and AST reduced by 22.08 u/L. A systematic review by Bower et al.¹⁴ found similar results, with an average reduction in ALT of 11.63 u/L and AST of 3.91 u/L across all studies up to five years post-surgical intervention. Reducing transaminase levels is associated with a decreased risk of progression to NASH, hepatocellular carcinoma, and end-stage liver disease. A study evaluating elevated liver enzymes on all-cause mortality demonstrated patients with sustained elevations in AST had a 2.88 increased relative mortality rate (HR 1.93; aHR 1.54) and a 1.33 increased relative mortality rate (HR .72; aHR 1.38) when compared to patients with normal liver enzyme levels.¹⁷

Few prior studies have investigated reductions in liver enzyme levels based on obesity class in patients with NAFLD. The prevalence of NAFLD increases with increasing BMI, with non-obese individuals exhibiting 3% steatosis on average, individuals with class I or II obesity exhibiting 20% steatosis, and 40% steatosis exhibited by those diagnosed with class III obesity.¹ Our study found that participants with

class II obesity showed 48% lower ALT levels and 57% lower AST levels at one-year post-surgical intervention compared to patients with class III obesity (Figure 2). Additionally, significant correlations were noted between ALT and levels of blood glucose, HbA1c, and triglycerides in class II obesity patients compared to participants with class III obesity who showed reductions in glucose alone. Current guidelines to qualify for bariatric metabolic surgery from the American Society for Metabolic and Bariatric Surgery include a BMI of ≥ 40 kg/m², being 100 pounds overweight, or a BMI of ≥ 35 kg/m² with significant comorbidities. However, findings from this study suggested that earlier surgical interventions may yield better results with regards to reductions in associated co-morbidities.

At one-year post-surgical intervention in this study, average levels of HbA1c and fasting blood glucose of all participants were within the normal range, alongside statistically significant positive correlations between AST and glucose in participants with class III obesity and ALT and glucose in patients with class II obesity. Simultaneous reductions in blood glucose and liver transaminase levels suggested bariatric metabolic surgery in patients with NAFLD can decrease comorbid disease burden and prevent irreversible end organ damage.

Numerous long-term studies on patients with NAFLD and type II diabetes mellitus demonstrated significant improvements in blood glucose and potential remission of type II diabetes mellitus following bariatric metabolic surgery.^{2,3} Xourafas et al.¹⁸ reported a significant positive correlation between ALT and HbA1c reduction at one-year post-surgical intervention with noted improvements in HbA1c from 8.3% to 6.1%, along with a 20% reduction in ALT among Roux-en-Y participants, and 17% reduction in laparoscopic adjustable gastric banding participants after three months post-surgical intervention. A meta-analysis by Panunzi et al.¹⁹ demonstrated 71% of patients with type II diabetes mellitus with preoperative BMI < 35 kg/m² and 72% of patients with preoperative BMI > 35 kg/m² experienced diabetes remission. Our study also showed a reduction in HbA1c, with an average HbA1c of 5.5% at one-year post-surgical intervention. However, we cannot claim that participants in this study achieved remission of diabetes given that some participants were still taking anti-diabetic medications following surgical intervention.

Of all the benefits gained from patients in this study undergoing bariatric metabolic surgery, some alternate findings suggested potential risks from the procedure. Patients in this study had elevations in alkaline phosphatase and total bilirubin levels up to one-year post-surgical intervention. Although these elevations were within normal limits of the laboratory range, the pathogenesis of these findings are not understood fully given current literature review, and elevations in alkaline phosphatase and bilirubin values were unexpected.^{20,21} Elevated bilirubin may be secondary to increased cholestatic liver patterns resulting in increased gallstone formation, primary biliary cholangitis, and potential development of cholangitis following bariatric metabolic surgery. The prevalence of gallstones in patients undergoing bariatric metabolic

surgery for obesity is estimated to be around 10% within 10 years after surgery.²² One theory behind this association included decreased post-operative fat-soluble vitamin absorption resulting in reductions in active vitamin D and increased oxalate levels. This resulted in low calcium reabsorption in the intestines allowing for oxalate precipitation and stone formation. Hypocitraturia and hyperoxaluria has been exhibited in 29 - 74% of patients following bariatric metabolic surgery.²¹ However, literature specific to patients with NAFLD who have undergone bariatric metabolic surgery to monitor cholestatic complications was sparse. This association will be important for future studies to target a potentially preventable adverse effect following surgical intervention.

Another potential adverse effect of bariatric metabolic surgery in this study is the observed elevation in alkaline phosphatase levels, indicating potential for early onset osteoporosis or osteomalacia from both bone demineralization and lack of fat-soluble vitamin absorption due to sequestration in adipose tissue among patients with NAFLD.²³ Risk of fracture seen in bariatric metabolic surgery is high, with an observed 10.2% decrease in femoral neck bone mineral density one-year post surgery.²⁴ However, these effects were not just short term; even when weight stabilizes, patients can experience an additional 2.7% decrease in bone density within the spine, radius, and tibia up to five years after surgery. Additional long-term studies regarding bone health in patients undergoing bariatric metabolic surgery among NAFLD patients specifically are needed to further characterize this observation and determine the best method to promote bone health in this at-risk population.

The strengths of this study included the observed reduction in transaminase levels among patients with NAFLD following bariatric metabolic surgery. In addition, this study was able to analyze the effects of bariatric metabolic surgery on comorbid conditions including type II diabetes mellitus and dyslipidemia. This study had an adequate sample size for a retrospective study allowing adequate correlations to be analyzed in the sample population. In addition, this study attained adequate follow up so that correlations up to one-year post-surgical intervention were able to be analyzed.

Limitations of this study included the retrospective design and absence of a control group for comparison of outcomes and management using the standard of care. Another limitation of this study was the lack of patients with class I obesity or overweight patients. Analysis of the effects of bariatric metabolic surgery on patients with NAFLD with concurrent class I obesity or being overweight may provide additional data to promote earlier surgical intervention. Another limitation of this study was the lack of diversity within the study with 80% of patients in this study being Caucasian and 79.2% being female. A larger, more diverse patient population would provide more generalizable results.

CONCLUSIONS

In conclusion, this study showed a significant improvement in liver enzyme levels following bariatric metabolic surgery in patients with NAFLD. This finding supported the use of bariatric metabolic surgery as a treatment modality for NAFLD to prevent increased liver fibrosis

and progression to end stage liver disease. This study also demonstrated a reduction in the prevalence of comorbid conditions including type II diabetes mellitus and hyperlipidemia. Future controlled prospective studies should quantify the potential adverse effects of bariatric metabolic surgery on both bone and biliary function, as these are both theoretically preventable adverse events that could be addressed with a better understanding of the underlying pathogenesis.

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CONFLICTS OF INTEREST

Tiffany Schwasinger-Schmidt, M.D., Ph.D., has conducted clinical trials research as principal investigator for the following pharmaceutical companies over the last twelve months: Allergan, Eisai, Lundbeck, Janssen, SAGE pharmaceuticals, Sarepta, Corcept, Boehringer Ingelheim, and AstraZeneca. All clinical trial and study contracts were with and payments were made to the University of Kansas Medical Center Research Institute, which is a research institute affiliated with University of Kansas School of Medicine-Wichita.

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Keywords: obesity, non-alcoholic steatohepatitis, NAFLD, liver steatosis, bariatric surgery