Improvements in nonalcoholic fatty liver disease (NAFLD) after metabolic surgery is linked to an increased hepatic fatty acid oxidation—a case report

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Abstract: Metabolic surgeries are regularly performed as a treatment for morbid obesity and have been shown to improve nonalcoholic fatty liver disease (NAFLD). The present case study aimed to evaluate the changes in hepatic fatty acid oxidation (FAO) before and 12-months after metabolic surgery in a patient who exhibited characteristics of NAFLD. A 34 year-old female with a body mass of 68.0 kg/m^2 underwent metabolic surgery (sleeve gastrectomy) and a blood sample and liver biopsy were obtained at the time of surgery. All procedures occurred without incident. Liver tissue was scored histologically to determine the extent of NAFLD using the NAFLD Activity Score (NAS) and fibrosis staging (NAS =5; Fibrosis =1). A follow-up liver biopsy and a blood sample were obtained at 12 months when she had roux-en-Y gastric bypass (RYBG). Hepatic FAO in whole liver lysate and isolated mitochondria was measured ex vivo at baseline and at 12-month. At 12-month post-metabolic surgery, the patient had lost 19% of her body weight (BMI 68.0 to 55.2 kg/m^2), and she exhibited lower concentrations of fasting plasma glucose (–16%), triglycerides (TG) (–17%), HbA1c (–4%), aspartate transaminase (AST) (–39%), and alanine aminotransferase (ALT) (–42%). Liver fat was reduced by 18% as measured via FibroScan®. *Ex-vivo* FAO in whole liver samples and in isolated hepatic mitochondria increased 1.6- and 4.2-fold, respectively. Histologically, NAS and fibrosis scores were markedly improved at 12-month (NAS =0; Fibrosis =0). This case highlights the significant improvements in liver histology that can occur following metabolic surgery in conjunction with an increased capacity for hepatic FAO. Thus, metabolic surgery-induced weight loss may be an effective therapy to treat NAFLD, in part due to improvements in hepatic mitochondrial function.

Keywords: Nonalcoholic fatty liver disease (NAFLD); fatty acid oxidation (FAO); bariatric; liver; metabolic surgery; case report

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Introduction

Obesity prevalence has been increasing over the last few decades—affecting over one-third of the population worldwide (1) and resulting in chronic conditions like hypertension, diabetes mellitus, and more recently, nonalcoholic fatty liver disease (NAFLD) (2). NAFLD is characterized by increased intracellular deposition of triglycerides (TG) in the liver and can lead to the more severe condition, nonalcoholic steatohepatitis (NASH), which can progress to fibrosis and cirrhosis (3). Currently, one-fourth of the population of the United States and worldwide exhibits characteristics of NAFLD—a condition that is significantly associated with obesity (4). Although several strategies have been utilized to aid obese patients in reducing their body weight (e.g., energy restriction and increased physical activity), metabolic surgeries have been shown to be most effective in achieving and maintaining weight loss (5). Due to the relationship between obesity and other chronic diseases, metabolic surgeries are also now considered as a treatment for type 2 diabetes (6) and have been shown to be promising for the resolution of NAFLD and NASH (7-9). However, limited data have been presented on the effectiveness of sleeve gastrectomy in the resolution of NAFLD and the majority of previous studies investigating liver health included patients undergoing roux-en-Y gastric bypass (RYBG) or gastric band. Further, to our knowledge, no studies have assessed the impact of metabolic surgery-induced weight loss on measures of hepatic mitochondrial fatty acid oxidation (FAO) following surgery. In accordance with the CARE reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-20-5/rc), we report here a case with a complete resolution of NAFLD characteristics after sleeve gastrectomy and a concurrent increase in hepatic FAO.

Case presentation

The study was approved by the Institutional Review Board (IRB) of the University of Missouri (IRB# 2008258), conducted according to the World's Medical Association Declaration of Helsinki (as revised in 2013), and registered at ClinicalTrials.gov (NCT03151798). As shown in *Figure 1A*, prior to the surgery, written informed consent was obtained from the patient during her pre-surgery orientation at the University of Missouri Health Systems Bariatric Surgery Clinic. The informed consent for publication was not obtained from the patient or the relatives after all possible attempts were made.

Patient characteristics

A 34 year-old female with a body mass index (BMI) of 68.0 kg/m^2 was studied. In line with ASMBS guidelines, before surgery, the patient participated in a screening visit and educational program that included a plan to consume a low-energy liquid-diet (600–1,000 kcals) for two weeks before her procedure. Her self-reported history of alcohol intake was zero g/week and in preparation for surgery, the patient agreed to consume no alcohol for two weeks before, and one year after surgery. The first surgery (sleeve gastrectomy) and research procedures occurred without any incident. Eight months postoperative, she presented reporting gastric reflux and occasional nausea. An esophagogastroduodenoscopy of the upper gastrointestinal tract demonstrated a small hiatal hernia, bile reflux in the stomach, and the presence of mild antral gastritis. After an examination of her gastric sleeve anatomy, the patient underwent revision surgery (RYGB) that occurred 12 months after the initial sleeve gastrectomy surgery.

Measurements

Prior to each surgery, a fasting blood sample was collected and a FibroScan® was performed to assess liver fat and stiffness. Blood samples were immediately processed for biochemical measurements. Plasma concentrations of total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), aspartate transaminase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were measured by a CLIA-standardized laboratory (Quest Diagnostics, St. Louis, MO, Lic. #26D0652092). The measurements of lipids were performed via auto-analyzer (Roche Cobas 8000 System, CV 0.6–0.9%, Indianapolis, IN, USA) using electrochemiluminescent immunoassay. Liver enzymes were measured using UV Absorbance (Roche Cobas 8000 System, CV 0.5–3.2% for AST and 0.5–3.1% for ALT, Indianapolis, IN, USA).

During each of her two surgeries, liver tissue (200–300 mg) was collected by the same surgeon 30 min. after induction of anesthesia using a standard wedge biopsy technique (10). Approximately 50 mg of tissue was fixed in 10% neutral buffer formalin for histological examination and ~100 mg was placed in mitochondrial isolation buffer for mitochondrial isolation. *Ex-vivo* FAO of [1-^{14}C] palmitate was carried out in both whole liver homogenate and

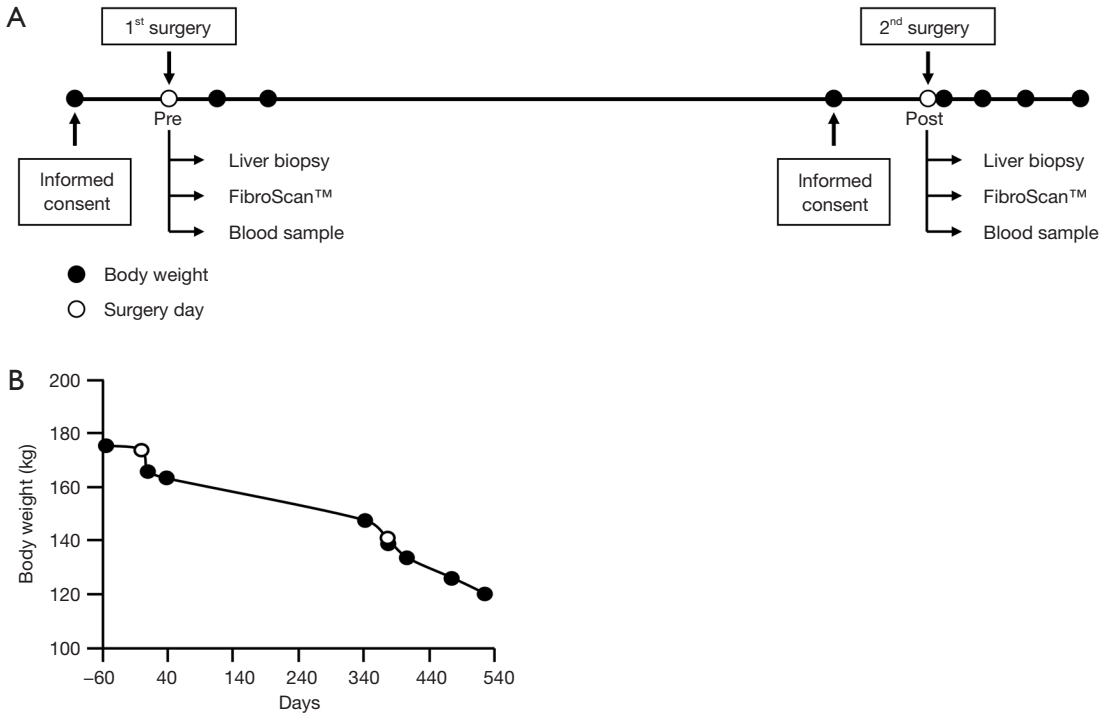

Figure 1 Study design and changes in body weight during the study. (A) Timeline for the case study; (B) participant's weight loss trend after the first and second surgery.

isolated hepatic mitochondria as previously described (11). Liver histology was performed by an experienced hepatopathologist, using hematoxylin-eosin and Masson's trichrome staining according to the Brunt scoring scale for NAFLD activity score (NAS) (12) and fibrosis score. Data obtained from measurements performed before the first surgery (sleeve gastrectomy) are referred to as "baseline" and the measurements performed before the second surgery (RYGB) are referred to as "follow-up" measurements.

Outcomes

Shown in *Table 1* are the subject characteristics, blood biochemistries, liver-related measurements, and changes observed as a result of metabolic surgery. Compared to baseline values, sleeve gastrectomy was associated with reductions in the patient's fasting plasma glucose and TG by 16% and 17%, respectively. Notable reductions were also observed for HbA1c (4%). As shown in *Figure 1B*, the subject's body weight was 176 kg during consenting. After two weeks of a pre-surgery liquid diet, her weight on the day of surgery was 174 kg. Ten days after the surgery, she had lost 8 kg of her body weight (166 kg). Lastly, at a one-year follow-up appointment prior to the revision surgery, her body weight was 141 kg (19% weight loss, BMI 55.2 kg/m^2) and at a four-month follow-up after revision surgery, her weight was reduced to 120 kg (31% weight loss, BMI 46.9 kg/m^2).

Liver-related outcomes

As shown in *Table 1*, marked reductions were observed 12 months after the first surgery for liver enzymes (AST, 39%; ALT, 42%; and ALP, 13%), liver fat (CAP, 18%), and liver stiffness (TE, 36%). Further, the histological scoring of the patient's baseline liver tissue exhibited characteristics that were commonly observed in patients with a severe form of liver disease (*Figure 2A*,*B*; steatosis grade 3, inflammation grade 1, and hepatocellular ballooning grade 1, as represented by total NAS of 5). Mild perisinusoidal fibrosis (fibrosis score 1A) was also observed. These characteristics were absent in a follow-up liver sample as evidenced by the NAS of 0 and a fibrosis score of 0; *Figure 2A*,*B*). Lastly, as shown in *Figure 2C*, compared to the baseline FAO measurements, one year after the metabolic surgery the whole liver lysate FAO and the isolated liver mitochondria

Table 1 Subject characteristic, blood biochemistries, and liver-related measurements

Subject characteristics	Pre	Post	% change
Age (y)	34	35	
Height (m)	1.6	1.6	
Weight (kg)	174	141	−19%
BMI (kg/m^2)	68.0	55.2	−19%
Blood biochemistries			
Plasma glucose (mg/dL)	94	79	−16%
Triglycerides (mg/dL)	116	96	−17%
HbA1c (%)	5.3	5.1	−4%
Cholesterol (mg/dL)	244	242	−1%
HDL (mg/dL)	45	39	−13%
Cholesterol/HDL	5.4	6.2	14%
LDL (calculated) (mg/dL)	176	182	3%
eGFR (mL/min/1.73 m^2)	113	118	4%
Liver-related measurements			
AST (U/L)	28	17	−39%
ALT (U/L)	26	15	−42%
ALP (U/L)	77	67	−13%
Total Bilirubin (mg/dL)	0.4	0.5	25%
Albumin (g/dL)	4.3	4.6	7%
CAP (dB/m)	354	291	−18%
TE (kPa)	7.6	4.9	−36%

Pre-measurements refer to data collected before her first surgery (sleeve gastrectomy) and post measurements are referred to data collected before her second surgery (Roux-en-Y gastric bypass). Abbreviations: BMI, body mass index; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CAP, controlled attenuation parameter—a measure of liver fat; TE, transient elastography—a measure of liver stiffness.

FAO were increased by 1.6- and 4.2-fold, respectively.

Discussion

Here, we report a case study documenting for the first time that metabolic surgery-induced improvements in histological features of steatosis, inflammation, and fibrosis are associated with a dramatic upregulation in hepatic mitochondrial FAO. The patient's follow-up liver tissue revealed resolution of hepatic steatosis, inflammation, ballooning, and mild perisinusoidal fibrosis. Three publications in the literature have reviewed 41 studies investigating the effects of RYGB, sleeve gastrectomy, and other forms of metabolic surgery on NAFLD (7-9), and the present results are wholly consistent with these findings demonstrating that surgeries inducing weight loss improve liver health. These studies, and another randomized controlled trial, have utilized liver histology measurements (13) to support the beneficial effects of metabolic surgery on NAFLD. Additionally, other studies (7,8) also reported a significant surgery-induced reduction in liver enzymes (AST, ALT, and ALP), a finding consistent with the current study. The noninvasive assessment of liver health using the FibroScan® demonstrated the patient's 18% reduction in CAP and 36% reduction in TE are consistent with the study of Garg and colleagues who paired FibroScan® data with liver histologic analysis in 42 patients before and after metabolic surgery (14). CAP score, an indicator of liver fat, was reduced progressively whereas TE was reduced by 30% (14). With regard to FAO, previous studies conducted in patients with advanced stages of NAFLD have shown a marked reduction in hepatic mitochondrial function (15) and impaired liver adenosine triphosphate (ATP) homeostasis (16). For the subject studied here, increases in FAO were observed in both whole liver preparations (1.6-fold) and isolated mitochondria (4.2-fold) following metabolic surgery. Although no other studies in the literature have conducted similar experiments in humans, the patient's results are consistent with previous experiments that utilized indirect measures of FAO in both humans and animal models (i.e., indirect calorimetry and adenosine monophosphate (AMP)/ATP ratio) (17,18). Indeed, whole-body FAO, measured by indirect calorimetry, suggests that these measurements may be partly (20–35%) influenced by hepatic FAO (19). Although the current study was not designed to identify the molecular mechanism involved in improvements in hepatic FAO, preclinical rodent studies suggest that metabolic surgery may alter the energy state of the liver, activating AMP kinase and improving hepatic mitochondrial function (17). This mechanism has yet to be confirmed in humans.

Clinical implications

Currently, weight loss is the effective treatment option available to improve NAFLD. Findings from this case study suggest that weight loss achieved after metabolic surgery

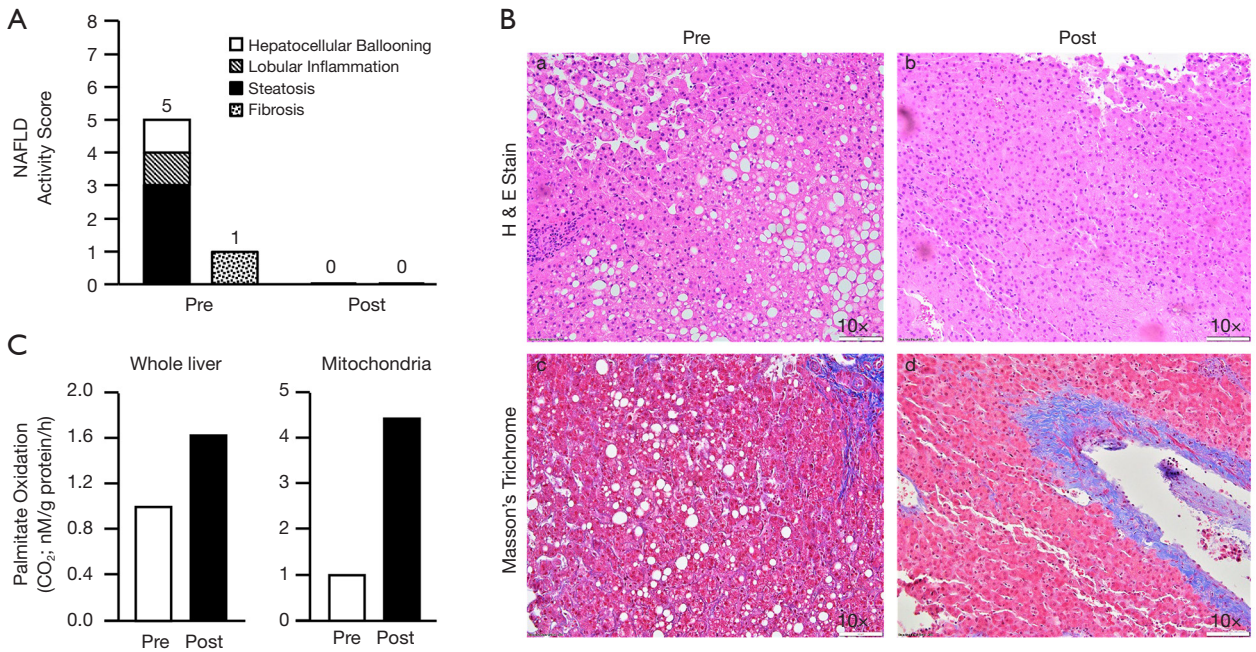

Figure 2 Changes in NAS score, fibrosis score, liver histology, and FAO before and after surgery. (A) NAS score (stacked bar) and fibrosis score before and after surgery; (B) the histological examination of the liver biopsy before and after the surgery. NAFLD activity score was performed using the Brunt scoring system. Histological examination was performed using hematoxylin-eosin (a,b) and Masson's trichrome staining (c,d); (C) changes in FAO in the whole liver (left bars) and isolated mitochondria (right bars) before (white bars) and after (black bars) surgery. NAS, NAFLD Activity Score; FAO, fatty acid oxidation; NAFLD, nonalcoholic fatty liver disease.

can improve the condition by increasing the liver's ability to burn fat. The complete resolution of this patient's condition at 12 months highlights the liver as a central organ negatively impacted by excess energy intake and provides further support for physicians to continue to advocate for weight loss in their patients who are overweight.

Conclusions

This case report demonstrated that weight loss achieved through sleeve gastrectomy can result in a substantial reduction in histologic evidence of hepatic steatosis, inflammation, ballooning, and fibrosis. The favorable histological changes were accompanied by increased hepatic mitochondrial FAO which suggests that after metabolic surgery, a significant component of NAFLD resolution may be due to an increase in hepatic mitochondrial function.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://asj.amegroups.com/article/view/10.21037/asj-20-5/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://asj.amegroups.com/article/view/10.21037/asj-20-5/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by

the Institutional Review Board, University of Missouri, Columbia, Missouri, USA (IRB# 2008258). Informed consent was obtained from the study participant before each surgery. The informed consent for publication was not obtained from the patient or the relatives after all possible attempts were made.

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