



# Increased Liver Fatty Acid Uptake Is Partly Reversed and Liver Fat Content Normalized After Bariatric Surgery

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## OBJECTIVE

Changes in liver fatty acid metabolism are important in understanding the mechanisms of diabetes remission and metabolic changes after bariatric surgery.

## RESEARCH DESIGN AND METHODS

Liver fatty acid uptake (LFU), blood flow, and fat content (LFC) were measured in 25 obese subjects before bariatric surgery and 6 months after using positron emission tomography/computed tomography and MRS; 14 lean individuals served as the control subjects.

## RESULTS

The increased LFU in obese subjects was associated with body adiposity. LFU was reduced postoperatively but was still high compared with the control subjects. LFC was normalized. Liver blood flow (per unit volume) was higher in obese subjects than in the control subjects at baseline and was further increased postoperatively; however, the total organ blood flow was unchanged as the liver volume decreased.

## CONCLUSIONS

The findings suggest that in a postoperative state, intrahepatic fatty acids are not stored in the liver but are used for oxidation to provide energy. Changes in perfusion may contribute to improved liver metabolism postoperatively.

Hepatic metabolism and insulin sensitivity are improved after bariatric surgery (BS). The current study explored the mechanisms of surgery-induced metabolic changes by measuring liver fatty acid uptake (LFU) in conjunction with the quantification of hepatic blood flow and liver fat content (LFC).

## RESEARCH DESIGN AND METHODS

The study recruited 25 morbidly obese female participants who were scheduled for BS (1). Of the subjects, 16 did not have diabetes, and 6 had impaired fasting glucose and/or impaired glucose tolerance. Nine subjects with type 2 diabetes (2) were taking oral medication, which was discontinued 24 h before the study. The control subjects were 14 healthy, lean, age-matched individuals.

The obese subjects were studied before BS and 6 months after. The operation was a sleeve gastrectomy (SG) in 16 or a Roux-en-Y gastric bypass (RYGB) in 9 (1). All subjects signed an informed consent form before the inclusion. The study protocol was approved by the Ethics Committee of Hospital District of Southwest Finland.

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**Positron Emission Tomography Imaging and Data Analyses**

The subjects underwent positron emission tomography/computed tomography imaging after an overnight fast. Liver blood flow was measured with <sup>15</sup>O-labeled radiowater (<sup>15</sup>O-H<sub>2</sub>O) and dynamic imaging using a hybrid GE Discovery VCT scanner. Subsequently, the LFU was measured with a palmitate analog fluoro-6-thiaheptadecanoic acid (<sup>18</sup>F-FTHA) (3) 64–77 min after the injection. During the LFU imaging session, plasma free fatty acids (FFAs), radioactivity, and metabolites were measured (4).

Hepatic time-activity curves from <sup>15</sup>O-H<sub>2</sub>O and <sup>18</sup>F-FTHA images were obtained by manual drawings using Carimas 2 software. Liver perfusion was calculated from <sup>15</sup>O-H<sub>2</sub>O– derived data by using tissue-derived arterial and portal input functions (5). LFU was calculated from the fractional uptake of <sup>18</sup>F-FTHA by using arterialized metabolite corrected plasma

radioactivity as an input function and multiplied by mean plasma FFA levels (4).

**Liver Fat, Volume, and Biopsies**

A whole-body MRI scan (Gyrosan Intera CV Nova Dual; Philips, Amsterdam, the Netherlands) was performed to obtain liver volume and LFC (6,7). Abdominal visceral and subcutaneous fat masses were calculated using SliceOmatic, version 4.3, software. Liver tissue was obtained from a needle biopsy during the bariatric procedure and was placed/preserved in formalin for histologic analyses. Biopsy specimens were evaluated according to a standardized histologic scoring system for nonalcoholic fatty liver disease (8,9).

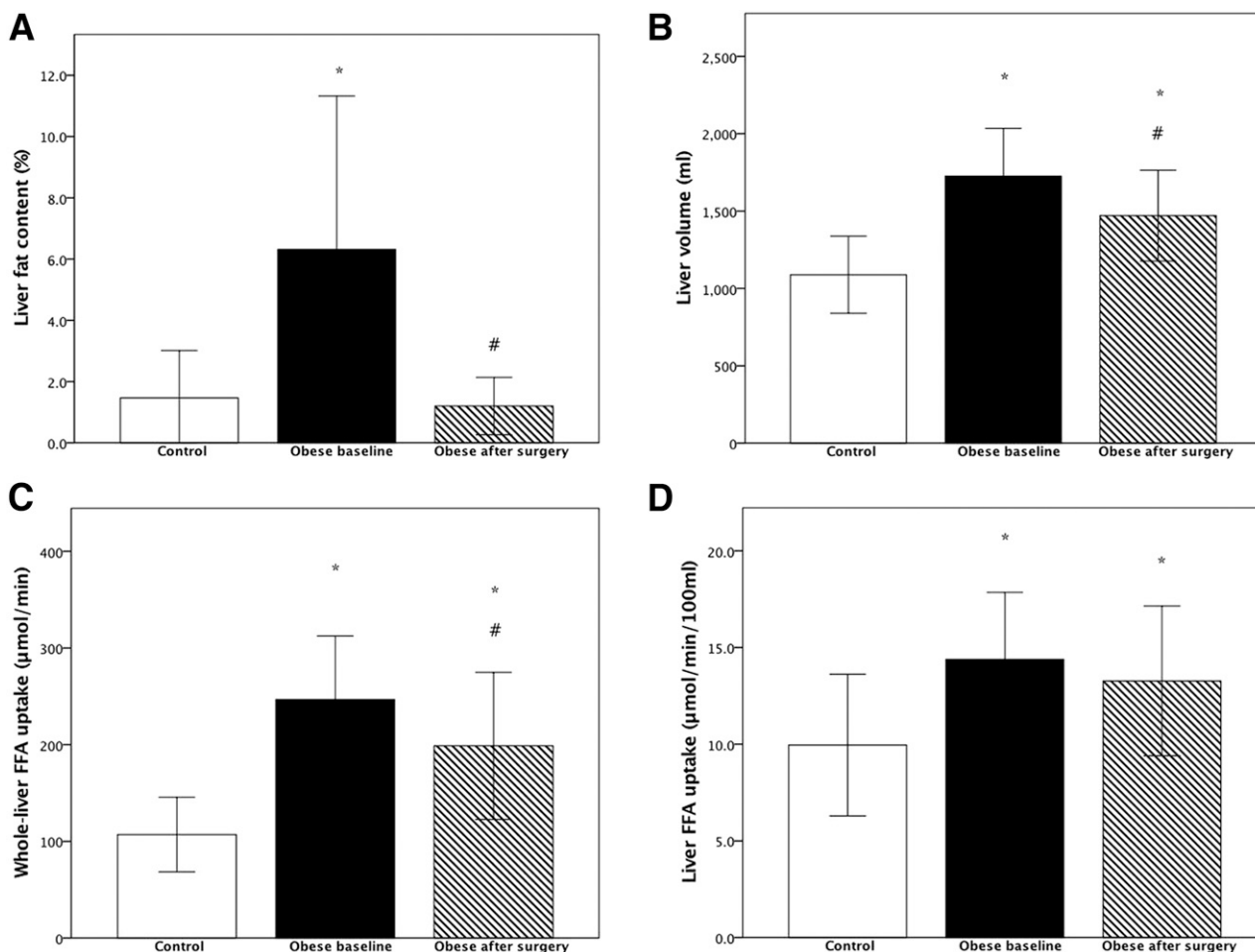
Measurements of insulin sensitivity and statistical analyses are presented in the Supplementary Data.

**RESULTS**

The mean weight loss was 25.5 ± 8.3 kg, with no differences between the SG and

RYGB procedures. Oral glucose insulin sensitivity was normalized to that of the control subjects, and HOMA-insulin resistance was improved. Remission from diabetes occurred in six of the nine subjects. Patients without remission all underwent an SG and lost less weight than patients with remission (15.5 ± 2.2 kg vs. 24.8 ± 3.9 kg, respectively, *P* = 0.01).

Before the operation, the obese subjects had high LFC, and borderline steatohepatitis was noted in the liver biopsy specimens of two subjects. LFC normalized within 6 months (Fig. 1A). Moreover, liver volume decreased but remained elevated postoperatively (Fig. 1B). Compared with the control subjects, LFU was higher before the operation (Fig. 1C and D), driven by higher circulating FFAs in obese subjects. No significant difference in LFU or in LFC was measured between subjects with diabetes, subjects with impaired fasting glucose/impaired glucose tolerance, and those without diabetes. Plasma FFA



**Figure 1**—LFC (A), liver volume (B), whole-liver FFA uptake (C), liver FFA uptake per volume of tissue (D), and whole-liver (E), arterial (F), and portal venous blood flow (G) in control subjects and in obese subjects at baseline and after surgery. \**P* < 0.05 vs. control subjects; #*P* < 0.05 vs. obese subjects at baseline.

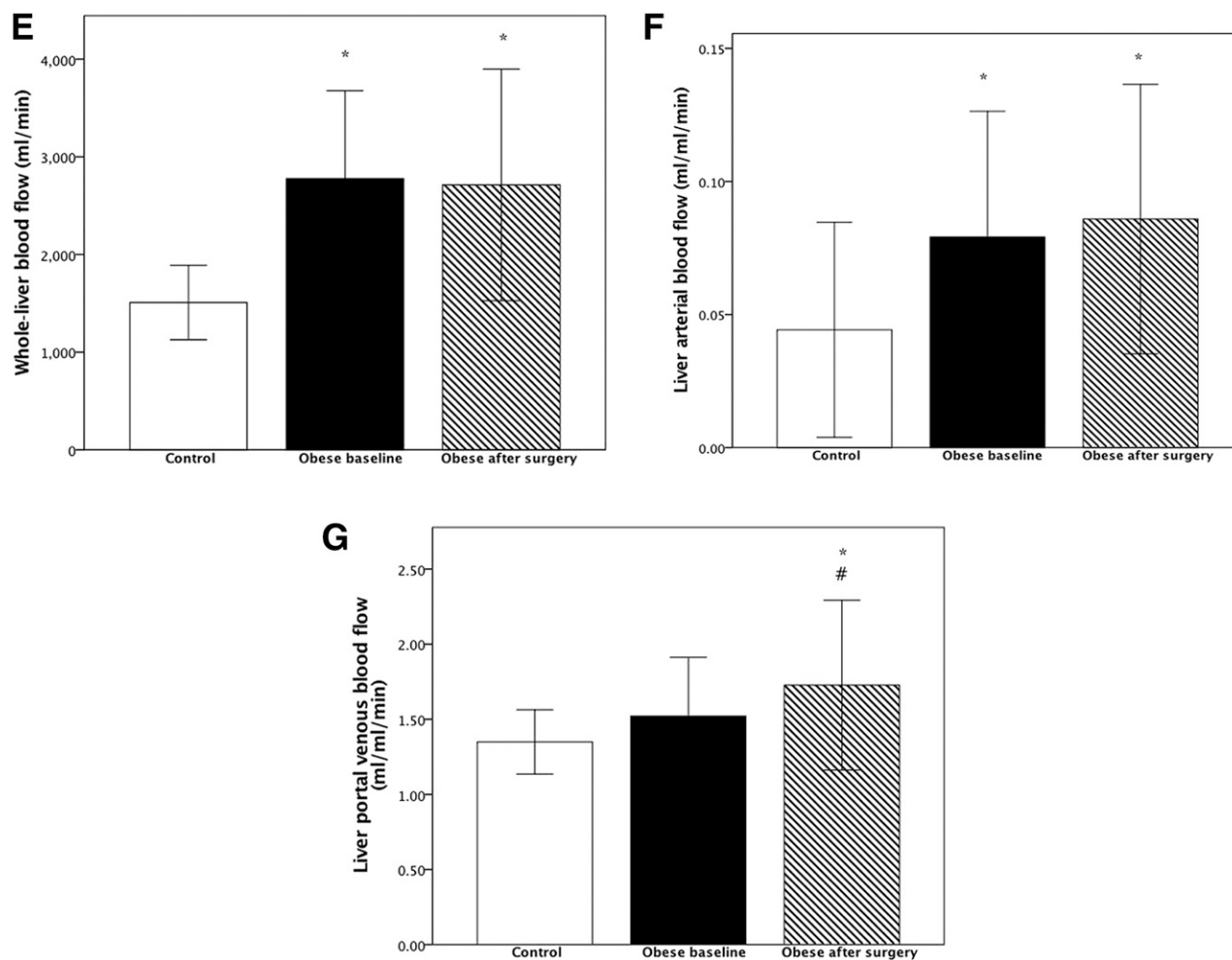


Figure 1—Continued.

remained elevated, and the fractional uptake rate was unchanged postoperatively. SG and RYGB led to similar effects on LFU. The reduction in liver volume resulted in a postoperative decrease in the whole-organ LFU (Fig. 1C). Perfusion of the whole liver remained elevated (Fig. 1E).

At baseline, in the pooled data, the whole-organ LFU correlated with body adiposity assessed by visceral fat mass ( $r = 0.493$ ,  $P = 0.002$ ), BMI ( $r = 0.736$ ,  $P < 0.0001$ ), whole-body fat content ( $r = 0.656$ ,  $P < 0.0001$ ), abdominal subcutaneous fat ( $r = 0.731$ ,  $P < 0.001$ ), and leptin ( $r = 0.682$ ,  $P < 0.0001$ ). However, LFC and LFU were not associated ( $r = 0.256$ ,  $P = 0.131$ ). The portal venous blood flow in the obese subjects at baseline was inversely correlated with LFU ( $r = -0.684$ ,  $P < 0.0001$ ).

## CONCLUSIONS

The study demonstrated that LFU was increased in morbid obesity, as expressed

by a per liver volume unit (~40%) or in the whole organ (~130%). The BS resulted in a normalization of the LFC. The LFU was reduced after BS but not normalized compared with the control subjects (~30% higher per mL of tissue and ~90% higher in the whole organ). The results are in line with our previous study on moderately obese subjects where the LFU (per mL of tissue) was reduced by 26% after a 6-week period of a very low-calorie diet (10). The persistence of high FFA uptake compared with lean control subjects, together with the marked reduction in LFC, suggests fatty acids may be preferentially directed into oxidation after BS instead of being accumulated in the liver.

This study also provided novel data on changes in liver blood flow in obesity and after surgery-induced weight loss. The study demonstrated that whole-liver blood flow is 84% higher in obese compared with lean subjects. Portal blood flow per volume

of tissue was increased after BS, but as the liver volume decreased along with the surgery-induced weight loss, the whole-organ blood flow was unchanged. The reason for the increase in portal vein blood flow is not clear but may partly depend on postoperative changes in vasoactive substances such as incretin hormones. Interestingly, portal vein blood flow and LFU were inversely related. Correlations do not establish causality, and we can only speculate whether the increase in postsurgery liver blood flow limits the amount of FFA uptake and exposure in the liver by increasing substrate washout from the hepatic circulation.

Our results showed that LFU was related to body adiposity. Increased adiposity was accompanied by an increase in the FFA released from adipose tissue. We have shown that at fast, LFU relies primarily upon systemic lipolysis (11). We note that arterialized peripheral FFA concentrations were measured and that

concentrations of FFA in the portal vein might be higher. Results from our previous study suggest that obese individuals have a higher visceral fat FFA contribution compared with lean subjects (12). The difference in FFAs appearing in the portal versus systemic circulation was significant in obese subjects and less pronounced in the control subjects. Accordingly, using peripheral FFA concentrations to measure LFU may lead to a (more) severe underestimation of the FFA uptake when visceral fat stores are increased. This might explain some of the differences between our results and the study by Klein et al. (13), where adipose tissue lipolysis was decreased after gastric bypass. Cumulatively, our data suggest that LFU is promoted by enlarged body adiposity and high circulating FFA levels and is suppressed at/by higher portal blood flow rates.

Surgery-induced weight loss has a rapid effect on LFC. Although increased LFU is expected to play a role in lipid accumulation, LFU and LFC were not related. In addition to increased FFA uptake, other factors, such as increased de novo lipogenesis, reduced lipoprotein secretion, and impaired FFA oxidation, may contribute to lipid accumulation and to the development of nonalcoholic fatty liver disease. Increased LFU could augment lipid oxidation. The decrease in insulin levels, as seen postoperatively, could be predicted to decrease LFC by diverting FFA flux from lipogenesis to oxidation (14).

In conclusion, we have shown that morbid obesity is characterized by increased LFU. BS and concomitant weight loss leads to a resolution of fatty liver and improvement in hepatic insulin sensitivity. Increased LFU is partly reversed by surgery-induced weight loss. The persistence of high FFA uptake, despite a normal fat content in the liver, suggests a change in the use of fatty acids from storage to oxidation after surgery.

Accelerated portal blood flow may relate to improved liver metabolism after surgery.

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**Author Contributions.** H.I. assisted in the study design, performed the analyses, and drafted the manuscript. J.C.H. and P.I. contributed to the study design, data analysis, and drafting of the manuscript and critically reviewed the manuscript. N.K., V.S., J.L., T.L., and T.P. contributed to data analysis, data interpretation, and editing of the manuscript. J.P. contributed to data interpretation and to drafting of the manuscript. P.S. contributed to the study design and conduct of the study and critically reviewed the manuscript. P.N. obtained funding; contributed to the study design, data analysis, and drafting of the manuscript; and critically reviewed the manuscript. All authors approved the final manuscript as submitted. P.N. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## References

- Honka H, Koffert J, Hannukainen JC, et al. The effects of bariatric surgery on pancreatic lipid metabolism and blood flow. *J Clin Endocrinol Metab* 2015;100:2015–2023
- World Health Organization, International Diabetes Federation. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia. Report of a WHO/IDF Consultation.* Geneva, World Health Organization, 2006

- DeGrado TR, Coenen HH, Stocklin G. 14(R,S)-[<sup>18</sup>F]fluoro-6-thia-heptadecanoic acid (FTHA): evaluation in mouse of a new probe of myocardial utilization of long chain fatty acids. *J Nucl Med* 1991;32:1888–1896
- Iozzo P, Turpeinen AK, Takala T, et al. Liver uptake of free fatty acids in vivo in humans as determined with 14(R,S)-[<sup>18</sup>F]fluoro-6-thia-heptadecanoic acid and PET. *Eur J Nucl Med Mol Imaging* 2003;30:1160–1164
- Kudomi N, Slimani L, Järvisalo MJ, et al. Non-invasive estimation of hepatic blood perfusion from H<sub>2</sub><sup>15</sup>O PET images using tissue-derived arterial and portal input functions. *Eur J Nucl Med Mol Imaging* 2008;35:1899–1911
- Thomsen C, Becker U, Winkler K, Christoffersen P, Jensen M, Henriksen O. Quantification of liver fat using magnetic resonance spectroscopy. *Magn Reson Imaging* 1994;12:487–495
- Szczepaniak LS, Babcock EE, Schick F, et al. Measurement of intracellular triglyceride stores by H spectroscopy: validation in vivo. *Am J Physiol* 1999;276:E977–E989
- Brunt EM, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA; NASH Clinical Research Network (CRN). Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology* 2011;53:810–820
- Kleiner DE, Brunt EM, Van Natta M, et al.; Non-alcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005;41:1313–1321
- Viljanen AP, Iozzo P, Borra R, et al. Effect of weight loss on liver free fatty acid uptake and hepatic insulin resistance. *J Clin Endocrinol Metab* 2009;94:50–55
- Rigazio S, Lehto HR, Tuunanen H, et al. The lowering of hepatic fatty acid uptake improves liver function and insulin sensitivity without affecting hepatic fat content in humans. *Am J Physiol Endocrinol Metab* 2008;295:E413–E419
- Iozzo P, Bucci M, Roivainen A, et al. Fatty acid metabolism in the liver, measured by positron emission tomography, is increased in obese individuals. *Gastroenterology* 2010;139:846–856, 856.e1–856.e6
- Klein S, Mittendorfer B, Eagon JC, et al. Gastric bypass surgery improves metabolic and hepatic abnormalities associated with nonalcoholic fatty liver disease. *Gastroenterology* 2006;130:1564–1572
- Yki-Järvinen H. Type 2 diabetes: remission in just a week. *Diabetologia* 2011;54:2477–2479