Received: 25 October 2017 | Revised: 31 December 2017 | Accepted: 6 January 2018

DOI: 10.1111/dom.13228

WILEY

ORIGINAL ARTICLE

Morbid obesity and type 2 diabetes alter intestinal fatty acid uptake and blood flow

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Funding information
This study was funded by Maud Kuistilan Muistosäätiö; Kyllikki ja Uolevi Lehikoisen säätiö; Suomen Lääketieteen Säätiö; Suomen akatemia.

Aims: Bariatric surgery is the most effective treatment to tackle morbid obesity and type 2 diabetes, but the mechanisms of action are still unclear. The objective of this study was to investigate the effects of bariatric surgery on intestinal fatty acid (FA) uptake and blood flow.

Materials and Methods: We recruited 27 morbidly obese subjects, of whom 10 had type 2 diabetes and 15 were healthy age-matched controls. Intestinal blood flow and fatty acid uptake from circulation were measured during fasting state using positron emission tomography (PET). Obese subjects were re-studied 6 months after bariatric surgery. The mucosal location of intestinal FA retention was verified in insulin resistant mice with autoradiography.

Results: Compared to lean subjects, morbidly obese subjects had higher duodenal and jejunal FA uptake ($P < .001$) but similar intestinal blood flow (NS). Within 6 months after bariatric surgery, obese subjects had lost 24% of their weight and 7/10 diabetic subjects were in remission. Jejunal FA uptake was further increased ($P < .03$). Conversely, bariatric surgery provoked a decrease in jejunal blood flow ($P < .05$) while duodenal blood flow was preserved. Animal studies showed that FAs were taken up into enterocytes, for the most part, but were also transferred, in part, into the lumen.

Conclusions: In the obese, the small intestine actively takes up FAs from circulation and FA uptake remains higher than in controls post-operatively. Intestinal blood flow was not enhanced before or after bariatric surgery, suggesting that enhanced intestinal FA metabolism is not driven by intestinal perfusion.

KEYWORDS

bariatric surgery, diabetes, free fatty acids, obesity, small intestine blood flow

1 | INTRODUCTION

The pandemic rise in obesity and type 2 diabetes has increased interest in weight loss mechanisms after bariatric surgery. The gut senses dietary fat[1,2] and regulates energy intake and utilization.[3,4] While the gastrointestinal tract is the first organ to encounter ingested food and nutrients, only few studies have addressed the role of bariatric interventions in small intestinal plasma fatty acid (FA) handling and blood flow and their importance in weight reduction.

Recent studies in the area of type 2 diabetes pathogenesis support a role of increased epithelial permeability, altered intestinal microbiota and subsequent metabolic endotoxemia as causal factors,[5,6] but findings are inconclusive.[7] An increase by 45% to 55% in intestinal blood flow has been shown in diabetic animals compared to control animals.[8] Studies on the effects of obesity or diabetes on intestinal flow and FA metabolism in humans are lacking.

The aim of this study was to compare intestinal blood flow and FFA uptake between lean and morbidly obese subjects, with and without type 2 diabetes, who were eligible for bariatric surgery. We hypothesized that intestinal blood flow and FA uptake are increased in subjects with morbid obesity and type 2 diabetes and are normalized after bariatric surgery. We used a multimodal imaging approach with positron emission tomography (PET), which

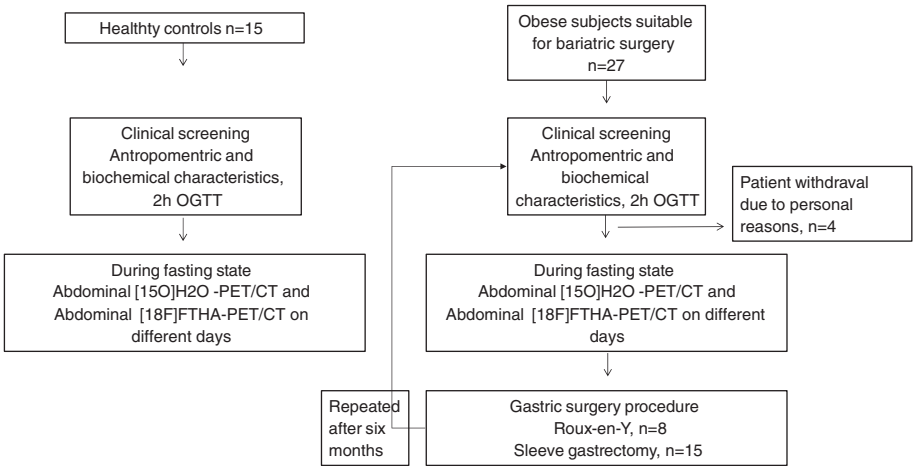


FIGURE 1 Clinical study flow chart and design

enables assessment of intestinal FA uptake and blood flow in an organ-specific manner in humans.[9] Furthermore, the mucosal location of intestinal FA uptake was verified in insulin resistant mice with autoradiography.

2 | METHODS

2.1 | Participants

A total of 27 morbidly obese subjects, who were evaluated for bariatric surgery according to standard bariatric surgery criteria, and 15 lean controls were recruited from a larger data collection, SleevePET2 (NCT01373892)[10]. Before surgery, 10 obese subjects had type 2 diabetes, 11 subjects had normal glucose tolerance and 6 had impaired glucose tolerance according to American Diabetes Association criteria.[11]

Exclusion criteria were eating disorder, known cardiovascular disease, hypertension, insulin-dependent diabetes and previous or present abnormal renal or hepatic function. The ethics committee of the Hospital District of Southwestern Finland approved the experiments, and all subjects gave written informed consent before participation.

2.2 | Design

The clinical study flow chart and experimental design are shown in Figure 1. Clinical screening included history, physical examination, anthropometric measurements (Table 1) and fasting measurements of plasma biochemical data and 2-hour oral glucose tolerance test (OGTT), followed by imaging in the supine position with a PET/-computed tomography (CT) scanner (Discovery VCT, General Electric Medical Systems, Milwaukee, Wisconsin) after an overnight fast.

TABLE 1 Anthropometrics and basic characteristics

		Obese patients (n = 27)		
	Controls (n = 15)	Pre-surgery	*P*	Post-surgery
Anthropometrics				
Sex (female/male)	17/0	27/0		
Age (years)	44 (12)	42 (10)	NS	43 (9)
Weight (kg)	61.8 (7.1)	113.5 (15)*	<.00001	86.8 (14)*
BMI (kg/m^2)	22.6 (2.8)	41.4 (4.0)*	<.00001	31.7 (4.3)*
Abdominal SAT(kg)	3.2(0.6)			
Abdominal VAT(kg)	0.7(0.3)			
Body fat (%)	32.0 (5.7)	50.3 (3.7)*	<.00001	42.6 (4.2)*
T2DM (n/%)	0/0	10/37%		3/14%
Biochemical data				
FFA (mM)	0.49(0.20)	0.72 (0.26)*	.67	0.67 (0.27)*
Fasting glucose (mM)	5.3 (0.6)	6.1 (1.0)*	.008	5.4 (0.7)
Fasting insulin (mU/L)	5.5 (3.5)	15.1 (9.8)*	.008	8.5 (6.0)*
Insulin sensitivity indices				
$HOMA_{IR}$ (fraction)	1.1 (0.8)	4.3 (3.0)*	.005	2.1 (1.6)
2-hour OGIS (mL/min//m^2)	438.4 (70)	342.9 (47)*	<.00001	435.6 (56)

Abbreviations: $HOMA_{IR}$, homeostatic model assessment for insulin resistance; IGT, impaired glucose tolerance; OGIS, oral glucose insulin sensitivity index; SAT, subcutaneus adipous tissue; VAT, visceral adipous tissue. Data are presented as mean (SD). *P < .05 for obese patients pre and post intervention vs controls in Student's t test.

Experiments were performed 4 weeks before the planned bariatric surgery and initiation of the standard very-low calorie diet. Catheters were placed in both antecubital veins, one for tracer administration and the other for blood sampling. A CT scan was performed for attenuation correction and as an anatomical reference to the abdomen. To assess small intestine BF, a dynamic PET scan of 310 seconds was performed following an intravenous bolus injection of ^{15}O-water. Effective radiation dose per [^{15}O]H_2O injection was 0.47 mSv. The total injected amount of radioactivity was 574 (128) MBq. After 10 minutes, a 14(R,S)-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA) bolus was administered intravenously, and dynamic PET imaging was initiated. Effective radiation dose per [^{18}F]FTHA injection was 7.4 mSv and total injected amount of radioactivity was 179 (12) MBq. After 86 (3.3) minutes, the abdomen was imaged (frames, 5 × 180 seconds). During the entire imaging session, arterialized blood was drawn frequently to measure plasma glucose, insulin, free fatty acids (FFAs) and total radioactivity concentration and radiometabolites. Moreover, blood pressure and clinical well-being of the subjects were constantly monitored. The aforementioned experiments were repeated 6 months after the bariatric surgery procedure.

To asses organ-specific fatty acid uptake (FAU) we used the palmitate analogue [^{18}F]FTHA.[12] After entry into cells, it undergoes partial mitochondrial-oxidation and is essentially trapped.[13] The production of [^{18}F]FTHA (t1/2110 minutes) was as described previously.[14] For blood flow measurements, we used ^{15}O-water, as described previously.[15] The radiochemical purity for both tracers exceeded 95%.

Four obese subjects (1 with type 2 diabetes) did not proceed to bariatric surgery. The remaining subjects underwent laparoscopic Roux-en-Y gastric bypass (n = 8) or laparoscopic sleeve gastrectomy (n = 15), as described previously[10].

2.3 | PET image analysis, ROI definition and calculations

PET data were corrected for dead time, time decay and measured photon attenuation and were reconstructed in a 256 × 256 matrix. Image analysis was performed using Carimas 2.9 (http:// www.turkupetcentre.fi). Intestinal time-activity curves (TAC) from [^{18}F]FTHA and [^{15}O]H_2O were obtained by manually drawing multiple volumes of interest in the small intestine.

Intestinal FA uptake was calculated from the fractional uptake of [^{18}F]FTHA[16] using arterialized blood sampling data as an input function. Here, the blood radioactivity curve was corrected for metabolites,[17] and the assumption was made that any residual activity after 30 minutes could be entirely ascribed to radiometabolites. The fractional [^{18}F]FTHA uptake was multiplied by the mean plasma FFA level during the imaging period to obtain the basolateral intestinal FA uptake rate.

For blood flow analysis, an image-derived input function was obtained from the abdominal aorta, as described previously.[18] For reliable analysis, CT scans were used as an anatomical reference. Blood flow was calculated from [^{15}O]H_2O-derived data by using a one-tissue compartment model.[19] Intestinal TACs were corrected for a delay between arterial and target tissue radioactivity. To estimate the efficiency of FA uptake, we also calculated FA extraction ratio, that is, the ratio of FA uptake to FFA delivery (= mean FFA concentration times blood flow in %).

2.4 | Measures of insulin sensitivity and β-cell function

After baseline samples were obtained, a standard 75-g OGTT test was initiated, and blood was drawn at time points 30, 45, 60, 90 and 120 minutes to measure plasma glucose, insulin and C-peptide. From these and anthropometric data, insulin sensitivity was estimated, by both homeostasis model assessment of insulin resistance and the oral glucose insulin sensitivity index. β-cell modelling, as described previously by Mari et al.[20] was used.

2.5 | Indirect calorimetry

Open-system indirect calorimetry (Deltatrac, Datex, Helsinki, Finland) was used for measurement of O_2 consumption (VO_2) and CO_2 production (VCO_2), from which whole-body energy expenditure and substrate oxidation rates were calculated as previously reported.[21] Resting energy expenditure (REE) was calculated as REE (kcal/d) = (3.941*VCO_2 + 1.11*VO_2)*1.44.[22] Food diaries were used to document dietary intake.

2.6 | Experimental animals

For intestinal [^{18}F]FTHA validation, 4 hypercholesterolemic low-density lipoprotein receptor-deficient mice, expressing only apolipoprotein B100 with type 2 diabetes caused by pancreatic overexpression of insulin-like growth factor II (IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$, A. I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland)[23] were fed with a high-fat diet (0.2% total cholesterol, TD 88137) (Harlan Teklad, Harlan Laboratories, Madison, Wisconsin) for 5 months, starting at the age of 2 months. Four age-matched healthy C57BL/6N mice, fed with normal chow diet, served as controls.

Each animal was sacrificed after a 4-hour fast and a bolus of [^{18}F]FTHA. The abdominal cavity was rapidly accessed, and tissue samples of multiple splanchnic organs were obtained to investigate relative intestinal distribution of [^{18}F]FTHA using gamma counter and digital autoradiography, reported as tissue-specific %ID/g and photostimulated luminescence per square millimetre (PSL/mm^2)-values, respectively (for more details see Appendix S1).

2.7 | Statistical analysis

Statistical analyses were performed using SAS 9.4 software for Windows (SAS Institute). Data are presented as means and standard deviation (SD). Normality was examined by a Shapiro-Wilk test, and equality of variances was tested with Levene's test. Student's *t*-test for unpaired and paired data was used for comparisons of between- and within-group differences, respectively. Univariate analyses are presented as Pearson or Spearman correlation coefficients, as appropriate. A *P* value of less than .05 was considered statistically significant.

3 | RESULTS

3.1 | Anthropometric and biochemical changes

Before surgery, the obese group was insulin resistant and had higher plasma glucose and FFA levels than the lean group (Table 1). Bariatric surgery resulted in significant weight loss, normalization of fasting and 2-hour plasma glucose, glycosylated haemoglobin HbA1c,[24] and insulin sensitivity. However, serum FFA levels remained elevated and were higher than those in lean subjects (Table 1).

A total of 10 subjects had type 2 diabetes preoperatively, but 7 went into remission (defined as HbA1c < 6.5%, fasting plasma glucose <7.0 mM and 2-hour glucose <11.1 mM without the use of antidiabetic drugs).[25] Still, in the obese group, level β-cell function remained impaired compared with that of healthy control subjects.[25]

3.2 | Intestinal blood flow and FA uptake before and after surgery

Morbidly obese subjects had higher FA uptake in the duodenum ($P < .01$) and jejunum ($P < .001$) compared to lean subjects (Figure 2A). This was the result of higher availability of FA in the circulation, while the fractional tracer uptake rates (K_i) were similar. Unexpectedly, intestinal blood flow was not altered in morbidly obese subjects as compared to controls (Figure 2B). Intestinal blood flow and FA uptake were not associated with each other. In addition, no differences were found between subjects with or without type 2 diabetes.

Six months after surgery FA uptake from the circulation into the jejunum was further increased to 4.3(2.0) mmol*100 g^{-1}*min^{-1}($P < .03$ vs baseline) (Figure 2A). Interestingly, the increase in jejunal FA uptake was associated with a lower 2-hour (OGTT) and fasting plasma glucose ($r = -0.65$; $P = .06$ and $r = -0.68$; $P < .05$, respectively) in morbidly obese patients with diabetes before the operation.

Bariatric surgery led to a decrease in jejunal blood flow (0.41 (0.33) vs 0.25 (0.14) ml*100 g^{-1}*min^{-1}, $P < .05$), while no statistical differences were found between type of bariatric surgery in jejunal or duodenal FA uptake ($P = .66$ and $P = .20$, respectively) or in blood flow ($P = .43$ and $P = .86$, respectively). Glucose tolerance did not impact fasting blood flow when subjects were divided into subgroups according to OGTT results. Consequently, the ratio of FA uptake to FFA delivery rate (FFA*blood flow) was doubled in the jejunum from 11.1 (4.6) to 22.6 (9.4) ($P = .003$).

3.3 | Nutrition and fat oxidation before and after surgery

Reported calorie intake tended to be lower in obese subjects compared to healthy controls (1304 (570) kcal vs 1625 (518), $P = .07$, respectively). Obese subjects decreased total calorie intake by 35% after bariatric surgery ($P < .0001$). Nutrient intake was lower postoperatively, while carbohydrate-, protein- and fat-intake decreased by 27% ($P = .0001$), 18% ($P = .007$) and −6% ($P = .04$) respectively.

Measured REE was 1830 kcal/day in preoperative group and 1300 kcal/day in the control group ($P > .001$), while total fat oxidation was increased compared to controls (8 (2) mg/min vs 6 (3) mg/min, $P = .002$). No statistical differences were seen in glucose and FA oxidation rate (10 (5) mg/min vs. 8 (3) mg/min; $P = .16$ and 2.5(0.7) umol/kg/min vs 2.92(0.9) umol/kg/min; $P = 0.091$, respectively).

REE decreased after bariatric intervention (−14%, $P = .0021$), while total lipid oxidation decreased by 26% ($P = .03$).[26] Glucose, FA and protein oxidation remained unchanged after bariatric surgery. Daily calorie balance (caloric intake – REE) correlated with intestinal FA uptake (in pooled data, controls and post-operative group) but not in the pre-operative group (Figure 3).

3.4 | Experimental animals

[^{18}F]FTHA tracer was taken in different parts of the small intestine and similarly in IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$ and in lean mice. IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$ mice had higher FFA and glycerol plasma concentrations after the scanning (0.50 (0.11) mmol/L vs 0.22 (003), $P = .003$ and 0.35 (0.10) mmol/L vs 0.12 (0.03), $P = 0.0007$, respectively) while no differences were seen in baseline. [^{18}F]FTHA uptake was enhanced compared to lean controls in the mucosal layer of the small intestine as determined by PSL (Figure 4). Mucosa: non-mucosa PSL−ratios varied from 1.8 to 3.8 in the small intestine.

Radioactivity measurements of faecal samples showed a movement of [^{18}F]FTHA from blood circulation into the intestinal lumen, but no significant differences were seen in faecal activity between groups (16.2 ± 1.2 ID% g^{-1} vs 12.5 ± 2.9, $P = .057$ in the duodenum,

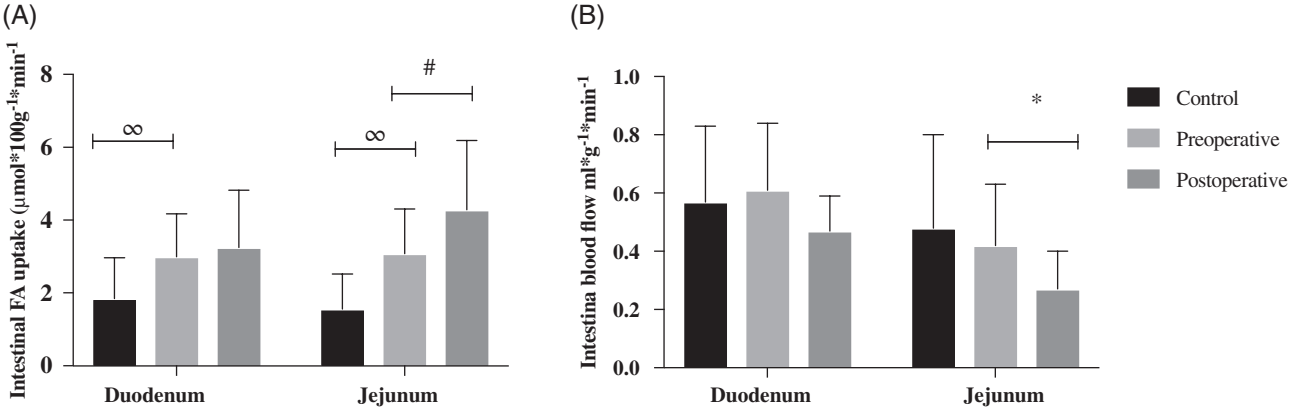


FIGURE 2 Bariatric surgery increased FA uptake in jejunum (A) and decreased blood flow in jejunum (B). *$P < .05$ vs baseline, # $P < .03$ vs baseline, ∞ $P < .005$ vs control in Student's t-test

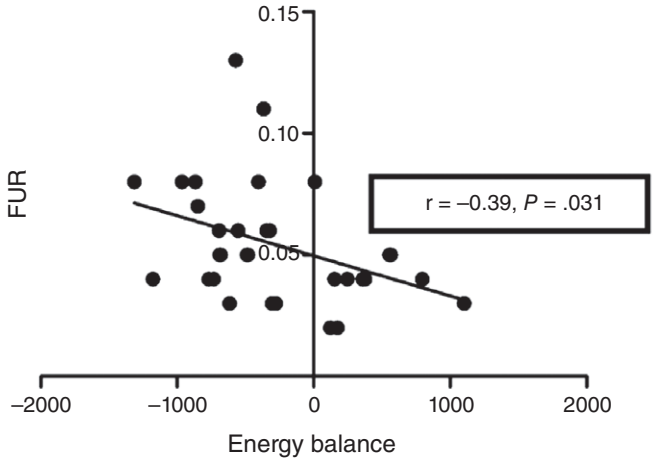


FIGURE 3 Relationship between daily calorie balance, REE and intestinal fractional fatty acid uptake (FUR). FUR correlated with daily energy balance (daily calorie intake – REE). Controls and post-surgery groups. Pearsons univariate analyses

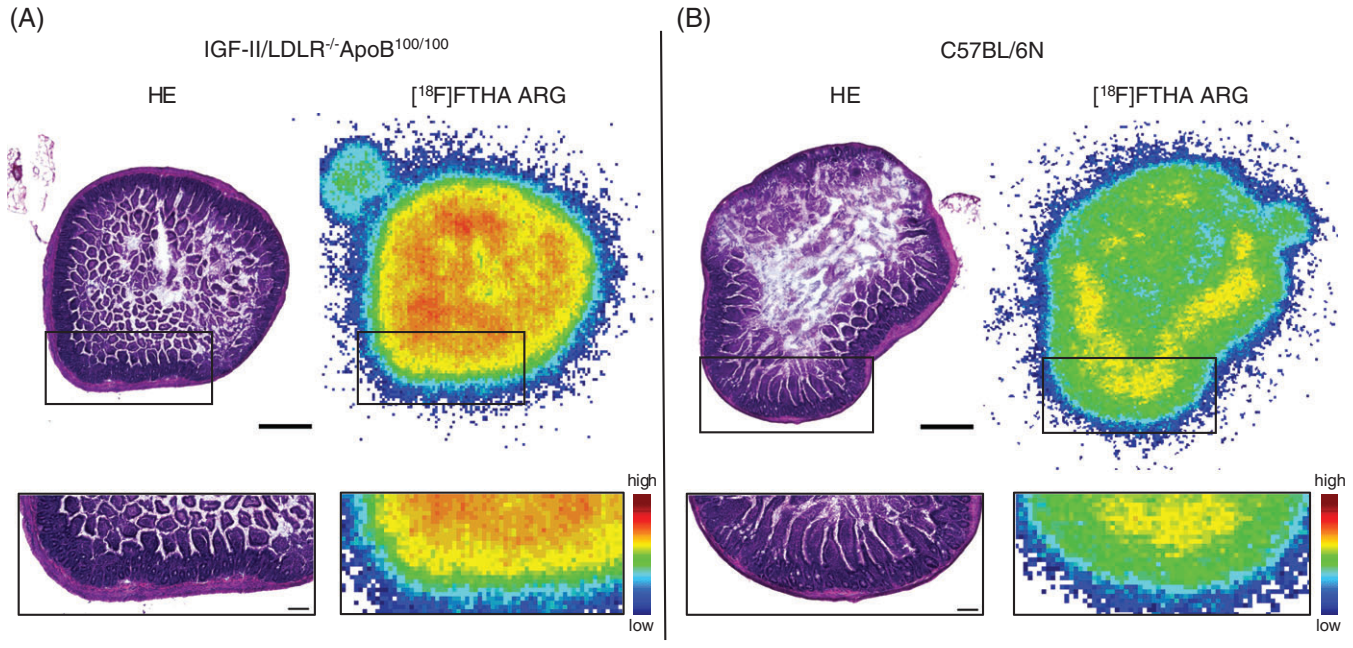
6.7 ± 6.7 vs 8.1 ± 4.8, $P = 0.75$ in the jejunum and 4.9 ± 0.7 vs. 8.3 ± 3.5, $P = .11$ in the ileum). Faecal to intestine wall biodistribution ratio varied from 1.8:1 to 2.5:1 in different small intestinal segments.

4 | DISCUSSION

This study demonstrates, for the first time in humans, that FFAs are taken up from the circulation into the small intestine, more so in obese than in lean subjects, and this situation remains after bariatric surgery. In contrast to the study hypothesis, intestinal blood flow is not enhanced in the obese, and intestinal blood flow is decreased after bariatric surgery. However, this is in line with other abdominal tissues, since also abdominal adipose tissue[26] and pancreatic flow[25] decreased.

Obesity increases FFA extraction to the small intestine from the circulation, and this phenomenon is independent of diabetes, in humans and mice. FA uptake even further increased after bariatric surgery (Figure 2). Enhanced FA uptake of enterocytes is a contradictory finding compared to other organs, as liver (unpublished observation), pancreas[25] and fat[26] tissue were FAU decreased in post-operative conditions.

Jejunal FFA uptake correlated with study patients' energy balance (REE registered with calorimetry, calories taken according to nutrition diagries) in the control and post-operative groups, but not in the pre-surgery group (Figure 3). This might express the normalization of the intestinal metabolism in obese patients with type 2 diabetes



(C)

	IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$	C57BL/6N	*P value*
Body weight (g)	34 ± 9.8	32 ± 5.0	0.685
[^{18}F]FTHA (PSL/mm^2)			
Duodenum	580 ± 59	440 ± 50	0.031
Jejunum	400 ± 13	330 ± 15	0.002
Ileum	250 ± 7.5	260 ± 8.5	0.154

Values are mean ±SD. PSL/mm^2; photosmulated luminescence per square millimeter

FIGURE 4 Representative haematoxylin and eosin-stained small intestine cryosections and corresponding autoradiographs showed that IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$ mice (A) had higher FTHA uptake compared with lean controls (B) in the mucosal layer of the small intestine as determined by photo-stimulated luminescence. ^{18}F]FTHA uptake was higher in IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$ mice in jejunum and duodenum (C). Scale bar = 500 μm (100 μm in inserts). Student's *t*-test for unpaired measurements

after surgery. The FAU-to-FFA delivery ratio doubled post-operatively, while no changes were seen between lean and obese subjects before surgery. We have demonstrated earlier that intestinal insulin action is blunted in the morbidly obese and is partly ameliorated after bariatric surgery.[27] In conjunction with the present data, this suggests that intestinal insulin resistance in the obese leads to changes in the glucose-FFA energy ratio, and in the catabolic state after bariatric surgery, peripheral adipose tissue releases FFA to circulation for nutritional demands. While the increment in FAU correlated with lower glycaemia and negative energy balance, this suggests a defensive role of FAU in treating type 2 diabetes.

Small intestine mucosa have a unique duality in FFA handling; FFAs entering the mucosa from the luminal side esterified mainly to triglycerides and serve to store energy. In contrast, plasma FFAs are primarily used for caloric and structural requirements of the epithelium.[28,29] We hypothesized that reduced FFA loss in feces could contribute to weight gain in mice, but this was not confirmed. We were unable to measure luminal [^{18}F]FTHA activity in humans and further studies are warranted to investigate FFA movements in intestinal mucosa after bariatric surgery.

In our study, insulin resistant mice had increased mucosa: non-mucosa ratios, demonstrating increased basolateral FA uptake in the mucosal layer, while no difference in luminal FTHA levels was seen between groups. This may be explained by the fact that the IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$ mouse model is not a typical obesity model. However, the IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$ mouse is a well-characterized model of insulin resistance, hyperglycaemia and hypercholesterolaemia that resembles the metabolic abnormalities and macrovascular complications of diabetes.[23]

The radiowater PET method, using freely diffusible [^{15}O]H_2O, is considered to be the gold standard for assessment of tissue nutritive flow in all human tissues. Here, we demonstrate that neither obesity nor type 2 diabetes increases small intestine blood flow in humans. Hill and Larkins[30] reported that intestinal blood flow is increased in diabetic mice as a result of marked intestinal hyperplasia, which is thought to be a consequence of hyperphagia. Previous studies in intestinal blood flow in diabetic rodents are inconclusive, probably related to differences in the type of diabetes, the nutritional state and the lack of insulin stimulation. A marked portion of previous animal studies has been done with insulin depletion, leading to starvation, glucosuria and weight reduction.[8,30,31] In the study of Lucas and co-workers,[8] obesity decreased, while hyperglycaemia increased, intestinal blood flow. Study subjects with type 2 diabetes had good or moderate glycaemic control with oral medication. Therefore, baseline blood flow measurements showed no difference between study groups. Even when study subjects were divided into subgroups according to pre-surgery OGTT results, no difference in small intestine blood flow was seen.

Unexpectedly, intestinal blood flow decreased after bariatric surgery in the jejunum and tended to be lower in the duodenum (Figure 2A). This is in line with a previous study in rats concerning diet restriction[30] and hepatic and pancreatic blood flow in the same study. In our previous study, intestinal blood flow remained unchanged in a smaller group of obese subjects when studied in a fasting state 3 months after surgery.[2] The type of bariatric surgery did not affect fasting blood flow in the small intestine, despite the anatomical changes. This is in line with our previous findings,[2] and suggests, along with existing literature, that fasting intestinal blood flow is regulated by oxygen demand for oxidative metabolism.[32] The intestine oxidizes glucose and FFA for metabolic needs, and post-operative changes in basolateral FA uptake might shift the need for oxygen in the mucosal layer, leading to decreased blood flow.

There are some limitations to this study. First, we are assessing only FFA uptake from the circulation into the intestinal enterocyte, and not FFA absorption from the intestinal lumen. Second, because of the limited spatial resolution of human PET imaging, it was not possible to provide detailed information on the intestinal mucosa [^{18}F]FTHA uptake and, potentially, its leakage into the lumen. When biodistribution of [^{18}F]FTHA in luminal content and intestinal segments was compared in the mice model, no differences were found between control and insulin-resistant obese animals. Third, excessive motion artefacts as a result of peristalsis, cardiovascular pulsation and respiration present challenges when the scanning time is more than a few seconds. ROIs were defined to quite fixed locations in the small intestine and the anatomical correspondence was confirmed from the PET image, using kidneys, spine and surrounding muscles as landmarks. Fourth, only female subjects were studied, and thus, the findings may not be generalizable to males.

In conclusion, obesity and type 2 diabetes influence the metabolism of the small intestine by increasing basolateral FA uptake of the mucosa, which cannot be normalized by bariatric surgery. This phenomenon is not driven by intestinal perfusion. Whether the alterations in mucosal FFA handling are the cause or the consequence of type 2 diabetes remains unsolved.

ACKNOWLEDGMENTS

We thank the staff of Turku PET Centre for all their expertise in the imaging analyses.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Author contributions

J. K. contributed to the design of the study, acquired and researched data, and wrote the manuscript. M. S. and A. R. contributed to the design of the animal study and discussion, researched data, and edited the manuscript. H. K. and P. S. contributed to the design of the human study and discussion, acquired data, and edited the manuscript. P. I. contributed to the discussion/revision of the manuscript. P. N. was the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of these data and the accuracy of the data analysis. All 7 authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Koffert J, Ståhle M, Karlsson H, et al. Morbid obesity and type 2 diabetes alter intestinal fatty acid uptake and blood flow. *Diabetes Obes Metab*. 2018;1–7. https://doi.org/10.1111/dom.13228