Renal hemodynamics and fatty acid uptake: effects of obesity and weight loss

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Abstract

Human studies of renal hemodynamics and metabolism in obesity are insufficient. We hypothesized that renal perfusion and renal FFA uptake are higher in morbidly obese as compared to lean subjects and that they both decrease after bariatric surgery. Cortical and medullary hemodynamics and metabolism were measured in 23 morbidly obese women and 15 age- and sex-matched nonobese controls by PET scanning of [^{15}O]-H_2O (perfusion) and 14(*R,* S)-[^{18}F]fluoro-6-thia-heptadecanoate (free fatty acid [FFA] uptake). Kidney volume and radiodensity were measured by CT, cardiac output by MRI. Obese subjects were re-studied 6 months after bariatric surgery.

Obese subjects had higher renal volume but lower radiodensity, suggesting accumulation of water and/or lipid. Both cardiac output and glomerular filtration rate (eGFR) were increased by ~25% in the obese. Total renal blood flow was higher in the obese (885 [317] *vs* 749 [300] ml/min of controls, p=0.049). In both groups, regional blood perfusion was higher in the cortex than medulla; in either region, FFA uptake was ~50% higher in the obese as a consequence of higher circulating FFA levels. Following weight loss (26±8 kg), total renal blood flow was reduced (p=0.006). Renal volume, eGFR, cortical and medullary FFA uptake were decreased but not fully normalized.

Obesity is associated with renal structural, hemodynamic, and metabolic changes. Six months after bariatric surgery, the hemodynamic changes are reversed, and the structural changes are improved. On the contrary, renal FFA uptake remains increased, driven by high substrate availability.

Keywords: PET, obesity, bariatric surgery, free fatty acids, renal hemodynamics

Abbreviations: BMI: body mass index; BSA: body surface area; Chronic Kidney Disease Epidemiology Collaboration: CKD-EPI; CT: computerized tomography; FFA: free-fatty acids; FOV: field of view; FTHA: 14(*R,* S)-[^{18}F]fluoro-6-thia-heptadecanoic acid; FUR: fractional uptake rate; Glomerular filtration rate: GFR; HU: Hounsfield units; MRI: Magnetic resonance imaging; OGIS: oral glucose insulin sensitivity; OGTT: oral glucose tolerance test; PET: positron emission tomography; RFAU: renal fatty acid uptake; ROI: region of interest; RYGB: Roux-en-Y gastric bypass; SGLT2: sodium glucose cotransporter 2; T2D: type 2 diabetes; WHP: waist-to-hip ratio

Introduction

The incidence of obesity is on the rise virtually worldwide (40). While diabetes and hypertension are the two most common risk factors for the development of chronic kidney disease (CKD) (12), mounting evidence indicates that obesity *per se* poses an additional risk (39). Human studies of the renal hemodynamics and metabolism in obesity are scanty, however, in part due to the

difficulty of accounting for the heteromorphism of renal cell types and the diversity in perfusion and function in different renal regions (35).

The kidney is a richly perfused organ, receiving approximately 20% of cardiac output, and has a unique perfusion system. Blood supply to the renal cortex occurs through the afferent arterioles of each nephron while blood supply to the medulla occurs only through the vasa recta of the juxtaglomerular nephrons. It follows that perfusion in the renal cortex is higher than in the medulla. This high cortical perfusion serves for the filtration of large volumes of blood through the glomeruli as well as the reabsorption of proteins, substrates and electrolytes; the main function of the medulla is the active reabsorption of water and solutes.

The energy for these processes is provided by very active metabolic processes. Tubular cells in the cortex, such as those in proximal tubules and the thick ascending limb of the loop of Henle, are rich in mitochondria and depend predominantly on oxidative metabolism, with fatty acids, ketone bodies, and lactate being the preferred substrates (2). On the other hand, cells in the inner medulla, such as those of the thin descending and ascending limbs of the loop of Henle and the collecting duct, have few mitochondria and depend predominantly on glycolysis for energy production (26). The renal cortex also contributes to gluconeogenesis (28); renal gluconeogenesis is confined to the proximal tubule since the key enzymes in the pathway – glucose-6-phosphatase, fructose-1,6-biphosphatase, and phosphoenolpyruvate carboxykinase – are only found there (33).

Regulation of renal hemodynamics is primarily achieved by changes in arteriolar resistance, which can jointly affect both renal blood flow and glomerular filtration rate (GFR) (32). However, some basic aspects regarding the interplay between renal perfusion and cardiac output have not been clarified. Thus, cardiac output is increased in obese subjects (19) and decreases after weight loss (24). However, it is not known how these changes affect renal perfusion and metabolism. Therefore, aims of the present study were to simultaneously measure regional, *i.e.,* cortical *vs* medullary, hemodynamics and metabolism *in vivo* in obese subjects – with or without type 2 diabetes (T2D) – and nonobese controls, and to determine the effects of major weight loss. As free fatty acids (FFA) are the main substrate for the kidney in the fasting state, we employed positron-emitting tomography (PET) to quantitate both perfusion (with the use of ^{15}O-labelled water) and FFA uptake (using the long-chain fatty acid analog 14(*R*,S)-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]-FTHA)).

Methods

Participants and study design We studied 23 morbidly obese women and 15 age- and sex-matched healthy nonobese controls. Obese patients were studied before and 6 months after bariatric surgery, and controls were studied only once along with the patients. Inclusion and exclusion criteria have been described in detail (13). Based on ADA criteria (1), 10 obese patients had type 2 diabetes (T2D) and 13 were nondiabetic (ND), including 4 with impaired glucose tolerance and 1 with impaired fasting glucose before the operation. Nine of the obese subjects had a diagnosis of arterial hypertension. Eight obese were treated with laparoscopic Roux-en-Y gastric bypass (RYGB) and 15 with laparoscopic sleeve gastrectomy. Data on adipose tissue (4) and liver (16) fatty acid uptake from these subjects have been previously reported. The protocol was approved by the Ethics Committee of the Hospital District of Southwestern Finland, and all subjects gave written informed consent before participating in the study (NCT01373892).

Study protocol Clinical screening, anthropometric and biochemical measurements were performed as described (14). Blood pressure was measured with OMRON 711 automatic blood pressure monitor (Omron Corporate, Kyoto, Japan). Subjects then underwent positron-emitting tomography/computerized tomography (PET/CT) measurements in the fasting state using a hybrid GE discovery STE and VCT scanners (General Electric Medical Systems, Milwaukee, WI, USA). In obese patients, the imaging studies were performed before the standard 4-week very-low calorie diet that preceded surgery. For the PET studies, 2 catheters were inserted in the antecubital veins, one for the administration of radiolabeled tracers and the other for arterialized blood sampling. Subjects underwent CT scans that served as attenuation map and as anatomical reference for PET images. Subjects were injected with an intravenous bolus (554 ± 124 Mbq) of ^{15}O-labelled water (([^{15}O]-H_2O) followed by dynamic PET acquisition in the abdominal region (26 frames *x* 310 s). After 10 min, study subjects were given an intravenous bolus (185 ± 46 MBq) injection of [^{18}F]-FTHA, following which the dynamic PET imaging of thoracic and upper body regions started (4, 16). After 86 ± 3 min, the abdomen was scanned (5 frames *x* 180 s) (14). Blood samples were drawn during the entire scanning period to measure FFA as well as radioactivity levels.

Radiotracers The production of [^{15}O]-H_2O ($t_{½}$ = 122 s) (10) and [^{18}F]-FTHA ($t_{½}$ = 110 min) (15) have been described previously.

PET data analysis PET images were reconstructed in 256 *x* 256 matrix after correction for decay time, dead time, and photon attenuation. Image analysis was performed using Carimas v.2.9 (http://www.turkupetcentre.fi/). To obtain the time-radioactivity curves, the regions of interest (ROIs) were manually drawn on PET/CT fusion images in renal cortex and medulla (**Figure 1A&1B**). In particular, consecutive thin ROIs were drawn in the renal cortex while avoiding tissue borders in 4-5 consecutive planes on both kidneys for [^{18}F]-FTHA, and in 10-12 consecutive planes

in each kidney for [^{15}O]-H_2O, due to larger inhomogeneity in the signal. A second thin ROI was drawn more centrally on the same slices, representing the medulla.

Renal blood flow was calculated from radiowater PET scans using a one-tissue compartmental model, as previously described by Inaba *et al.* (17) and Kudomi *et al*. (22). The image-derived input function from abdominal aorta was used in the calculation (14). Glomerular filtration rate (eGFR, in mL/min/1.73m^2) was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (23). eGFR in mL/min was obtained using the individual values of body surface area (BSA) calculated according to Du Bois and Du Bois (6).

For the calculation of FFA uptake (FAU) from [^{18}F]-FTHA-PET acquisitions, metabolite correction was performed for the radioactivity curves on the assumption that any residual activity after 30 min is attributable to metabolites. Plasma and tissue time-radioactivity curves were analyzed graphically using the linearization method (29). The slope of the plot in the graphical analysis equals the fractional uptake rate (FUR) of [^{18}F]-FTHA. FUR values were corrected for renal tissue density (1.05 kg·L^{-1}), and multiplied by the serum FFA concentration (μmol/L) during the [^{18}F]-FTHA-PET scanning to obtain the tissue FAU (μmol·min^{-1}·100g^{-1}).

Renal volume and tissue density Renal volume was measured using CT. Magnetic resonance imaging (MRI) was also used for those subjects in whom neither kidney was in the field of view in the CT. A 2-D mask was applied to all slices of each kidney thus creating a 3-D estimate of renal volume. The renal pelvis was excluded from the images. The final volume was obtained after visual inspection of each slice in order to fine-tune the voxels that would be part of the renal mask (**Figure 1C**). In all subjects, tissue radiodensity in Hounsfield units (HU) was also obtained. The analysis of images was performed using Carimas v.2.9 (http://www.turkupetcentre.fi/).

Measurement of cardiac output Cardiac output was measured by MRI as previously described (20).

Indirect calorimetry Open-system indirect calorimetry (Deltatrac®) was used for the 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 described (34).

Selected metabolites Selected plasma metabolites were measured by nuclear magnetic resonance spectroscopy, as previously described (36).

Calculations and statistical analysis Insulin sensitivity was estimated by the OGIS (Oral Glucose Insulin Sensitivity) method (25). On the assumption that cortical renal blood flow represents the near totality of blood flow to the kidney, total renal blood flow was obtained as the product of cortical blood perfusion and renal volume. The filtration fraction was calculated as the ratio of eGFR to total renal plasma flow.

Continuous variables are expressed as mean ± SD. The normality of distribution was assessed using the Shapiro-Wilkinson test; variables that were not normally distributed were logarithmically transformed before analysis. One-way analysis of variance (ANOVA) was used to compare control subjects with obese patients, and nondiabetic with T2D subjects at baseline. The effect of surgery was tested by Wilcoxon signed rank test. Two-way ANOVA for repeated measures was used to compare the data of nondiabetic and T2D subjects before and after surgery. Pearson's correlation coefficient was used to investigate associations between body composition and renal metabolism. Statistical analysis was performed using JMP; significance was set at $p \leq 0.05$.

Results

Clinical and metabolic characteristics (**Table 1**) The patients with T2D (n = 10) were matched to the nondiabetic obese participants (n = 13) by age (45 ± 7 *vs* 41 ± 11 years, *p*=ns) and BMI (40.4 ± 4.6 *vs* 41.7 ± 4.0 kg/m^2, *p*=ns), and were in good glycemic control (HbA_{1c} = 6.4 ± 0.7%, fasting plasma glucose = 6.4 ± 1.0 mmol/L). Except for HbA_{1c} and fasting glucose, none of the parameters measured in the obese participants in this study differed by T2D either before or after surgery; the data of nondiabetic and T2D participants were therefore pooled for further analysis.

As expected, obese participants had higher waist-to-hip ratio (WHR), fat mass, plasma FFA and glycerol concentrations as compared to controls, while eGFR (per 1.73 m^2 of body surface area) was similar.

Hemodynamics Cardiac output was increased by ~25% in the obese group as were VO_2, VCO_2, and energy expenditure (**Table 2**). In the pooled baseline data, all these parameters were strongly related to the BMI (or other measures of body size, such as body weight, body surface area, and lean body mass), such that differences between obese and control participants were no longer statistically significant when adjusted for BMI.

In the kidney, cortical perfusion (per unit tissue volume) was significantly higher as compared to medullary perfusion ($p<0.0001$) in both obese and controls. Cortical and medullary blood perfusion rates (per unit tissue volume) were not different between the two groups.

- The total volume (both kidneys) was higher in the obese, but the radiodensity index (HU) was lower, indicating an increased content of water or lipid (or both) in the obese. By attributing the cortical blood perfusion to the entire measured volume, renal blood flow was higher (p=0.049) in obese than lean participants. The filtration fraction averaged 22 ± 4% in the leans, and 23 ± 5% in the obese, and was not significantly different between the two groups. In the pooled baseline data, both total renal blood supply and eGFR were

directly related to cardiac output, and to each other (**Figure S1**). Data supplements can be found here: https://doi.org/10.6084/m9.figshare.9763955

FFA uptake In the respective selected ROIs, fatty acid uptake was higher in the medulla than in the cortex ($p<0.0001$), the two rates being highly correlated with each other ($r = 0.96$, $p<0.0001$). Both cortical and medullary fatty acid uptake were higher in obese as compared to lean participants ($p=0.001$ and $p=0.0008$, respectively). When fatty acid uptake is expressed as a fraction of fatty acid delivery to tissue, uptake remained significantly higher ($p=0.01$) only in the medulla (**Table 3**). Renal fatty acid uptake was well correlated with whole-body fat oxidation both in the cortex and the medulla (**Figure 2**).

In addition to plasma FFA and glycerol, obese participants were also characterized by raised circulating levels of branched-chain amino acids (BCAA), lactate, pyruvate, and citrate (Table 1). In the pooled baseline data, the ß-OH/AcAc ratio was positively associated with both cortical and medullary FA uptake (**Figure 3**) as well as with whole-body fat oxidation ($r = 0.37$, $p=0.025$).

Effects of bariatric surgery Six months following bariatric surgery, participants had lost 26 ± 8 kg, without any difference between RYGB and sleeve gastrectomy (data not shown). Along with HbA_{1c}, circulating concentrations of BCAA, glycerol and pyruvate, but not FFA or ketones, were all decreased (**Table 1**). Plasma insulin concentrations tended to decrease and insulin sensitivity (as indexed by OGIS) significantly improved. Cardiac output, gas exchange rates, and energy expenditure decreased, and there was a trend for whole body fat oxidation also to be reduced (Table 2). Renal volume was decreased while tissue density was increased ($p=0.0001$ for both), and eGFR was reduced. In contrast, perfusion (per unit volume) was unchanged, and neither cortical nor medullary FA uptake was significantly reduced, either as absolute values or as a fraction of FFA delivery to the kidneys. When accounting for renal volume, total renal blood flow was decreased (885 [317] *vs* 760[367], $p=0.006$). No difference was seen between RYGB and sleeve gastrectomy also regarding the change in renal volume, tissue density, or total renal flow (data not shown).

Discussion

The simultaneous measurement of systemic and renal hemodynamics parameters and FFA uptake in this study yielded several main findings. Firstly, renal volume was increased in the obese, in keeping with the results of Rea *et al*.(31), who reported larger glomerular planar surface areas in obese as compared to lean kidney donors (total renal volume was not measured). In our study, the lower radiodensity in the obese suggests that the nephromegaly might be due to an increase in the

water/lipid component. Studies in both animals and humans have demonstrated fat accumulation in the renal sinus and renal parenchyma. Fat accumulation in the renal sinus is of special interest, since it may lead to compression of the renal vein and lymphatic vessels, which in turn result in increases in renal interstitial pressure (27). Obese rabbits with larger fat deposits within the renal sinus exhibit larger kidneys (7). In humans a ''fatty kidney'' – or the renal sinus fat volume – has been shown to associate with a higher risk of hypertension (8) and with the number of prescribed antihypertensive medications (3). Importantly, in the present study the decrease in renal radiodensity was almost completely reversed following weight loss over a 6-month time period (**Table 2**). Taken together, our data indicate that after bariatric surgery any fat accumulation within the renal parenchyma or renal edema (or combination of the two) can regress to quasi-normal levels.

Secondly, in the obese renal perfusion (per unit tissue mass**)** was maintained at the level of the nonobese participants, but their total renal blood flow was higher. Both total eGFR and total blood flow were increased in proportion to cardiac output (**Table 3 and Figure S1**). In a large biopsy study of living kidney donors (5), obesity was independently associated with a higher single-nephron GFR but a normal number of nephrons. Importantly, weight loss reduced the increases in eGFR, and total blood flow, thereby attenuating the risk of long-term hyperperfusion and kidney damage.

Thirdly, fatty acid uptake was increased in the obese by ~50% in both cortical and medullary ROIs. [^{18}F]-FTHA, *i.e.,* a long-chain fatty acid analogue, undergoes partial metabolism in mitochondria and is then trapped. Tissue accumulation of [^{18}F]-FTHA includes both storage and oxidation of FFA (18). Of note, since FTHA (like fatty acids) is tightly bound to plasma albumin, it is not filtered by the glomeruli but is extracted from plasma at the basolateral membrane of tubular cells. From our data it can be calculated that in obese participants the kidneys extract an average 66 μmol/L, or 8.3%, of the FFA concentration in perfusing plasma. This estimate is in keeping with the data of Owen *et al.* (28), who used renal catheterization to measure renal FFA extraction (averaging 85 μmol/L) in a small group of obese individuals. The very good agreement between the two studies supports the use of [^{18}F]-FTHA-PET to measure FFA uptake *in vivo* non-invasively. In terms of the intrinsic ability of renal tissue to extract FFA from the plasma (*i.e.,* the fractional uptake parameter, FUR, **Table 3**), obesity was not associated with an enhanced avidity for this substrate (especially in the cortex), and the increased FFA uptake was almost entirely the result of increased delivery of the substrate. The direct correlation between renal FFA uptake and whole-body fat oxidation (**Figure 3**) supports the interpretation that the kidneys share with other organs and tissues the increased exposure to fatty substrates resulting from unrestrained lipolysis (4, 16).

To the extent that the ß-OH/AcAc ratio reflects the mitochondrial redox state (21), its positive association with renal FFA uptake (**Figure 4**) as well as with whole-body fat oxidation suggests that the higher renal FFA uptake in the obese induced a higher oxidation of these substrates. In this context, the raised circulating levels of citrate, lactate, and pyruvate can be regarded as markers of mitochondrial overload (30).

Finally, surgically induced weight loss led to only an attenuation of renal FFA uptake. As plasma FFA also did not return to the level of nonobese participants, this finding indicates that 6 months after surgery the obese participants were still in a state of negative energy balance and increased lipolysis. Of note is that the presence of well-controlled, uncomplicated T2D in the obese group was not associated with any difference in the measured hemodynamic and metabolic parameters. However, we cannot rule out that more severe hyperglycemia may impact renal hemodynamics and FFA handling above and beyond the effect of surgery.

In previous studies using the PET methodology in obese and nonobese individuals, we have quantified FFA uptake in liver, subcutaneous and visceral adipose tissue, and skeletal muscle (4, 16, 38). It is of interest to compare FFA uptake across different tissues. Per unit tissue mass, renal FFA uptake is much larger than in abdominal subcutaneous (0.28 $\mu mol \cdot min^{-1} \cdot 100g^{-1}$) or visceral adipose tissue (0.57 $\mu mol \cdot min^{-1} \cdot 100g^{-1}$) or resting skeletal muscle (0.36 $\mu mol \cdot min^{-1} \cdot 100g^{-1}$), but only about half that of liver (10.4 $\mu mol \cdot min^{-1} \cdot 100g^{-1}$). By multiplying tissue uptake rates by the respective total mass, the contribution of muscle is similar to that of the liver and higher than either kidney or adipose tissue (**Figure 4**). Of note, the sum of fat uptake rates by these organs averages 3 $\mu mol \cdot min^{-1} \cdot kg^{-1}$, an estimate well within the range of values for FFA turnover obtained with the use of tracers of oleate or palmitate (11).

Our study has limitations**.** Firstly, GFR was estimated and not directly measured, which precludes a reliable estimation of intraglomerular pressure and afferent and efferent arteriolar resistance (*e.g.*, by applying Gomez formula (9)). Secondly, the resolution of the PET/CT scanner we used does not delineate a clear separation between cortex and medulla. Therefore, ROIs had to be drawn based on the anatomical references: a thin band of voxels into consecutive planes for the cortex just underneath the renal capsule and a parallel inner band for the medulla were used. When anatomically small structures are analyzed, the partial volume and the spillover effect may give rise to some underestimation and overestimation of the values, respectively. Radiowater is freely diffusible in and out of cells and thus measures true tissue perfusion. However, it was not possible to take into account the traffic of water within the kidney medulla and urinary excretion; this methodological aspect and the adequacy of the arterial input function need further study. Furthermore, as shown in Figure 1, perfusion in the cortex does not seem homogeneous. The

potential heterogeneity in glomerular blood flow and filtration in different nephron populations, especially between cortical and juxtamedullary nephrons, has been remarked in the past (37). Also, the physics of positron emission, such as partial volume effects and spillover, may give rise to some overestimation of medullary perfusion. PET and cardiac MRI measurements were not obtained simultaneously, so cardiac output may have changed slightly during the PET scan. Finally, the current study included only women, due to the difficulty in our Center in recruiting morbidly obese men. Whereas inclusion of both genders would have been more representative of the general population, our data on renal FFA uptake and perfusion are in close agreement with those of other studies that have included subjects of both genders (17, 28).

In conclusion, our study demonstrates that obesity leads to structural, metabolic and hemodynamic renal changes. More specifically, in the obese renal volume, FFA uptake and total renal perfusion are higher as compared to lean participants. After bariatric surgery, total renal blood flow, and eGFR are decreased, thereby attenuating the risk for progression of obesity-induced chronic kidney disease. On the contrary, 6 months after bariatric surgery renal FFA uptake is not normalized.

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451

452 **Figure legends**

453

454 **Figure 1** – Region of interest (ROI) placement in the renal cortex and medulla in a [^{15}O]-H_2O
455 image (A) and an [^{18}F]-FTHA image (B). (C): Volume of interest depicting how renal volume was
456 measured.

457 **Figure 2** – In the whole dataset, whole-body fat oxidation correlated positively with cortical (A)
458 and medullary FFA uptake (B).

459 **Figure 3** – ß-OH/AcAC, a surrogate of the mitochondrial NAD^+/NADH balance, correlated
460 positively both with cortical (A) and medullary FFA uptake (B). ß-OH: ß-OH-butyrate; AcAC:
461 acetoacetate.

462 **Figure 4** – FFA uptake in several tissues measured in the same subjects. Whereas renal FFA
463 uptake per unit tissue mass is only second to hepatic FFA uptake, when accounting for the tissue
464 mass renal FFA uptake is similar to those of fat depots. In all tissues FFA uptake was higher in the
465 obese as compared to the lean controls. SC: abdominal subcutaneous fat, VF: visceral fat, SM:
466 skeletal muscle. Entries are mean±SE.

467

Table 1 - Clinical and metabolic characteristics of the 2 study groups [§]

	Controls (n = 15)	Obese (n = 23)		
		Before	After	p^{o}
Age (years)	45 ± 12	43 ± 10	-	-
BMI (kg/m^2)	22.6 ± 2.8	41.1 ± 4.2*	31.8 ± 4.2#	<0.0001
WHR (cm/cm)	0.77 ± 0.05	0.89 ± 0.07*	0.87 ± 0.09#	0.04
Fat mass (kg)	19 ± 6	56 ± 10*	37 ± 9#	<0.0001
Fat-free mass (kg)	42 ± 4	56 ± 9*	49 ± 6#	<0.0001
eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)	107 ± 10	103 ± 14	105 ± 17	ns
Systolic BP (mmHg)	128 ± 16	130 ± 15	127 ± 14	ns
Diastolic BP (mmHg)	78 ± 9	85 ± 10	80 ± 11	0.04
TG ($mmol \cdot L^{-1}$)	0.66 ± 0.32	1.18 ± 0.42*	1.09 ± 0.54#	ns
Glucose ($mmol \cdot L^{-1}$)	5.13 ± 0.34	5.71 ± 1.03*	5.30 ± 0.79	ns
Insulin ($\mu U \cdot mL^{-1}$)	3.0 [3.5]	9.5 [10.8]*	4.0 [3.0]	(0.06)
OGIS ($ml \cdot min^{-1} \cdot m^{-2}$)	426 [91]	351 [67] *	444 [63]	<0.0001
HbA_{1c} (%), (mmol/mol)	5.6±0.3, (38±3)	6.0±0.7, (42±7)*	5.4±0.4, (36±5)	<0.0001
FFA ($mmol \cdot L^{-1}$)	0.55 ± 0.17	0.80 ± 0.22*	0.77 ± 0.17#	ns
Glycerol (µmol/L)	67 ± 23	113 ± 31*	108 ± 53#	0.01
BCCA (µmol/L)	250 ± 45	294 ± 42*	241 ± 48	<0.0001
ß-OH-butyrate (µmol/L)	110 [180]	140 [140]	188 [218]	ns
Acetoacetate (µmol/L)	36 [49]	44 [34]	55 [36]	ns
Lactate (µmol/L)	1186 ± 182	1460 ± 322*	1337 ± 226#	ns
Pyruvate (µmol/L)	72 ± 18	88 ± 25*	78 ± 25	0.046
Citrate (µmol/L)	110 [22]	125 [33]*	127 [29]#	ns

[§] Data are mean ± SD or median [IQR]; BCAA= branched-chained amino acids; * $p \leq 0.05$ obese *vs* controls; ° after *vs* before surgery; # $p \leq 0.05$ obese after surgery *vs* controls.

Table 2 – Whole-body parameters.[§]

	Controls	Obese		
		Before	**After**	p^{o}
Cardiac output (CO) ($L \cdot min^{-1}$)	5.2 [1.2]	6.5 [2.8]*	5.9 [1.9]#	0.0019
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.11 [0.61]	3.01 [1.07]	3.11 [0.76]	ns
Heart rate (bpm)	59 ± 11	59 ± 10	56 ± 8	ns
VO_2 ($mL \cdot min^{-1}$)	185 ± 18	259 ± 30*	230 ± 34#	<0.0001
VO_2 ($mL \cdot min^{-1} \cdot kg_{FFM}^{-1}$)	4.4 ± 0.4	4.7 ± 0.4	4.7 ± 0.5	ns
VCO_2 ($mL \cdot min^{-1}$)	155 ± 15	212 ± 26*	192 ± 33#	0.001
VCO_2 ($mL \cdot min^{-1} \cdot kg_{FFM}^{-1}$)	3.7 ± 0.3	3.8 ± 0.34	3.9 ± 0.6	ns
Fat oxidation ($\mu mol \cdot min^{-1}$)	59 ± 18	89 ± 26*	76 ± 35#	(0.06)
CHO oxidation ($\mu mol \cdot min^{-1}$)	611 ± 199	771 ± 297*	755 ± 441#	ns
Energy expenditure ($kcal \cdot day^{-1}$)	1299 ± 122	1807 ± 212*	1614 ± 240#	<0.0001

[§] Data are mean ± SD or median [IQR]; VO_2 = oxygen consumption; VCO_2 = carbon dioxide production; CHO = carbohydrate; * $p \leq 0.05$ obese *vs* controls; ° after *vs* before surgery; # $p \leq 0.05$ obese after surgery *vs* controls.

Table 3 – Renal parameters.[§]

		Obese		
	Controls	**Before**	**After**	***p*°**
Renal volume (mL)	256 [63]	340 [118]*	310 [118]#	0.0001
Radiodensity (HU)	31.5 [9.8]	15.3 [13.1]*	26.9 [9.0]	<0.0001
Cortical blood perfusion ($mL \cdot min^{-1} \cdot 100mL^{-1}$)	268 [104]	262 [62]	246 [62]	ns
Medullary blood perfusion ($mL \cdot min^{-1} \cdot 100mL^{-1}$)	163 [72]	149 [51]	166 [53]	ns
Total renal BF ($mL \cdot min^{-1}$)	749 [300]	885 [317]*	760 [367]	0.006
Renal BF/CO (%)	16 ± 4	15 ± 4	15 ± 6	ns
eGFR (mL/min)	104 ± 11	129 ± 23*	118 ± 24#	0.0025
Hematocrit (%)	36.6 ± 2.7	39.5 ± 2.2*	38.3 ± 3.7	(<0.1)
Filtration fraction (%)	22 ± 4	23 ± 5	24 ± 5	ns
Cortical FAU ($\mu mol \cdot min^{-1} \cdot 100g^{-1}$)	4.1 ± 1.5	6.3 ± 1.8*	6.0 ± 1.8#	ns
Cortical FUR (%)	7.7 ± 1.2	8.2 ± 1.3	8.1 ± 1.9	ns
Medullary FAU ($\mu mol \cdot min^{-1} \cdot 100g^{-1}$)	4.6 ± 2.1	7.5 ± 2.2*	6.9 ± 1.9#	ns
Medullary FUR (%)	8.4 ± 2.1	9.9 ± 1.5*	9.4 ± 1.9	ns

[§] Data are mean ± SD or median [IQR]; BF = blood flow; CO = cardiac output; FUR = fractional FA uptake; FAU = FFA uptake; * $p \leq 0.05$ obese *vs* controls; ° after *vs* before surgery; # $p \leq 0.05$ obese after surgery *vs* controls.

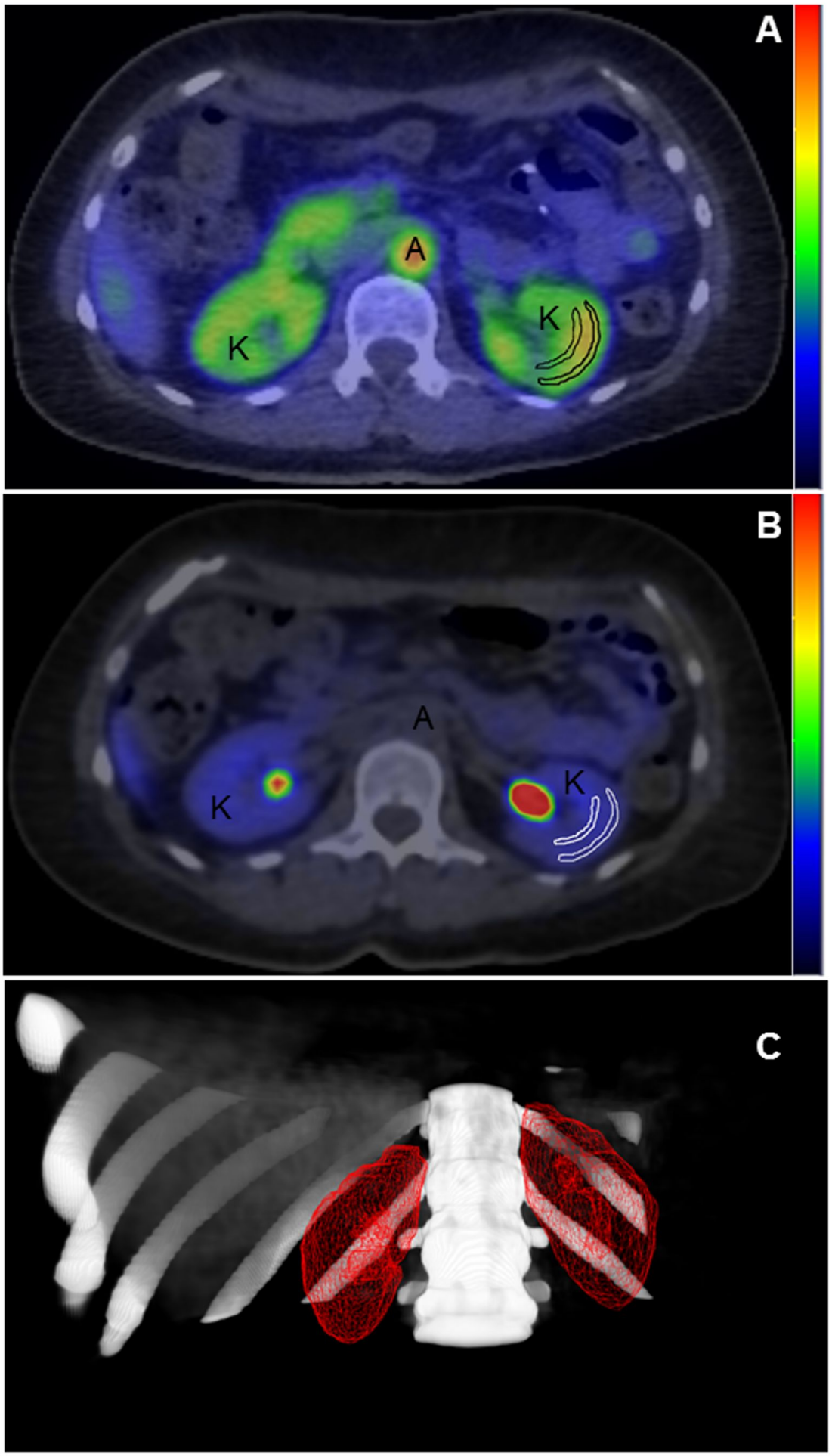


Figure 1

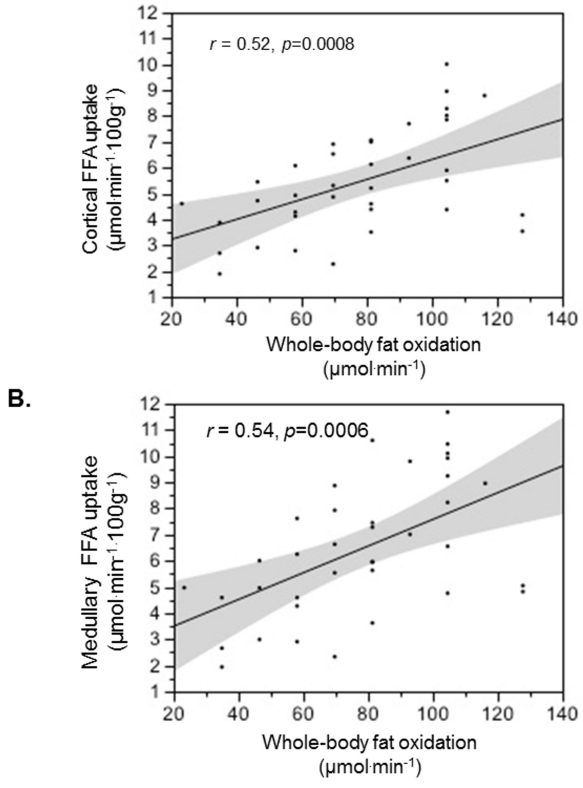
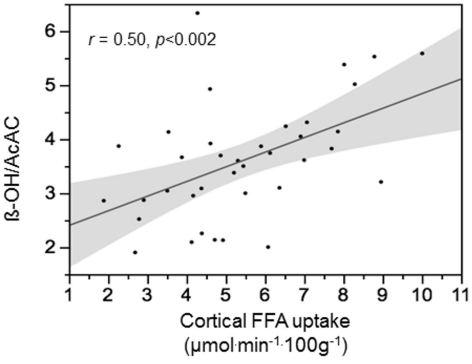

A.
r = 0.52, p=0.0008
Cortical FFA uptake
(μmol·min-1·100g-1)
Whole-body fat oxidation
(μmol·min-1)
B.
r = 0.54, p=0.0006
Medullary FFA uptake
(μmol·min-1·100g-1)
Whole-body fat oxidation
(μmol·min-1)

Figure 2

A.


r = 0.50, p<0.002
ß-OH/AcAC
Cortical FFA uptake
(µmol·min-1·100g-1)

B.

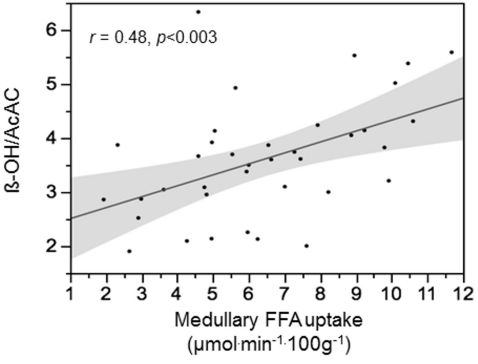

r = 0.48, p<0.003
ß-OH/AcAC
Medullary FFA uptake
(µmol·min-1·100g-1)

Figure 3

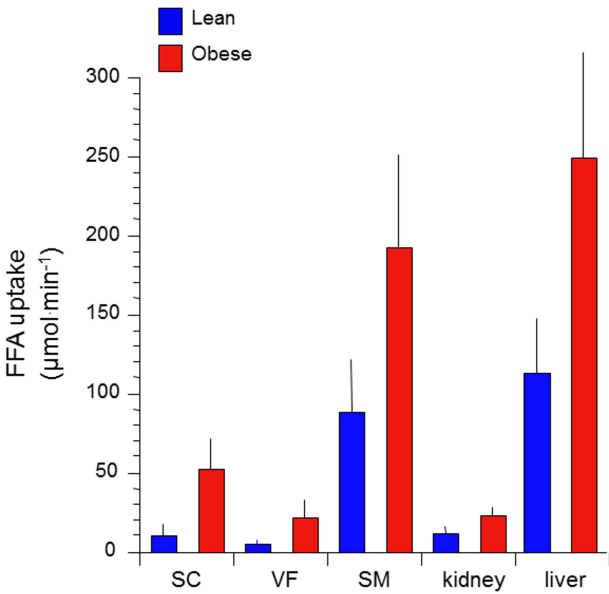

Lean
Obese
FFA uptake
(μmol·min-1)
300
250
200
150
100
50
0
SC
VF
SM
kidney
liver

Figure 4