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ORIGINAL ARTICLE

# Visceral fat is better related to impaired glucose metabolism than body mass index after kidney transplantation

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## Summary

The role of visceral adipose tissue (VAT) in post-transplant hyperglycaemia is not known. We evaluated 167 patients without diabetes 8-10 weeks after kidney transplantation, performing oral glucose tolerance tests and measuring VAT content from dual-energy X-ray absorptiometry scans. Median VAT weight in normal glucose tolerance patients was 0.9 kg, impaired fasting glucose patients 1.0 kg, impaired glucose tolerance patients 1.3 kg and patients with post-transplant diabetes (PTDM) 2.1 kg ($P = 0.004$, indicating a difference between groups). Percentage VAT of total body fat was associated with fasting ($R^2 = 0.094$, $P < 0.001$) and 2-h glucose concentration ($R^2 = 0.062$, $P = 0.001$), while BMI was only associated with 2-h glucose concentration ($R^2 = 0.029$, $P = 0.028$). An association between BMI and 2-h glucose concentration was lost in adjusted models, as opposed to the associations between VAT as percentage of total body fat and glucose concentrations ($R^2 = 0.132$, $P < 0.001$ and $R^2 = 0.097$, $P = 0.001$, respectively for fasting and 2-h glucose concentration). In conclusion, VAT is more closely related to impaired glucose metabolism than BMI after kidney transplantation. The association with central obesity should encourage additional studies on lifestyle interventions to prevent PTDM.

## Introduction

Abnormal glucose metabolism is a common complication in kidney transplant recipients and is strongly associated with adverse long-term outcomes such as cardiovascular events, premature graft failure and mortality [1–5].

Post-transplant diabetes mellitus (PTDM), previously also called new-onset diabetes mellitus (NODAT) [6], resembles type 2 diabetes in many ways [7]. However, with immunosuppressive drugs and noninfectious inflammation as additional provoking factors after transplantation, PTDM is currently classified as a 'drug or chemical-induced' type of diabetes [8,9]. Immunosuppressive drugs have been shown to impair insulin secretion (e.g. calcineurin inhibitors) and increase insulin resistance (e.g. steroids), but the contribution of each of these mechanisms to the development of PTDM may vary in the presence of different risk factors [10,11].

Increasing body mass index (BMI) is associated with the risk for developing PTDM [12–14]. However, high values of BMI do not necessarily reflect elevated fat mass, and BMI does not reflect the distribution of fat [15]. Visceral fat is considered to be the main mediator of the adverse effects related to obesity, and excess visceral fat has been



 

closely linked to insulin resistance [16,17] and has also been found to precede type 2 diabetes [18]. Visceral fat mass may therefore be the most relevant compartment in relation to glucose homeostasis and may thus play a role also in development of PTDM. Lifestyle prevention of PTDM has only been tested in one small intervention study with a modest improvement in postprandial glycaemia in the intervention group [19].

Visceral adipose tissue (VAT) is traditionally evaluated by computed tomography (CT) scans, but the attendant cost and radiation dose preclude screening of large cohorts in a clinical setting [20,21]. However, VAT content may now be quantified with a recently developed software applied on standard dual-energy X-ray absorptiometry (DXA) scans, at a lower cost and with lower radiation exposure than with CT [22].

As studies in the nontransplant population suggest that VAT facilitates development of type 2 diabetes [23], we hypothesized that VAT also would be higher in patients who develop PTDM than in those who maintain with normal glucose tolerance after transplantation. In this study, we did not study the aetiological factors of PTDM, which we have addressed previously [24,25]. The aim of this study was to examine the association between VAT, plasma glucose concentrations and insulin resistance in kidney transplant patients in a stable phase early after kidney transplantation.

## Patient material and methods

### Study design and population

The study was a cross-sectional cohort study of patients who received a kidney allograft at our National Transplant Centre at Oslo University Hospital – Rikshospitalet in Norway, between October 2010 and May 2013. All kidney transplant recipients at our centre are scheduled for a comprehensive standard care evaluation 8–10 weeks after transplantation including an oral glucose tolerance test (OGTT), fasting insulin measurements and DXA scans (bone density measurements). Of the total number of patients registered in the hospital biobank with relevant blood samples and a relevant DXA scan ($n = 234$), we included 167 patients without an acknowledged diagnosis of diabetes before transplant (see patient disposition chart, Fig. 1). All data (OGTT, DXA scans, blood samples) used in this study were collected at the same time from each patient at the time of their follow-up 8–10 weeks after transplantation. Blood samples were analysed consecutively, while stored frozen plasma samples were retrieved from the hospital biobank enabling analysis of insulin for this study and DXA scans were also analysed later for this study. The study was performed according to the Helsinki declaration. The patients gave written informed consent for use of all data, and the study was approved by the Regional Ethics Committee for South East Norway. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul.

### Blood samples, analyses and diabetes categories

All blood samples were drawn in the morning after an overnight fast and during the subsequent 75 g OGTT. Glucose was measured in fresh venous whole blood using Hemocue AB B-glucose analyser and presented as plasma glucose [26]. Insulin was analysed with an enzyme-linked immunosorbent assay kit (AH-diagnostics, Aarhus, Denmark). The homeostatic model assessment-insulin resistance (HOMA-IR) index was used as an measure of insulin resistance and was calculated from fasting glucose and insulin; HOMA-IR index = (fPG (mmol/l) × fInsulin (μU/ml)) / 22.5 [27]. Lipids and creatinine were analysed with enzymatic methods on Modular P (Roche Diagnostics, Pleasanton, CA, USA). Classification into glucose tolerance categories was performed on the basis of glucose tolerance tests and according to ADA criteria for plasma glucose concentration [28]: normal glucose tolerance (NGT): fasting plasma glucose (fPG) < 5.6 mmol/l and 2-h plasma glucose (2hPG) < 7.8 mmol/l; impaired fasting glucose: fPG 5.6–6.9 mmol/l and 2hPG < 7.8 mmol/l; impaired glucose tolerance (IGT): fPG < 7.0 mmol/l and 2hPG 7.8–11.0 mmol/l; post-transplant diabetes mellitus (PTDM): fPG ≥ 7.0 mmol/l or 2hPG ≥ 11.1 mmol/l.

### Determination of visceral adipose fat (VAT)

Total body composition was measured by DXA, as described elsewhere [29]. Total body composition was determined using a narrow fan-beam GE Healthcare Lunar Prodigy densitometer, and all the scans were analysed using enCORE$^{R}$ software version 14.10 (GE Healthcare, Lunar Corp., Madison, WI, USA). Two certified densitometry technologists performed all scans. The short- and long-term coefficients of variation for our densitometer are 0.8% and 1.4%, respectively. The VAT short-term repeat measurement error coefficient of variance is 9.8% [30].

Analyses of VAT with the enCORE$^{R}$ software were performed by manually placing lines on defined bone landmarks on the DXA scan images followed by a computer-generated output of the body composition in different regions. The calculation of VAT is fully described and documented by Olarescu *et al.* [31], who have also validated the measurement of DXA-derived VAT against the gold standard CT for quantification of VAT. All scans were analysed by one operator, with an intra-individual coefficient of variance <1% tested in five repeated measures in twenty patients (data not shown).

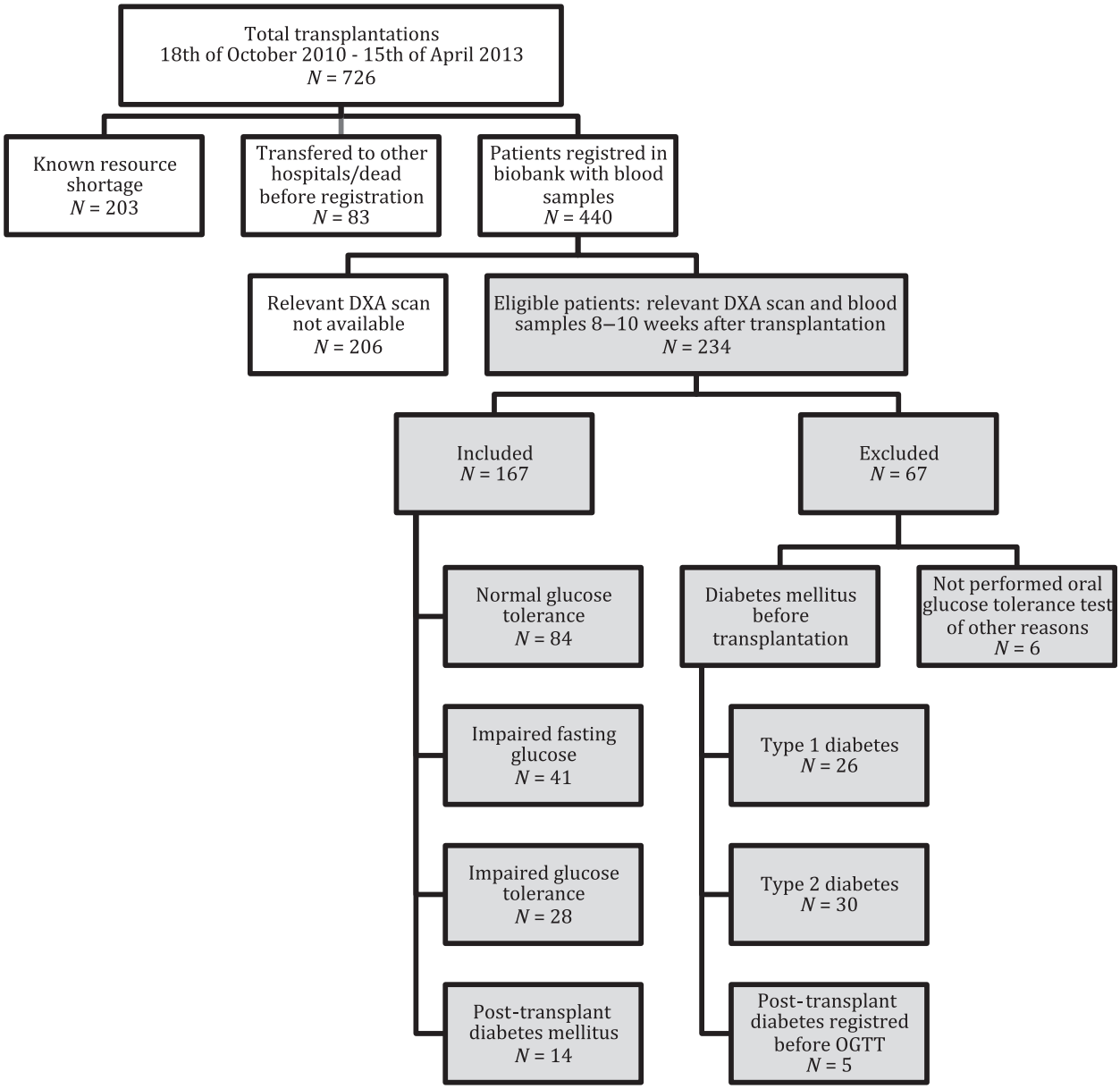


**Figure 1** Flow chart of patients included in the analysis.

### Immunosuppression and statin treatment

Most patients (120 of 167, 72%) received oral tacrolimus (Prograf® capsules; Astellas Pharma US Inc., Northbrook, IL, USA). According to the centre transplant protocol, initial dosage was 0.04 mg/kg or 0.05 mg/kg total body weight twice daily for standard risk patients or high-risk patients, respectively. Dosage was subsequently adapted by measuring whole-blood trough concentrations to maintain concentrations within the range of 3–7 μg/l in standard risk patients or 8–12 μg/l in high-risk patients. High-risk patients were defined by panel-reactive antibody >20% and/or presence of donor-specific antibodies. Forty-seven patients (28%) received cyclosporine instead of tacrolimus. They received an initial dose of 5 mg/kg and concentration was measured 2 h after intake (C2 monitored) to maintain a concentration between 800 and 1200 μg/l in the relevant time period.

In addition to tacrolimus or cyclosporine, the immunosuppressive regimen consisted of mycophenolate mofetil (1.5 g/day in tacrolimus patients and 2.0 g/day in cyclosporine patients, without target concentration intervention) and steroids. The steroid protocol consisted of 250 mg intravenous methylprednisolone on the day of


 

transplantation, followed by oral prednisolone (days 1–14: 20 mg/day, days 15–28: 15 mg/day, days 29–60: 10 mg/day, days 61–179: 7.5 mg/day and from day 180 on: 5 mg/day). Patients also received induction therapy with basiliximab (days 0 and 4: 20 mg). High-risk patients received a similar regimen with some adjustments: intravenous methylprednisolone (day 0: 500 mg, day 1: 80 mg), oral prednisolone (day 2: 80 mg, days 3–7: tapered to 20 mg daily, days 8–28: 20 mg, days 29–60: 15 mg, days 61–179: 10 mg and from day 180: 5 mg) and additional induction therapy with intravenous human immune globulins and rituximab.

In our centre, statins are routinely discontinued at the time of transplantation and are considered continued or started after 3 months post-transplant.

### Statistical analyses

All statistical analyses were conducted with SPSS version 22 (IBM SPSS Statistics, Armonk, NY, USA). Normal distribution was tested by visual inspection on histograms, with Shapiro–Wilk test and with Kolmogorov–Smirnov test. Kruskal–Wallis ANOVA test and Pearson chi-square test were used as appropriate.

Descriptive data are presented as median with interquartile range (IQR). Univariable and multivariable linear regression analyses were used for assessment of association between visceral fat and other relevant covariates versus hyperglycaemia. Covariates chosen for multivariable linear regression were variables with $P < 0.20$ in univariable regression and without multicollinearity in the multivariable model. Total cholesterol and LDL were highly correlated, and only LDL was included in the multivariable model. Forward regression based on all potential predictors was performed as sensitivity analysis. *P*-value for inclusion was 0.05. We also ran the forward variable selection with *P*-value for inclusion 0.20, with similar results. VAT (kg) alone better explained 2-h plasma glucose concentration ($R^2 = 0.066$) than the next best variable VAT as percentage of total body fat ($R^2 = 0.062$). VAT as percentage of total body fat better reflects abdominal obesity (a person with more total body fat is likely to have more visceral fat than a person with less total body fat) and we therefore chose to include this variable instead of the absolute amount of VAT in the multivariable linear regression predicting 2-h plasma glucose concentration.

## Results

Demographic and transplant data for patients categorized into groups of glucose tolerance according to the ADA criteria [28] are shown in Table 1. Of the 167 patients evaluated 8–10 weeks after transplantation, 84 patients (50.3%) were classified as having normal glucose tolerance, 41 patients (24.6%) as having impaired fasting glucose, 28 patients (16.8%) as having impaired glucose tolerance and 14 patients (8.4%) as having post-transplant diabetes.

All patients classified as PTDM had received a primary transplant ($P = 0.011$). Interquartile range for prednisolone dose was highest in patients with PTDM (10.0–11.3), although the median was the same in all groups (10 mg/day) ($P = 0.048$). There were no significant differences between glucose tolerance groups concerning recipient age, gender, pre-emptive transplantation, type of calcineurin inhibitor immunosuppression (cyclosporine vs. tacrolimus) or donor characteristics.

Table 2 shows body fat composition data, insulin measures and other relevant biochemical data according to glucose tolerance categories. Absolute amount of VAT and VAT as a percentage of total body fat were significantly different between glucose tolerance groups ($P = 0.004$ and

**Table 1.** Demographic and transplant data 8–10 weeks after transplantation.

| | All included ($n = 167$) | Patients with NGT ($n = 84$) | Patients with IFG ($n = 41$) | Patients with IGT ($n = 28$) | Patients with PTDM ($n = 14$) | Comparison between groups |
|---|---|---|---|---|---|---|
| Recipient age, median (IQR) | 54.0 (41.0–63.0) | 48.0 (41.0–61.0) | 56.0 (38.5–66.0) | 57.5 (43.3–63.8) | 59.5 (46.3–69.5) | $P = 0.288^{A}$ |
| Male gender, *n* (%) | 119 (71.3) | 56 (66.7) | 30 (73.2) | 19 (67.9) | 14 (100) | $P = 0.081^{B}$ |
| First transplant, *n* (%) | 138 (82.6) | 63 (75.0) | 39 (95.1) | 22 (78.6) | 14 (100) | $P = 0.011^{B}$ |
| Pre-emptive transplantation, *n* (%) | 50 (29.9) | 26 (31.0) | 11 (26.8) | 8 (28.6) | 5 (35.7) | $P = 0.964^{B}$ |
| Months of dialysis, median (IQR) | 11.0 (5.5–22.5) | 10.0 (4.0–24.0) | 12.0 (8.0–20.3) | 11.0 (6.5–23.5) | 14.0 (7.5–29.0) | $P = 0.394^{A}$ |
| Donor age, median (IQR) | 50.6 (40.1–62.4) | 48.7 (39.9–60.9) | 53.9 (38.6–61.3) | 51.1 (40.5–63.5) | 60.3 (41.7–70.0) | $P = 0.410^{A}$ |
| Living donor, *n* (%) | 51 (30.5) | 25 (29.8) | 13 (31.7) | 8 (28.6) | 5 (35.7) | $P = 0.964^{B}$ |
| Prednisolone dose (mg/day) at 8–10 weeks, median (IQR) | 10.0 (10.0–10.0) | 10.0 (10.0–10.0) | 10.0 (7.5–10.0) | 10.0 (10.0–10.0) | 10.0 (10.0–11.3) | $P = 0.048^{A}$ |
| *Cyclosporine*, *n* (%) | 47 (28.1) | 21 (25.0) | 13 (31.7) | 8 (28.6) | 5 (35.7) | $P = 0.785^{B}$ |
| *Tacrolimus*, *n* (%) | 120 (71.9) | 63 (75.0) | 28 (68.3) | 20 (71.4) | 9 (64.3) | |

Kruskal–Wallis ANOVA test was used for continuous variables (A) and chi-square test for categorical variables (B).
NGT, Normal glucose tolerance; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; PTDM, Post-transplant diabetes mellitus.

$P = 0.002$, respectively). By contrast, total body fat mass and BMI were not significantly different between the same groups ($P = 0.063$ and $P = 0.074$, respectively). Fasting insulin values and HOMA-IR index were significantly higher in patients with PTDM than the other glucose tolerance groups ($P = 0.040$ and $P < 0.001$, respectively).

The left panel of Fig. 2 illustrates that VAT as a percentage of total body fat is significantly different among the patient categories of glucose tolerance ($P = 0.002$). The right panel illustrates by contrast that BMI was not significantly different between the categories ($P = 0.074$).

Univariable regression analyses of determinants of fasting and 2-h blood glucose including VAT and other relevant covariates are presented in Table 3. VAT variables were the only parameters significantly associated with both fasting (VAT as a percentage of total body fat, $P < 0.001$) and 2-h blood glucose concentrations (VAT as a percentage of total body fat, $P = 0.001$). BMI was only significantly associated with 2-h glucose concentration ($P = 0.028$). VAT as a percentage of total body fat better explained the variability in both fasting plasma glucose ($R^2 = 0.094$) and 2-h plasma glucose concentrations ($R^2 = 0.062$) compared to BMI and total body fat mass, which only explained a small part of the variability in 2-h plasma glucose concentration (BMI; $R^2 = 0.029$, total body fat mass; $R^2 = 0.036$).

Multivariable linear analyses of determinants for fasting and 2-h blood glucose are shown in Tables 4 and 5, respectively. VAT as a percentage of total body fat was a significant predictor for both fasting and 2-h blood glucose concentrations in the multivariate regression analyses, and together with low-density lipoprotein (LDL), it explained 13% of the variability in fasting blood glucose concentration ($R^2 = 0.132$), and together with high-density lipoprotein (HDL) and daily prednisolone dose, VAT as percentage of total body fat explained 10% of the variability in 2-h plasma glucose concentration ($R^2 = 0.097$). Moderate-to-strong correlations between predictors and scatterplots between some of the predictors are given in the supplementary.

Univariable predictors of insulin resistance as calculated by HOMA-IR index included BMI ($R^2 = 0.181$, $P < 0.001$), total body fat ($R^2 = 0.155$, $P < 0.001$), absolute amount of VAT ($R^2 = 0.095$, $P < 0.001$) and VAT as a percentage of total body fat ($R^2 = 0.050$, $P = 0.004$). In multivariable linear regression, BMI and recipient age explained 20% of the variability in HOMA-IR index ($P < 0.001$, $P = 0.036$), while VAT as a percentage of total body fat was not a significant predictor of HOMA-IR index ($P = 0.128$) (data not shown in the tables).

The distribution of both fasting and 2-h glucose concentrations was slightly skewed, but the results were similar using the log-transformed versions in linear regression (sensitivity analyses).

## Discussion

In the present study, we showed that visceral fat was a significant predictor of post-transplant hyperglycaemia and PTDM. This is a novel finding in kidney transplant patients, and to our knowledge, it has not been examined in other solid organ transplant patients either. The measures of visceral fat (VAT) were obtained in a relatively large cohort of 167 patients with a simple, noninvasive and harmless method using a newly developed software applied on DXA scans [30]. We found that absolute and relative measures of VAT were highest in patients who had developed PTDM early after transplantation and significantly different across the categories of glucose tolerance. Interestingly, there was no significant difference in total body fat or BMI among the same groups. In linear regression analyses, an association between BMI and 2-h plasma glucose concentration was lost in adjusted models, and the VAT percentage of total body fat was the only variable independently associated with both fasting plasma glucose and 2-h plasma glucose concentrations.

PTDM and IGT are associated with impaired long-term outcomes for cardiovascular disease and death [1–5], and VAT is a potentially modifiable risk factor. Our findings are in line with studies from other nontransplanted population identifying VAT and abdominal obesity as a risk factor for type 2 diabetes [16,18,23,32]. Given this background, the results of the present study are clinically relevant. Visceral fat could be considered a risk factor for development of PTDM similar to what is the case for type 2 diabetes in the general population. Although there are acknowledged differences between type 2 diabetes and PTDM, visceral fat seems to have a negative impact in both conditions.

BMI as a risk factor for PTDM has been confirmed in several studies [4,12,13], and in a report identifying a risk score for development of PTDM, BMI was one of seven variables used in the probability model [14]. However, BMI does not distinguish between lean mass and fat mass, and metabolically healthy and metabolically unhealthy phenotypes [33]. With the present study, we show that the distribution of fat and especially visceral fat is more important for glucose metabolism and development of PTDM than BMI.

Insulin resistance and hyperinsulinaemia are hallmarks of type 2 diabetes and are also present in PTDM [10]. In the present material, we demonstrated a significant increase in fasting insulin values and HOMA-IR index across the categories of glucose intolerance. This is in concordance with a study by Bayes *et al.* [34] who showed that pretransplant fasting insulin levels and HOMA-IR indices were higher in patients that developed PTDM compared to normoglycaemic patients. The same study showed low levels of adiponectin as an independent predictor of PTDM, an

**Table 2.** Body composition, serum markers for glucose metabolism, lipids and renal function 8–10 weeks after transplantation.

| | All included ($n$ = 167) | Patients with NGT ($n$ = 84) | Patients with IFG ($n$ = 41) | Patients with IGT ($n$ = 28) | Patients with PTDM ($n$ = 14) | Comparison between groups |
|---|---|---|---|---|---|---|
| BMI (kg/m$^2$) | 24.8 (22.2–28.0) | 24.3 (22.1–27.5) | 24.2 (22.6–26.5) | 26.4 (23.7–30.1) | 27.4 (21.7–30.0) | $P$ = 0.074[A] |
| Visceral fat, kg, median (IQR) | 1.0 (0.4–1.9) | 0.9 (0.4–1.6) | 1.0 (0.4–1.7) | 1.3 (0.7–2.4) | 2.1 (1.0–2.7) | $P$ = 0.004[A] |
| Total body fat, kg, median (IQR) | 22.3 (16.8–30.4) | 21.5 (16.3–30.7) | 21.5 (17.1–26.0) | 28.2 (17.5–34.7) | 29.8 (18.6–34.7) | $P$ = 0.063[A] |
| % Visceral fat of total body fat, median (IQR) | 4.6 (2.3–6.7) | 4.2 (2.1–5.9) | 4.6 (1.8–6.8) | 5.4 (3.8–7.2) | 7.5 (4.9–8.6) | $P$ = 0.002[A] |
| % Visceral fat in android area, median (IQR) | 51.4 (34.4–64.9) | 49.0 (32.5–60.1) | 51.4 (29.0–66.7) | 53.0 (42.9–65.8) | 71.4 (58.6–79.7) | $P$ = 0.003[A] |
| % Subcutaneous fat in android area, median (IQR) | 48.6 (35.1–65.6) | 51.0 (39.9–67.5) | 48.6 (33.3–71.0) | 47.0 (34.2–57.1) | 28.6 (20.3–41.4) | $P$ = 0.003[A] |
| % Fat of total body tissue, median (IQR) | 31.6 (26.2–37.8) | 32.2 (25.5–38.2) | 29.6 (26.2–33.4) | 34.9 (27.1–43.2) | 32.7 (28.6–38.1) | $P$ = 0.096[A] |
| % Fat of total body mass, median (IQR) | 30.4 (25.1–36.6) | 31.1 (24.4–37.1) | 28.7 (25.2–32.1) | 33.9 (26.1–41.9) | 31.7 (27.6–36.9) | $P$ = 0.091[A] |
| Fasting glucose concentration (mmol/l) | 5.3 (4.9–5.9) | 5.0 (4.7–5.2) | 5.8 (5.7–6.2) | 5.5 (5.0–6.0) | 7.2 (6.6–7.4) | $P$ < 0.001[A] |
| 2-h glucose concentration (mmol/l) | 6.3 (5.5–7.6) | 5.6 (5.1–6.3) | 6.2 (5.7–6.6) | 9.0 (8.1–9.5) | 11.7 (8.5–12.5) | $P$ < 0.001[A] |
| Insulin, pmol/l, median (IQR) | 95.5 (66.6–134.6) | 85.3 (61.4–127.1) | 94.3 (76.3–136.9) | 118.6 (80.4–160.6) | 109.3 (76.4–172.6) | $P$ = 0.040[A] |
| Proinsulin, pmol/l, median (IQR) | 1.9 (1.0–3.4) | 1.7 (1.0–3.4) | 1.5 (0.7–2.8) | 2.7 (1.7–4.7) | 3.1 (1.6–6.1) | $P$ = 0.003[A] |
| HOMA-IR index, median (IQR) | 3.3 (2.2–4.6) | 2.7 (1.9–4.1) | 3.7 (2.8–5.5) | 4.4 (2.8–5.9) | 5.2 (3.5–8.1) | $P$ < 0.001[A] |
| Cholesterol, mmol/l, median (IQR) | 6.1 (5.1–7.2) | 6.2 (5.3–7.2) | 5.3 (4.4–7.2) | 6.0 (5.5–7.5) | 6.1 (4.9–7.0) | $P$ = 0.175[A] |
| High-density lipoprotein, mmol/l, median (IQR) | 1.5 (1.2–1.9) | 1.6 (1.2–1.9) | 1.5 (1.3–1.7) | 1.5 (1.3–1.9) | 1.2 (0.9–1.5) | $P$ = 0.049[A] |
| Low-density lipoprotein, mmol/l, median (IQR) | 3.9 (2.9–4.8) | 3.9 (3.1–4.9) | 3.0 (2.6–4.9) | 3.9 (3.5–5.2) | 4.2 (3.0–4.7) | $P$ = 0.130[A] |
| Triglycerides, mmol/l, median (IQR) | 1.5 (1.1–2.2) | 1.7 (1.1–2.2) | 1.4 (1.1–2.1) | 1.5 (1.1–1.9) | 1.9 (1.2–2.2) | $P$ = 0.497[A] |
| Creatinine µmol/l, median (IQR) | 111.0 (93.0–137.0) | 109.5 (94.3–131.0) | 111.0 (94.0–136.5) | 109.5 (83.3–155.0) | 125.5 (97.8–162.8) | $P$ = 0.422[A] |

[A]Kruskal–Wallis test; [B]Pearson chi-Square.

% Fat of total body mass = Fat mass / (Total body mass) = Fat mass / (Lean mass + fat mass + bone mass).

% Fat of total body tissue = Fat mass / (Total body mass − bone mass) = Fat mass / (Lean mass + fat mass).

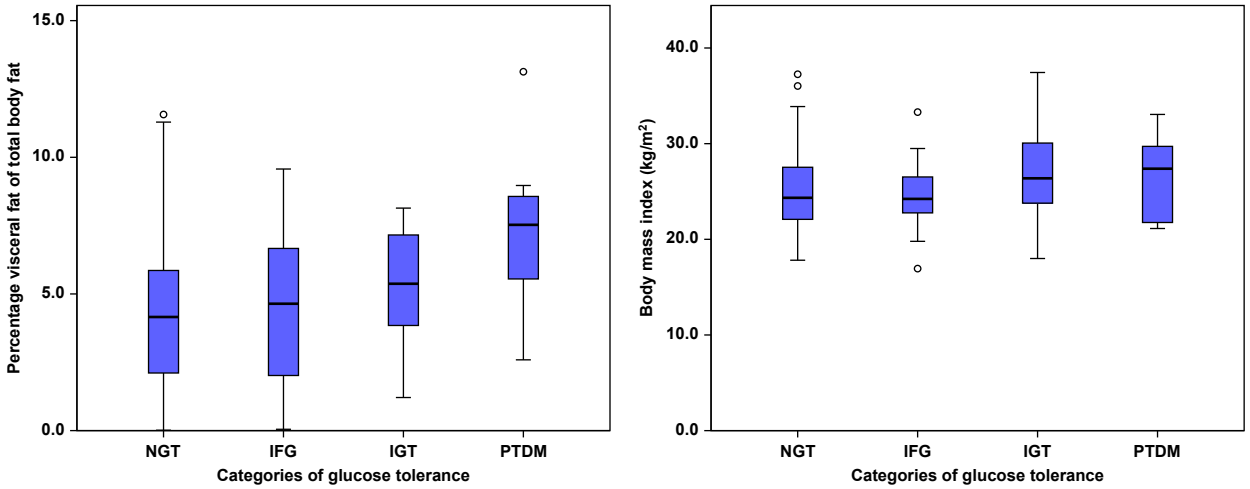


**Figure 2** The left panel shows a boxplot of percentage visceral fat of total body fat according to glucose tolerance groups, and the right panel shows a boxplot of BMI according to the same groups. NGT, Normal glucose tolerance; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; PTDM, Post-transplant diabetes mellitus.

**Table 3.** Univariable linear regression analysis of determinants of plasma glucose concentration.

| | Fasting glucose concentration before OGTT | | | | 2-h glucose concentration after OGTT | | | |
|---|---|---|---|---|---|---|---|---|
| | $R^2$ | Unstandardized beta | Standardized beta | *P*-value | $R^2$ | Unstandardized beta | Standardized beta | *P*-value |
| Recipient age | 0.010 | 0.006 | 0.102 | 0.189 | 0.014 | 0.017 | 0.118 | 0.128 |
| Male gender | 0.043 | 0.361 | 0.208 | 0.007 | 0.017 | 0.595 | 0.130 | 0.095 |
| BMI | 0.018 | 0.026 | 0.134 | 0.083 | 0.029 | 0.085 | 0.170 | 0.028 |
| Deceased donor | 0.012 | −0.189 | −0.111 | 0.153 | 0.000 | −0.032 | −0.007 | 0.926 |
| Cholesterol | 0.020 | −0.075 | −0.142 | 0.066 | 0.000 | −0.024 | −0.017 | 0.827 |
| High-density lipoprotein | 0.017 | −0.228 | −0.131 | 0.091 | 0.031 | −0.805 | −0.175 | 0.024 |
| Low-density lipoprotein | 0.012 | −0.068 | −0.109 | 0.160 | 0.001 | 0.054 | 0.033 | 0.672 |
| Triglycerides | 0.008 | −0.091 | −0.087 | 0.266 | 0.002 | −0.128 | −0.047 | 0.554 |
| Creatinine | 0.008 | 0.002 | 0.089 | 0.252 | 0.010 | 0.006 | 0.100 | 0.197 |
| Visceral fat (kg) | 0.053 | 0.172 | 0.229 | 0.003 | 0.066 | 0.507 | 0.257 | 0.001 |
| Total body fat (kg) | 0.005 | 0.006 | 0.071 | 0.361 | 0.036 | 0.039 | 0.190 | 0.014 |
| % Visceral fat of total body fat | 0.094 | 0.091 | 0.307 | <0.001 | 0.062 | 0.195 | 0.249 | 0.001 |
| % Visceral fat in android area | 0.096 | 0.012 | 0.309 | <0.001 | 0.043 | 0.021 | 0.208 | 0.007 |
| % Fat of total body tissue | 0.001 | −0.002 | −0.027 | 0.733 | 0.023 | 0.038 | 0.153 | 0.048 |
| % Fat of total body mass | 0.001 | −0.003 | −0.027 | 0.732 | 0.023 | 0.038 | 0.153 | 0.049 |
| Prednisolone dose | 0.001 | 0.006 | 0.026 | 0.745 | 0.019 | 0.083 | 0.139 | 0.074 |
| Tacrolimus use | 0.009 | −0.168 | −0.96 | 0.216 | 0.000 | −0.029 | −0.006 | 0.936 |

Unstandardized coefficients refer to how many units the dependent variable changes per unit change in an independent variable. Standardized coefficients refer to how many standard deviations the dependent variable changes per standard deviation change in the independent variable, and this shows which independent variable has a greater effect on the dependent variable.

adipokine that has been shown to be inversely correlated with the amount of visceral fat [35].

Some studies on experimental animals [36–38], but not all [39], have shown that reduction in visceral fat mass decreases insulin resistance. Our data suggested that although visceral fat seems to be more important for glucose metabolism and a better predictor for development of PTDM, VAT explained less of the variability in insulin resistance compared to BMI and total body fat. This might be explained by a possible harmful effect of VAT not only on insulin resistance, but also on beta-cell function, although not yet proven in studies on nontransplanted subjects [40]. In a recent study, Hecking *et al.* [41] showed that beta-cell dysfunction as opposed to insulin resistance was the major mechanism in a large cohort of PTDM.

**Table 4.** Multivariable linear regression analysis of fasting plasma glucose concentration before oral glucose tolerance test.

| | Fasting plasma glucose concentration | | |
|---|---|---|---|
| | Standardized beta | *P*-value | $R^2$ |
| % Visceral fat of total body fat | 0.358 | <0.001 | 0.132 |
| Low-density lipoprotein (LDL) | −0.200 | 0.009 | |

Variables removed by backward regression ($P = 0.10$) were deceased donor, high-density lipoprotein (HDL), male gender, recipient age and BMI. A model with BMI and LDL gave $R^2 = 0.037$, $P = 0.004$. Introducing VAT as a percentage of total body fat increased $R^2$ with 0.095 to 0.132, $P < 0.001$. Adding BMI to the final model did not increase $R^2$.

**Table 5.** Multivariable linear regression analysis of 2-h plasma glucose concentration after oral glucose tolerance test.

| | 2-h plasma glucose | | |
|---|---|---|---|
| | Standardized beta | *P*-value | $R^2$ |
| % Visceral fat of total body fat | 0.206 | 0.008 | 0.097 |
| High-density lipoprotein (HDL) | −0.153 | 0.049 | |
| Prednisolone | 0.143 | 0.061 | |

Variables removed by backward regression ($P = 0.10$) were BMI, recipient age, creatinine and male gender. A model with BMI, high-density lipoprotein (HDL) and prednisolone gave $R^2 = 0.069$, $P = 0.009$. Introducing VAT as percentage of total body fat increased $R^2$ with 0.029 to 0.098, $P = 0.001$. Adding BMI to the final model only increased $R^2$ with 0.001.

Assessment of visceral fat in humans has until recently been cumbersome and expensive using computed tomography (CT) or magnetic resonance imaging (MRI). CT is also associated with harmful radiation. Less harmful tools have until recently been an unmet demand for assessment of VAT in patients both for clinical and research purposes [42]. By utilizing DXA scans and the recently validated software, we could retrieve analyses of visceral fat in a fairly large patient cohort with high reproducibility. With the present study, a significant association with VAT and PTDM could be established. Further analyses are necessary to find the underlying mechanisms for this association and whether VAT is also associated with cardiovascular outcomes. Visceral fat has been shown to be reduced although diet and exercise [43,44], and a study by Sharif *et al.* [19] provided evidence that active lifestyle modifications in kidney transplant patients could attenuate and in some cases reverse progression of glycaemic dysregulation. Whether a reduction in visceral fat mass pretransplant may prevent development of PTDM needs further studies.

Our study also has some limitations. $R^2$ from our multivariable linear regressions is not high, only 0.132 and 0.097 in prediction of fasting and 2-h plasma glucose concentration. Thus, other variables than those included in our models explain more of the variability in the outcome variables. Our study is observational and cross-sectional, and although higher VAT observed 8–10 weeks post-transplant most likely reflects the situation before the incident PTDM, our findings are prone to residual confounding and we cannot determine causality.

In conclusion, we found that both fasting and 2-h plasma glucose concentrations were associated with visceral fat in kidney transplant patients and that visceral fat was more closely related to impaired glucose metabolism than BMI early after kidney transplantation. Further studies on lifestyle intervention to reduce visceral fat and to prevent PTDM are therefore warranted.

## Authorship

MEVD: participated in planning of the study and study design, acquisition of data, analysed and interpreted data and drafted the manuscript. AH, TJ, JB and AÅ: contributed to the study design, contributed to the acquisition of data and editing of the manuscript. KG, DD and IE: contributed to the acquisition of data and editing of the manuscript. All authors approved the final version to be published.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Moderate-to-strong correlations ($r > 0.3$).

**Figure S1.** Scatterplot ($y$ = BMI, $x$ = visceral fat as percentage of total body fat).

**Figure S2.** Scatterplot ($y$ = fasting plasma glucose concentration, $x$ = visceral fat as percentage of total body fat).

**Figure S3.** Scatterplot ($y$ = 2-h plasma glucose concentration, $x$ = visceral fat as percentage of total body fat).

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