ASSOCIATION OF PANCREAS VOLUME AND INSULIN RESISTANCE WITH ABDOMINAL FAT DISTRIBUTION IN TYPE-2 DIABETES AS EVALUATED BY COMPUTED TOMOGRAPHY

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Abstract

Purpose. We aimed to assess the relationship between the regional body fat distribution and insulin resistance and pancreas volume (PV) in type-2 diabetes (DM) patients.

Methods. Fifty-three consecutive type-2 diabetic and 51 non-diabetic patients matched by age, gender and body mass index (BMI) were enrolled. Subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), waist circumference, and PV were measured with computed tomography. Insulin resistance was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR).

Results. Patients with type-2 DM had significantly lower PV than non-diabetic individuals. HOMA-IR ranged from 0.74 to 6.24; and from 0.37 to 3.26, in type-2 DM patients and non-diabetics, respectively. VAT was positively correlated with HOMA-IR in two groups. There were inverse correlations between PV and VAT and VAT/SAT but only in diabetics.

Conclusions. The VAT/SAT ratio may reflect the possible role of VAT to better understand the pathogenesis of obesity-related disorders in patients with type-2 DM.

Key words: Insulin resistance, pancreas volume, visceral adipose tissue, subcutaneous adipose tissue, CT.

INTRODUCTION

Type-2 DM results from a combination of genetic and acquired factors that cause varying degrees of insulin resistance and beta cell dysfunction. Insulin resistance is likely to be maximal already in the early stages of the disease. Throughout this period there is no hyperglycemia without beta cell dysfunction. With the decrease of compensatory insulin hyper-secretion, there is first impaired glucose tolerance and then overt diabetes (1, 2).

Obese individuals have varying degrees of decreased insulin-mediated glucose uptake (3).

In addition, obesity is associated with subclinical inflammation, hypertension, and cardiovascular disease (4). Adipose tissue expresses and secretes adipocytokines, which are known to regulate a host of physiological processes directly related to carbohydrate and fat metabolism. Some authors have attributed this variability of insulin resistance to differences in regional fat distribution in obese individuals (5-7).

The main components of body fat tissue are visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Traditionally, VAT has been considered a major culprit in the development of insulin resistance. Waist circumference and waist-to-hip ratio as anthropometric measurements of VAT have stronger associations with type-2 DM *versus* body mass index (BMI) (8, 9). Furthermore, there is a growing body of evidence supporting the role of SAT in the development of insulin resistance (10). Consequently the relative contributions of SAT and VAT to the pathophysiology of type-2 DM remain unclear (11, 12).

Pancreas volume (PV) is correlated with age, gender, ethnic origin, BMI, and body size (1, 13-15). In type-2 DM, PV is decreased and a correlation between pancreas volume and endocrine function has been reported (13-17). However, there are no studies highlighting the relationship between pancreas volume and regional fat distributions as a predictor of insulin resistance.

The aim of this study is to investigate the relationship between the regional fat distributions using VAT, SAT and VAT/SAT ratio assessed by computed tomography (CT), as well as insulin resistance and PV as an indicator of beta cell dysfunction in diabetic and non-diabetic patients.

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MATERIALS AND METHODS

Patients

From March 5 to October 30 2015, all hospitalized type-2 DM patients and non-diabetics admitted to the Endocrinology Department who had abdominal CT examination within 3 months were enrolled. Sixty-four consecutive patients with type-2 diabetic and 62 non-diabetic patients were included into the study. All patients were evaluated according to the American Diabetes Association (ADA) criteria for type-2 DM (18). We excluded 2 non-diabetic patients who had any abdominal condition potentially affecting pancreas morphology (e.g., pancreatitis, pancreatic tumor and peritonitis), in 6 type-2 diabetic and 6 non-diabetic patients whose precise delineation of the pancreas from adjacent structures was not possible. Five type 2 diabetic and 3 non-diabetic patients whose weight changed more than 3 kg in the 3 months prior to analysis were also excluded. Finally, 53 consecutive patients with type-2 DM along with 51 non-diabetics matched by age, gender and BMI were enrolled. These patients had type 2 DM with a history of 10.31 ± 7.35 years; 19 of them were treated by oral anti-diabetic medications and 34 by insulin therapy. Height and weight were measured using standard techniques. BMI was calculated as the weight in kilograms divided by the square of height in meters. This prospective study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in *a priori* approval by our institution's human research committee. Informed written consent was obtained from all individuals.

Biochemical analysis

A blood sample was withdrawn from all the participants after overnight fasting and serum was separated by centrifugation at 3000 rpm for 10 minutes. Plasma glucose was assayed by an automated glucose oxidase method. Fasting plasma insulin was measured by radioimmunoassay as reported previously (19). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting plasma glucose and insulin level by using the following formula: $\text{HOMA-IR} = \text{FPG (mg/dL)} \times \text{fasting insulin (}\mu\text{U/mL)} / 405$ (20). The patients with poor glycemic control were treated with insulin. Patients were switched to the treatment with sulfonylurea (glibenclamide 1.25 or 2.5 mg) instead of insulin on the night before the test to minimize the influence of insulin injected subcutaneously (21).

Computed tomography analysis

A multi-detector CT system (Activion 16-row CT scanner; Toshiba Medical Systems, Otawara, Japan) was used for CT imaging. The routine abdominal CT protocols were used for all patients including 120 kV, 144 effective mAs, a pitch factor of 0.938, a helical factor of 15.0, a rotation time of 0.75s and a reconstruction interval of 1 mm. Patients were administered oral contrast (EZ-Cat, barium sulphate suspension, EZ-Em, Westbury, NY). A total of 100 mL nonionic contrast agent (Ultravist 370; Bayer Schering Pharma, Berlin, Germany) was given at a rate of 2.0 mL/s via peripheral venous line.

VAT was defined as intra-abdominal fat bound by parietal peritoneum or the fascia transversalis excluding the vertebral column and the paraspinal muscles; SAT was defined as fat superficial to the parietal peritoneum including abdominal and back muscles. Both VAT and SAT were measured at one axial level (L4/L5 intervertebral disc), which was described as being the most accurate for approximating the VAT/SAT ratio of the entire abdomen (22, 23). The waist circumference was derived from the CT images at same axial level for VAT and SAT measurements (Fig. 1). The VAT and SAT were calculated by using a closed polygon tool with semiautomatic segmentation. The attenuation range was from -150 to -50 Hounsfield Units (HU) because it identifies adipose tissue (24). The VAT was isolated as the region of interest (ROI) by manually delineating the inner margin of the abdominal musculature surrounding the abdominal cavity using a cursor. The SAT was calculated by isolating the region superficial to the inner margin of the abdominal musculature using a cursor. The VAT and SAT pixels were identified as the pixels with this attenuation range within the ROI (Fig. 2). The normal pancreatic parenchyma was determined by 2-dimensional segmentation in the region. After tracing the pancreatic parenchyma in all slices, the pancreatic volume was determined *via* ROI volume measurements (Fig. 3).

For each patient, CT imaging analysis was measured by two independent radiologists with eight and six years of experience in abdomen imaging using image analysis software (OsiriX Foundation, Geneva, Switzerland) on a personal computer. The radiologists performing the measurements were blind to the clinical information. The reviewers could manipulate the images to optimize the visualization of the pancreas and adipose tissue. Intra-class correlation analysis shows the reproducibility estimate between two independent

Figure 1. Area-based measurements performed at the level of L4/L5 (a). The waist circumference was measured using a closed polygon tool (b).

Figure 2. A fixed attenuation range was used at the level of L4/L5 to delineate VAT and SAT with a closed polygon tool with semi-automatic segmentation (a) for the identification of SAT (b) and VAT (c).

readers. The intra-class correlation coefficient (ICC) was excellent when measuring maximum VAT and SAT areas (0.990, %95 CI > 0.873-0.997 and 0.993, %95 CI > 0.708-0.998, respectively) and PV (0.983, %95 CI > 0.708-0.995).

Statistical analysis

Statistical analyses were performed using SPSS software (ver. 19.0 for Windows; SPSS Inc., Chicago, IL, USA). Descriptive statistics of continuous variables are given as the mean, standard deviation, median, minimum, and maximum values. Categorical variables are presented as frequencies and percentages. The Shapiro-Wilk test was used to test normality. The Mann-Whitney U-test was used for non-parametric two-group comparisons. Inter-rater reliability of the measurements of two independent observers was assessed with the intraclass correlation coefficient

Figure 3. The calculation of pancreas volume. Pancreas areas were selected as regions of interest (ROI, green area) in each slice and the ROI volume was calculated using imaging software. Vessels, calcification, and dilated pancreatic duct were excluded from the selected pancreas areas.

(ICC). Multiple regression analysis was performed to identify predictors of HOMA-IR. For all statistical comparisons, a p value < 0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics of the study subjects are shown in Table 1. No statistically significant difference was found in age ($p=0.227$), gender ($p=0.872$) and BMI ($p=0.814$) between patients with type 2 DM and non-diabetic patients. In type 2 DM, HOMA-IR ranged from 0.74 to 6.24; in non-diabetics, it ranged from 0.37 to 3.26. There was a positive correlation between HOMA-IR and both VAT and SAT in type-2 diabetic patients ($r = 0.292$; $p = 0.034$ and $r = 0.373$; $p=0.006$, respectively) and also in non-diabetics ($r = 0.541$; $p<0.001$ and $r = 0.590$; $p<0.001$,

Table 1. Demographic characteristics of patients

	Type-2 Diabetes (n=53)	Non-Diabetes (n=51)	p Value
Male (%)	21 (39.6%)	21 (41.2%)	0.872
Age (years)	59 (28-85)	58 (23-80)	0.227
BMI (kg/m ²)	28.72 (20.44-52.45)	29.40 (19.95-41.73)	0.814
Fasting plasma glucose (mmol/L)	136 (94-178)	96 (75-110)	<0.001*
Fasting plasma insulin (mU/L)	7.7 (3.2-15)	6 (2-12)	<0.001*
HOMA-IR (μU/mol/L ³)	2.57 (0.74-6.24)	1.44 (0.37-3.26)	<0.001*

Abbreviations: BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2. CT measurements of body adipose tissue distribution and pancreas volume in type-2 diabetic and non-diabetic patients

	Type-2 Diabetes (n=53)	Non-Diabetes (n=51)	p-Value
Waist circumference (cm)	104.58 (74.25-138)	98.32 (77.31-133)	0.021*
SAT area (cm ²)	273.13 (32.51-571.91)	242.13 (77.91-556.08)	0.554
VAT area (cm ²)	183.65 (17-350.14)	122.58 (29.02-412.82)	0.004*
VAT/SAT Ratio	1.39 (0.58-4.91)	1.80 (0.80-6.73)	0.002*
Pancreas volume (cm ³)	49.14 (17.48-96.09)	55.67 (27.96-105.21)	0.043*

Abbreviations: SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

respectively). There was no correlation between VAT/SAT ratio and HOMA-IR ($r = -0.076$; $p = 0.588$ and $r = 0.174$; $p = 0.222$, respectively).

The VAT, VAT/SAT ratio and waist circumference were significantly higher in type-2 diabetic patients *versus* non-diabetic patients ($p = 0.004$, $p = 0.002$, and $p = 0.021$ respectively) (Table 2). However, there was no statistically significant difference in SAT between the groups ($p = 0.554$).

According to the multiple regression results, adjusted for age, HOMA-IR was statistically associated with only VAT and BMI ($p = 0.007$ and $p < 0.001$, respectively) among all variables including VAT, SAT, BMI and waist circumference in non-diabetic patients. 73.7% of the change in HOMA-IR is due to VAT and BMI. For these data, the best prediction equation is: $\text{HOMA-IR} = -2.149 + 0.002 \times \text{VAT} + 0.112 \times \text{BMI}$.

In type 2 DM, there was a statistically significant relationship between HOMA-IR and BMI among the same variables ($p < 0.001$); 43.9% of the change in the HOMA-IR is explained by BMI. The multiple regression equation for the prediction of HOMA-IR by BMI is $\text{HOMA-IR} = -1.464 + 0.147 \times \text{BMI}$.

PV was significantly lower in type-2 DM than non-diabetics ($p = 0.043$) (Table 2). Considering the effects of the regional fat distributions on PV in both groups, VAT and VAT/SAT ratio were inversely correlated with PV ($r = -0.355$; $p = 0.009$ and $r = -0.278$; $p = 0.044$, respectively). There was no significant association between PV and SAT in type-2 diabetic patients ($r = 0.075$; $p = 0.596$). In non-diabetic patients, PV was not associated with all of VAT, SAT and VAT/SAT ratio ($r = -0.095$; $p = 0.507$, $r = 0.070$; $p = 0.628$ and $r = -0.252$; $p = 0.074$, respectively).

Intra-class correlation analysis shows the reproducibility estimate between two independent readers. Intra-class correlation coefficient (ICC) was excellent when measuring maximum VAT and SAT areas (0.990, 95% CI > 0.873-0.997 and 0.993, 95% CI > 0.708-0.998, respectively), and PV (0.983, 95% CI > 0.708-0.995).

DISCUSSION

In our study, VAT and VAT/SAT ratio were significantly higher in type-2 diabetic patients than in non-diabetics. There were no significant differences in SAT among groups. Additionally, both the VAT and SAT were associated with HOMA-IR in diabetic and non-diabetics. Several recent studies on the insulin resistance in obesity show that both VAT and SAT are associated with insulin resistance. Consequently, it is well recognized that overall obesity causes insulin resistance (9, 10, 25-28). McLaughlin *et al.* showed that increased VAT, after adjustment for SAT and BMI, was associated with elevated risk for insulin resistance; increased SAT decreases the risk of insulin resistance (4). In another study, it was shown that SAT, as a component of central adiposity, has an association with insulin resistance as strong as VAT (26).

Although VAT or SAT alone provides little information regarding the relative distribution of body fat, an increased VAT/SAT ratio is a marker of a higher propensity to store excess fat viscerally (29). Miyazaki and DeFronzo reported that the VAT/SAT ratio correlated with hepatic insulin resistance, whereas VAT or SAT alone did not in patients with type-2 DM. However, peripheral insulin resistance is more closely related to VAT and SAT, but not to the VAT/SAT ratio (30). Furthermore, Kaess *et al.* observed that, in a sample of 3,223 participants (48% women) from the Framingham Heart Study, the VAT/SAT ratio was associated with insulin resistance assessed by HOMA-IR, independent of BMI and VAT (29).

However, overall obesity leads to substantial insulin resistance. As a hormonally active component of total body fat, VAT can play a more important role than SAT in the development of insulin resistance - both VAT and SAT are important (11). There is a debate regarding whether VAT or SAT is more strongly associated with insulin resistance. The results of this study confirm prior suggestions that VAT or SAT are associated with insulin resistance. Higher VAT/SAT ratios in type-2 DM patients suggest that the VAT is more valuable than the SAT in determining insulin resistance.

At this point, the value of the VAT and the VAT/SAT ratio comes to the fore in determining the impact of adipose tissue in type-2 DM. We recommend that even a small increase in VAT in patients with type-2 DM while having slightly less SAT may result in dramatically different VAT/SAT ratios. Thus, the VAT/SAT ratio itself may reflect the possible role of VAT to better understand the pathogenesis of obesity-related disorders in patients with type-2 DM.

In our study, PV is decreased in type 2 DM patients *versus* non-diabetics. This is similar to other reports (13, 15, 31). Saisho *et al.* revealed that PV increases with adulthood and obesity. Thus, it begins to decline gradually at about 60 years of age (15). In this study, the parenchymal PV of type-2 diabetic patients was decreased relative to non-diabetics. However, there was no difference in fat volume between subjects with type-2 DM compared to non-diabetic subjects. Moreover, they showed that the relationship between PV and BMI was similar (15). Similarly, Burute *et al.* showed that type 2 diabetics had a lower PV than normoglycemic individuals according to MRI for PV measurement (13). However, Phillippe *et al.* have not seen a significant difference between type-1 and type-2 DM regarding PV (14). One study assessing PV in normoglycemic, type-1 and 2 diabetic patients showed that type-1 diabetics had a significantly smaller PV than normoglycemic individuals and Type 2 diabetics (31). The differences in disease processes between Type 1 and Type 2 DM may also participate in the emergence of various PV (14, 31-33).

We found that PV was inversely correlated with the VAT and VAT/SAT ratios in diabetic patients but not with SAT. On the other hand, no relationship was found between the PV and VAT, SAT and VAT/SAT ratio in the non-diabetic cohort. As mentioned before VAT as a hormonally active component of total body fat contributes to chronic inflammation state and is higher in type 2 diabetic patients (11). Chronic inflammation state and loss of the trophic effects of insulin may result in decreased pancreatic volume in type 2 diabetes. Hence, we consider that VAT can contribute to pancreatic volume loss via enhancing chronic inflammation state.

In addition, multiple regression analysis showed that BMI was a main predictor of insulin resistance in both groups. Unfortunately, BMI could not estimate the impact of obesity on PV in the two groups. Saisho *et al.* showed that BMI was correlated with PV in type-2 diabetic and non-diabetic subjects, however PV was decreased in subjects with type-2 DM than non-

diabetic subjects (15). Based on this relationship, Kou *et al.* reported a positive correlation between BMI and PV in Japan (34). Considering the relationship between the parameters of body fat and both insulin resistance and PV, BMI remains the strongest predictor regarding insulin resistance even in normal subjects, but not in those with PV (15, 34, 35).

There are several limitations of this study. The first limitation is that we enrolled a relatively small number of patients from a single center. This could lead to selection bias. To minimize this selection bias, we tried to include all patients who met the inclusion criteria. The second limitation is that pancreatic volume was measured, not beta cell mass. New molecular imaging methods were used to assess pancreatic beta cell mass and function, but these are not yet clinically valid (36). The other limitation is the medication of type-2 diabetic patients that may have an influence on insulin resistance.

In conclusion, the results of our study demonstrated that VAT - unlike other parameters used for assessing body fat tissue - is associated with both insulin resistance and PV in type-2 DM. There is no consensus regarding which part of body fat has more important role in pathogenesis of obesity-related disorders. The measuring VAT and VAT/SAT ratio with a single abdominal CT image at L4/L5 intervertebral disc level which is the most accurate level for approximating the regional fat distribution of the entire abdomen would be useful in assessing obese individuals for predisposition to type-2 DM. In addition, BMI is still the easiest anthropometric measurement to predict insulin resistance. Comprehensive studies covering larger populations and long-term follow-up are needed to elucidate the role of VAT and SAT on type-2 DM.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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