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ORIGINAL ARTICLE

Pancreatic fat accumulation evaluated by multidetector computed tomography in patients with type 2 diabetes

Ayako Fukase[1], Tomoyasu Fukui[1]*, Hiroto Sasamori[1,2], Munenori Hiromura[1], Michishige Terasaki[1], Yusaku Mori[1], Toshiyuki Hayashi[1], Takeshi Yamamoto[1], Makoto Ohara[1], Satoshi Goto[1], Hiroe Nagaike[1], Tsutomu Hirano[1,3], Sho-ichi Yamagishi[1]

[1]Division of Diabetes, Metabolism and Endocrinology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan, [2]Alzclinic Pet Lab, Tokyo, Japan, and [3]Ebina Memorial Hospital, Ebina, Japan

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***Correspondence**
Tomoyasu Fukui
Tel.: +81-3-3784-8947
Fax: +81-6-3784-8947
E-mail address:
showauft@med.showa-u.ac.jp

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ABSTRACT

Aims: To clarify the clinical impact of pancreatic fat volume on beta cell function in type 2 diabetes patients.

Materials and Methods: One hundred thirty two consecutive type 2 diabetic patients (mean age, 63.7 years) were enrolled in this cross-sectional study. Total pancreatic volume (TPV), pancreatic fat volume (PFV), and pancreatic parenchymal volume (PPV), and visceral fat volume were examined quantitatively with multidetector computed tomography using SYNAPSE VINCENT image analysis system (Fujifilm Inc., Tokyo, Japan). Pancreatic fat was identified using Hounsfield Units of less than zero. The capacity of insulin secretion was assessed by C-peptide immunoreactivity (CPR) index (100 × fasting CPR/fasting plasma glucose). Insulin sensitivity was evaluated using CPR-insulin resistance (20/fasting CPR × fasting plasma glucose).

Results: TPV, PFV, PPV, and visceral fat volume were significantly correlated with body weight (BW). PPV/BW, but not PFV/BW, significantly decreased with increasing duration of diabetes and aging. PFV/BW was positively associated with body mass index and visceral fat volume/BW. PFV/BW was significantly correlated with CPR index, while inversely associated with insulin sensitivity. CPR index, but not CPRinsulin resistance was progressively decreased in patients with a longer duration of diabetes. When patients were divided into two groups according to a median PFV/BW value, CPR index in high PFV/BW group with diabetes duration >5 years was significantly lower than those ≤5 years. However, duration-dependent decrease in CPR index was not observed in low PFV/BW group.

Conclusions: Our present study suggests that PFV might predict the progression of beta cell dysfunction in patients with type 2 diabetes.

INTRODUCTION

A hallmark of type 2 diabetes is progressive β-cell exhaustion accompanying insulin resistance, the latter of which is mainly induced by central obesity associated with ectopic fat accumulation in non-adipose tissues, such as the liver, skeletal muscle and heart[1]. Ectopic fat accumulation also occurs in the pancreas[2]. Non-alcoholic fatty pancreas is considered to be a risk factor for chronic pancreatitis and pancreatic cancer, which might be partly caused by lipotoxicity and local inflammation[3-5]. In addition, fatty pancreas could contribute to β-cell dysfunction. Several cell culture and animal studies have shown that fat accumulation in the pancreas inhibits insulin secretion by inducing β-cell apoptosis[6-9]. However, there was some controversy about the pathological role of fatty pancreas in impaired insulin secretion in humans. Indeed, fatty pancreas defined by attenuation of computed tomography (CT) values of the pancreas has been shown to correlate with impaired insulin secretion after intravenous administration of 1 mg glucagon in patients with type 2 diabetes[10,11], whereas Tushuizen *et al.*[12] reported no association between pancreatic fat content evaluated by magnetic resonance

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imaging (MRI) and insulin secretion ability, which was assessed by an oral glucose tolerance test-derived insulinogenic index. Inconsistent findings in the clinical studies could be attributable to differences of assessment methods for β-cell function and insulin sensitivity, and/or inaccuracy of imaging modalities for evaluating the pancreatic fat content. Although attenuation of CT values is indicative of increased adipose content, it might be affected by other components in the target organ, such as content of manganese[13]. This might mask a change in attenuation of CT values caused by fat accumulation. Furthermore, although MRI, including MR spectroscopy, is considered to be the standard modality for assessment of fatty pancreas[12,14-16], the measured region of interest might not accurately represent the fat content in the entire pancreas because of heterogeneous nature of fat deposition in the pancreas[17].

Therefore, in order to investigate the clinical impact of pancreatic fat accumulation on β-cell function and insulin sensitivity more accurately, we first quantitatively measured total pancreas volume (TPV), pancreatic fat volume (PFV) and pancreatic parenchymal volume (PPV) with multidetector computed tomography (MDCT) using SYNAPSE VINCENT image analysis system (Fujifilm Inc., Tokyo, Japan). Then, we examined the relationships among each parameter of pancreatic volume, capacity of insulin secretion and insulin sensitivity in Japanese patients with type 2 diabetes.

METHODS

Patients

A total of 132 consecutive type 2 diabetes patients, who were admitted to Showa University Hospital, Tokyo, Japan, from January 2017 to January 2018, were enrolled in this cross-sectional study. Patients underwent abdominal CT for screening pancreatic tumor.

The exclusion criteria of the present study were as follows: patients aged <20 years, chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), positive for islet autoantibodies including diabetic ketoacidosis or ketosis, alcohol consumption of more than two drinks (10 g of alcohol per one drink unit) per day[18] or pre-existing pancreatic diseases.

Diabetic retinopathy was graded as simple, pre-proliferative and proliferative retinopathy judged by ophthalmologists. According to the criteria of the Japan Diabetes Society[19], the stage of diabetic nephropathy were determined based on eGFR values and the presence or absence of albuminuria as follows: stage 1, normoalbuminuria (urinary albumin-to-creatinine ratio (UACR) <30 mg/gCr); stage 2, microalbuminuria (300 > urinary albumin-to-creatinine ratio ≥ 30 mg/gCr); and stage 3, eGFR ≥ 30 mL/min/1.73 m^2 and overt albuminuria (urinary albumin-to-creatinine ratio ≥300 mg/gCr). Body mass index (BMI; kg/m^2) was calculated as bodyweight (BW) / (height squared). The study protocol was approved by the ethics committee of the Showa University School of Medicine, Tokyo, Japan (permit number: 2916).

Informed consent was obtained in the form of opt-out on the website because of the retrospective design.

Assessment of pancreatic volume by MDCT

CT was carried out by standard clinical protocol for abdominal/pelvis CT by MDCT, as reported in our previous study[20]. Iodine contrast medium was intravenously injected at a rate of 3 mL/s through an antecubital vein. Pancreatic volume (PV) was calculated from contrast-enhanced or plain 5-mm axial CT images.

We first measured the TPV (cm^3) using SYNAPSE VINCENT image analysis system (Fujifilm Inc.) according to the methods previously reported[21]. In brief, to avoid the influence of partial volume effect, the manually outlined pancreas on axial image slices were summed automatically throughout the entire pancreas. The volume of the pancreas where the Hounsfield units were <0 was defined as PFV. PPV (cm^3) was calculated as TPV (cm^3) minus PFV (cm^3). All scans were initially analyzed by a single experienced investigator (AF), and then confirmed by another radiologist who was blinded to the patients' medical records and histories (HS). Mean intraobserver and interobserver coefficients of variation (five repeated TPV measurements on five cases) were 5.28% and 3.31%, respectively. The difference in the TPV values by both contrast-enhanced and plain CT image (five cases studied) was 3.14% (HS).

Measurement of visceral and subcutaneous fat volume

Visceral and subcutaneous fat volume (FV) were measured with abdominal analysis application software (Fujifilm Inc.), as described previously[22].

Assessment of body composition

Whole body muscle and fat masses were evaluated with bioelectrical impedance analysis using an InBody770 (InBody770; Biospace, Seoul, Korea)[23].

Assessment of ability of insulin secretion and insulin sensitivity

We used C-peptide immunoreactivity (CPR) index and CPR-insulin resistance (CPR-IR) as markers of insulin secretion ability and insulin sensitivity, respectively. CPR index was calculated as 100 × fasting CPR (ng/mL) / fasting plasma glucose (mg/dL)[24]. CPR-IR, shown to correlate with the glucose disposal rate in hyperinsulinemic-euglycemic clamp, was calculated using the following formula: 20 / (fasting CPR [ng/mL] × fasting plasma glucose [mg/dL])[25].

Analysis of blood chemistry

Glycated hemoglobin (HbA1c; %) was estimated as a National Glycohemoglobin Standardization Program-equivalent value (%), as calculated by the following formula: HbA1c (%) = HbA1c (Japan Diabetes Society) (%) + 0.4%[26]. CPR and plasma glucose levels were measured with an immunoenzymometric assay and glucose oxidase method, respectively.

Statistical analysis

Comparisons between groups were carried out using Student's *t*-test or the non-parametric Mann–Whitney *U*-test. Non-parametric correlations were identified using the Spearman's rank correlation coefficient. Multiple regression analysis was carried out to determine the independent correlates of CPR index. Logistic regression model was used to identify independent factors associated with the high PFV group. Differences were considered significant at a two-tailed *P*-value of <0.05. All statistical analyses were carried out with JMP Pro 13.0 software (SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Clinical characteristics

Clinical and laboratory characteristics of the participants are shown in Table 1. The mean (standard deviation) age was 63.7 years (14.0 years), and 64.4 % of the patients were men. The mean duration of diabetes and BMI were 12.4 years (11.3 years) and 26.0 kg/m^2 (5.5 kg/m^2), respectively. The mean CPR index and CPR-IR were 1.21 (0.76) and 0.15 (0.16). Among 132 patients, just four patients were on nutrition and exercise therapy, 40 received metformin, 34 dipeptidyl peptidase-4 inhibitors, 17 sodium-glucose cotransporter-2 inhibitors and 94 insulin therapy. A total of 97 patients had no diabetic retinopathy, whereas the numbers of patients with stage 1, 2 and 3 of diabetic nephropathy were 102, 19 and 11, respectively.

Table 1 | Patient characteristics

Clinical characteristics	
n	132
Age (years)	63.7 (14.0)
Male sex, *n* (%)	85 (64.4)
Duration of diabetes (years)	12.4 (11.3)
Bodyweight (kg)	70.1 (18.7)
Body mass index (kg/m^2)	26.0 (5.5)
Glycated hemoglobin (%)	9.2 (2.0)
Fasting plasma glucose (mg/dL)	135.9 (29.2)
Fasting C-peptide (ng/mL)	1.60 (0.94)
C-peptide index	1.21 (0.76)
C-peptide-insulin resistance	0.15 (0.16)
Triglycerides (mg/dL)	132.3 (58.0)
High-density lipoprotein cholesterol (mg/dL)	45.5 (13.3)
Low-density lipoprotein cholesterol (mg/dL)	109.6 (32.3)
Aspartate aminotransferase (U/L)	29.3 (21.2)
Alanine aminotransferase (U/L)	36.9 (38.9)
Gamma-glutamyltransferase (U/L)	47.5 (51.5)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	76.3 (21.9)
Therapy for diabetes, *n* (%)	
Nutrition and exercise therapy only	4 (3.0)
Metformin	40 (30.3)
Sulfonylureas	5 (3.8)
Glinides	1 (0.8)
α-Glucosidase inhibitors	6 (4.5)
Pioglitazone	3 (2.3)
Dipeptidyl peptidase-4 inhibitors	34 (25.8)
Sodium–glucose cotransporter 2 inhibitors	17 (12.9)
Glucose-like peptide-1 receptor agonists	9 (6.8)
Insulin treatment	94 (71.2)
Diabetic microvascular complications, (*n*)	
Neuropathy (+/–)	74/58
Retinopathy (NDR/SDR/PPDR/PDR/unknown)	97/16/3/12/4
Nephropathy (stage 1/2/3)	102/19/11

Values are presented as mean (standard deviation) or *n* (%). NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.

CT images of pancreas, and histogram of pancreatic fat and parenchymal area

Figure 1a,b showed representative plain axial CT images of the pancreas of a type 2 diabetes patient with a higher fat area (52-year-old woman; BMI 33.9; estimated PFV 69.8 mL) and with less pancreatic fat (52-year-old women; BMI 20.7; estimated PFV 1.5 mL), respectively.

Correlation between pancreatic volume and BW in patients with type 2 diabetes

TPV, PFV and PPV were significantly correlated with BW in patients with type 2 diabetes ($r = 0.79$, $r = 0.62$, $r = 0.53$, $P < 0.0001$; Figure 1c–e). TPV was positively associated with PFV and PPV, whereas PFV was negatively related with PPV ($r = 0.24$, $P = 0.005$, $r = 0.62$, $P < 0.0001$ and $r = -0.49$, $P < 0.0001$, respectively; data not shown).Thus, TPV, PPV and PFV adjusted for BW were used in the following analyses.

Visceral FV adjusted for BW was positively associated with TPV/BW and PFV/BW ($r = 0.19$, $P = 0.03$ and $r = 0.69$, $P < 0.0001$, respectively), but not PPV/BW (Figure 1f–h).

There was a weak association of subcutaneous FV adjusted for BW with PFV/BW, but not with TPV/BW or PPV/BW ($r = 0.17$, $P = 0.048$).

Correlation of pancreatic volume with β-cell function and insulin sensitivity

TPV/BW and PFV/BW, but not PPV/BW, were significantly ($P < 0.005$) correlated with CPR index (Figure 2a–c).

TPV/BW and PFV/BW, but not PPV/BW, were inversely associated with CPR-IR (Figure 2d–f).

Correlation of CPR index and each pancreatic volume parameter with duration of diabetes

CPR index and PPV/BW were progressively decreased as disease duration of diabetes was longer, whereas there was no association of TPV/BW or PFV/BW with duration of diabetes (Figure 3a–d). CPR-IR was not associated with duration of diabetes (data not shown). As diabetes control correlates with insulin secretion, a multivariate regression analysis was carried out using the CPR index as the dependent variable, and PFV/BW, diabetes duration, HbA1c, sex and age as independent variables. The CPR index was independently associated with PFV/BW, duration of diabetes, HbA1c, age and sex (Table S1).

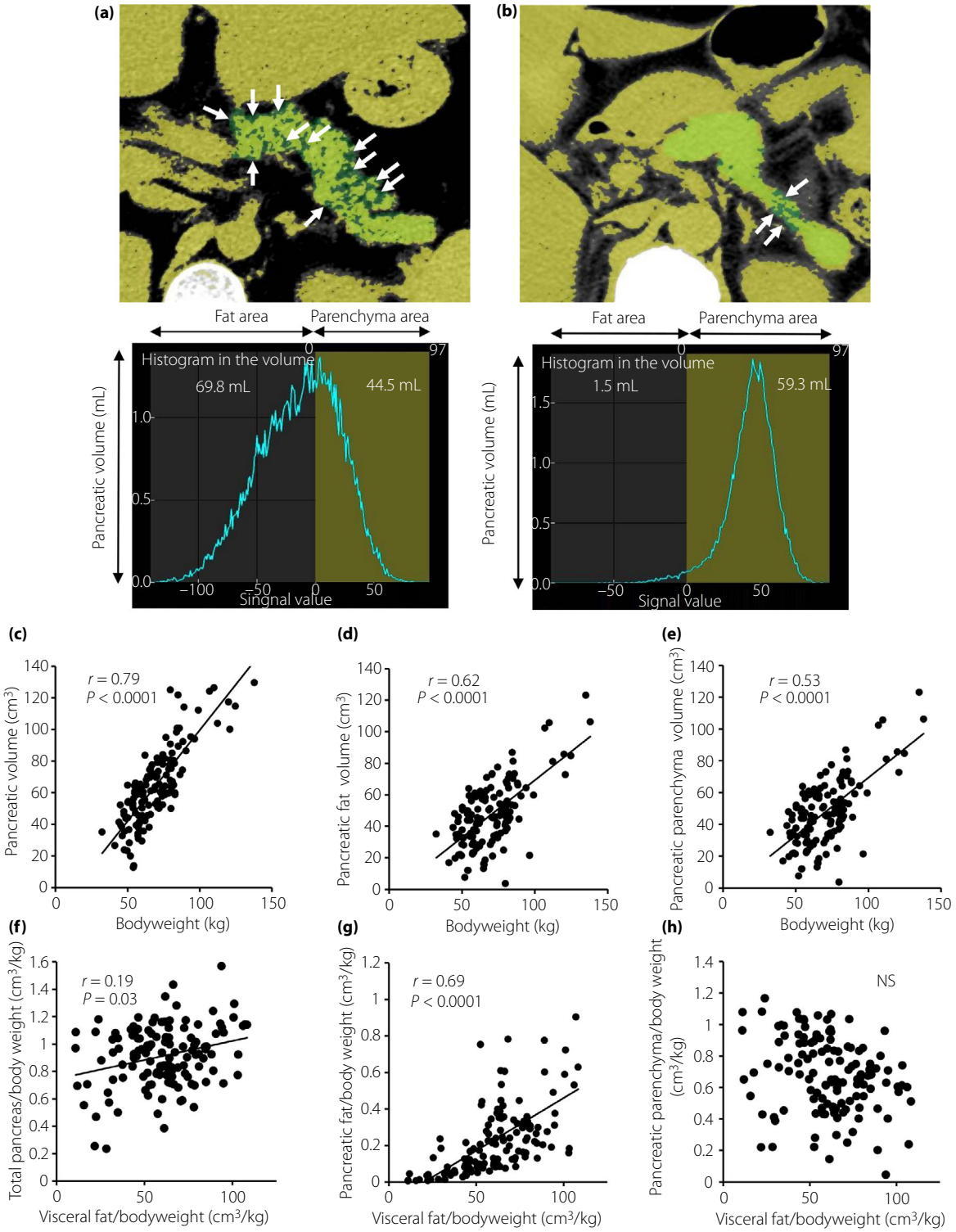

Figure 1 | (a,b) Computed tomography images of the pancreas, and histogram of pancreatic fat and parenchymal area. Representative plain axial computed tomography images of the pancreas in a type 2 diabetes patient with a higher fat area (52-year-old woman; body mass index 33.9; estimated PFV 69.8 mL) and with less fat (52-year-old woman; body mass index 20.7; estimated PFV 1.5 mL), respectively. White arrows indicate pancreatic fat. (c–h) Correlation among each parameter of pancreatic volume, bodyweight and visceral fat. NS, not significant.

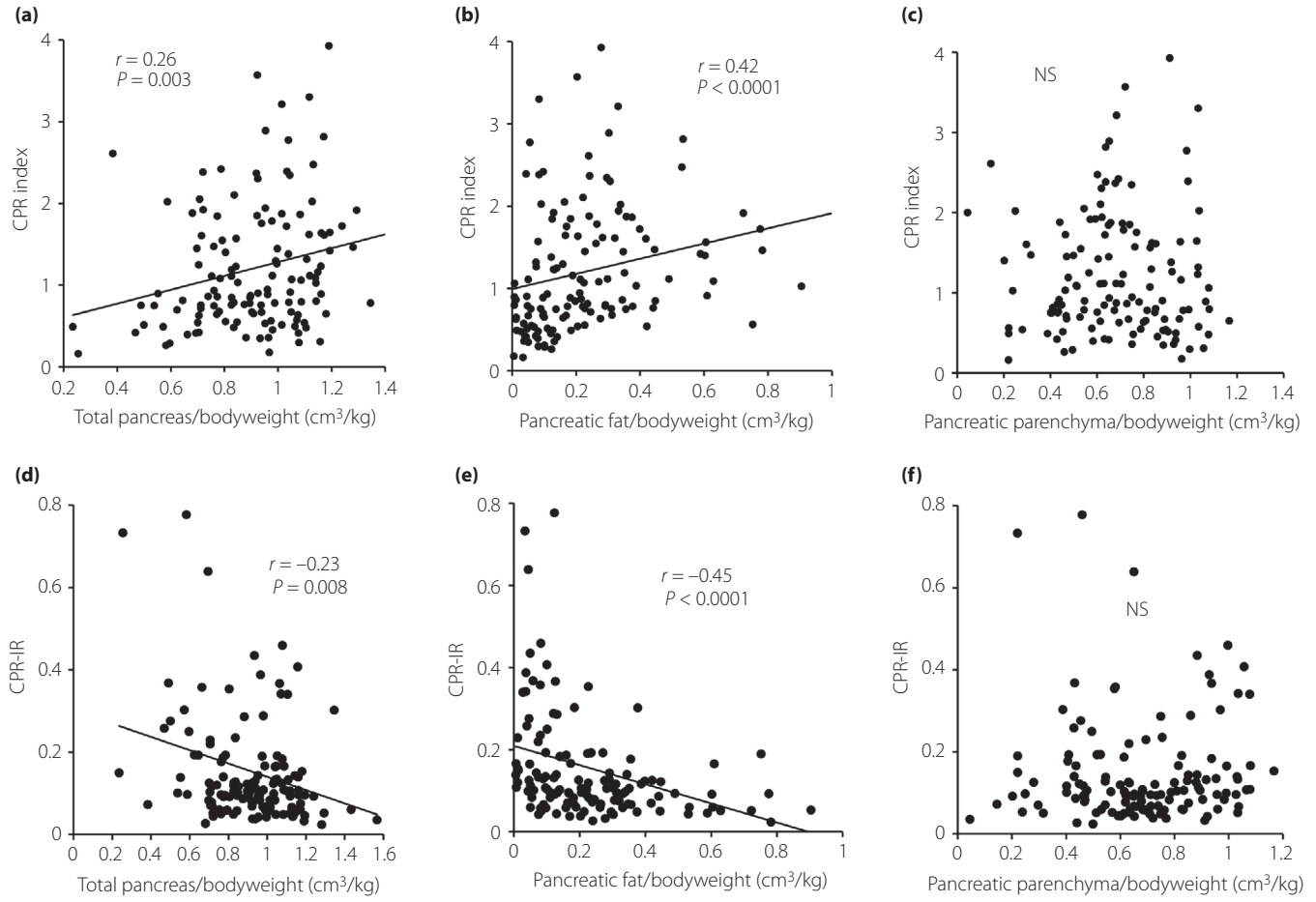

Figure 2 | Correlation of each parameter of pancreatic volume with (a–c) C-peptide immunoreactivity (CPR) index and (d–f) CPR-insulin resistance (CPR-IR). NS, not significant.

Clinical factors associated with PFV and PPV

As shown in Table 2, male sex, current BMI and BMI at age 20 years, waist circumference, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, uric acid, triglycerides, muscle and body fat mass, and total body fat content were positively associated with PFV/BW ($P < 0.05$), whereas high-density lipoprotein cholesterol levels were inversely correlated with PFV/BW. There was an inverse association of age and triglycerides with PPV/BW (Table 2). eGFR was positively correlated with PPV/BW.

Effect of pancreatic fat accumulation on β-cell function in type 2 diabetes with diabetes duration >5 years versus ≤5 years

When PFV was divided into two groups according to the median value of PFV/BW (0.183 cm^3/kg), the high PFV group had higher current BMI and BMI at aged 20 years, waist circumference, levels of liver enzymes, CPR index, PV/BW, and visceral FV/BW, and lower high-density lipoprotein cholesterol, eGFR, CPR-IR and PPV/BW compared with the low PFV group.

The CPR index in the high PFV/BW group patients with diabetes duration >5 years was significantly lower than those with diabetes duration ≤5 years. However, a duration-dependent decrease in CPR index was not observed in the low PFV/BW group patients (Figure 4a). There was no difference of diabetes medications between the high PFV/BW group with diabetes duration >5 years and that ≤5 years (Table S2).

When PFV was divided into two groups according to the median ratio of pancreatic fat in relation to total pancreatic volume (21.3%), the CPR index in the high PFV/TPV group patients with diabetes duration >5 years was significantly lower than those ≤5 years, whereas a decrease in the CPR index was not observed in the low PFV/TPV group patients with increased duration of diabetes (Figure 4b). Furthermore, there was no significant difference of the CPR index between patients with disease duration >5 years and ≤5 years, irrespective of visceral FV/BW (Figure 4c).

A multivariate logistic regression analysis was carried out using the high PFV group as the dependent variable, and visceral FV, obesity (BMI ≥25.0 kg/m^2), male sex, fatty liver,

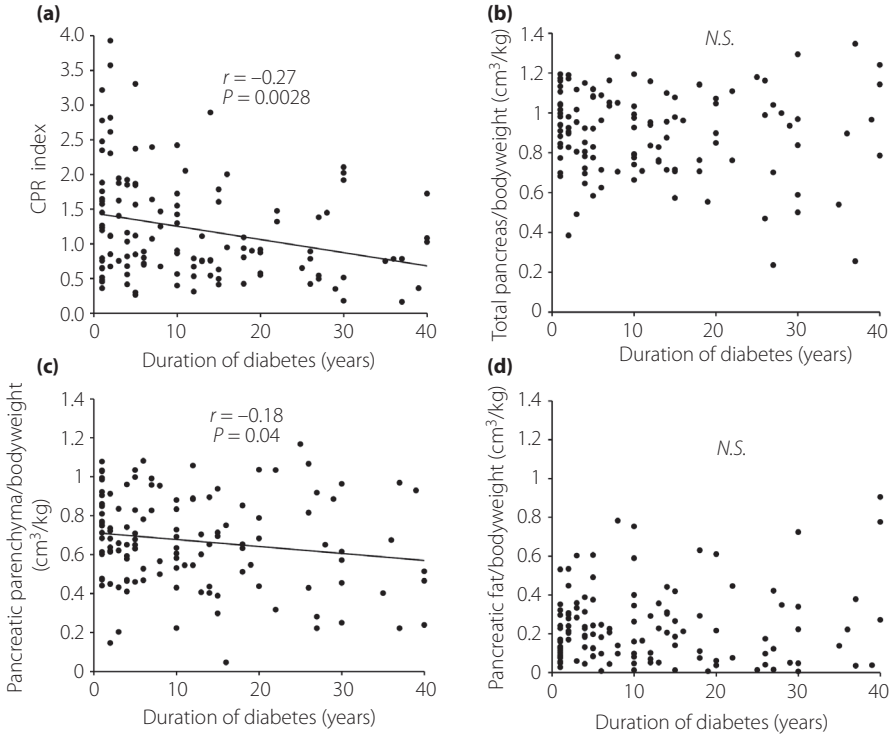

Figure 3 | Correlation of (a) C-peptide immunoreactivity (CPR) index and (b–d) each parameter of pancreatic volume with duration of diabetes. NS, not significant.

CPR-IR, increased triglycerides (≥150 mg/dL) and decreased high-density lipoprotein cholesterol (≤40 mg/dL) as independent variables. Multivariate analysis showed that visceral FV was a sole independent and significant correlate of the high PFV group (Table 3).

DISCUSSION

The salient findings of the present study are as follows: (i) PV, PFV and PPV evaluated by MDCT were positively correlated with BW; (ii) PV/BW and PFV/BW, but not PPV/BW, were associated with increased insulin secretion ability, as well as

Table 2 | Association of pancreatic fat and parenchymal volume with various clinical parameters

Factors	Pancreatic fat (cm^3/kg)		Pancreatic parenchyma (cm^3/kg)	
	r	*P*	*r*	*P*
Male sex	–0.17	0.0458	0.01	NS
Age (years)	0.07	NS	–0.3	<0.001
Current body mass index (kg/m^2)	0.5281	<0.0001	–0.15	NS
Body mass index at age 20 years (kg/m^2)	0.233	0.0101	–0.1085	NS
Waist circumference (cm)	0.5101	<0.0001	–0.1188	NS
Glycated hemoglobin (%)	0.052	NS	0.023	NS
Aspartate aminotransferase (IU/L)	0.2404	<0.01	–0.02	NS
Alanine aminotransferase (IU/L)	0.2211	0.0108	0.05	NS
Gamma-glutamyltransferase (IU/L)	0.3166	<0.001	0.0022	NS
Uric acid (mg/dL)	0.256	<0.01	–0.032	NS
Estimated glomerular filtration rate (mL/min/1.73 m^2)	–0.166	NS	0.27	<0.005
Triglycerides (mg/dL)	0.19	0.025	–0.177	0.04
High-density lipoprotein cholesterol (mg/dL)	–0.2489	<0.01	–0.05	NS
Muscle mass, kg (n = 108)	0.3087	<0.005	0.028	NS
Body fat mass, kg (n = 108)	0.5389	<0.0001	–0.156	NS
Total body fat content, % (n = 108)	0.4237	<0.0001	–0.188	NS

NS, not significant.

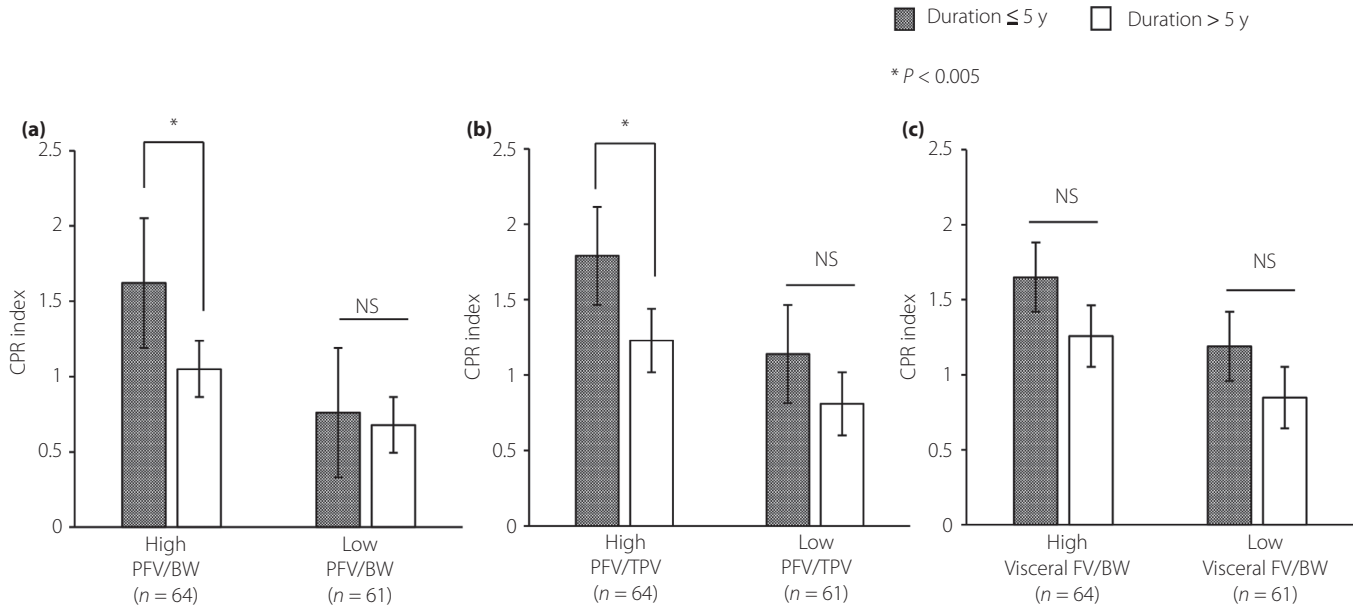

Figure 4 | C-peptide immunoreactivity (CPR)-index values in patients with diabetes duration >5 years and ≤5 years. (a) High versus low pancreatic fat volume (PFV)/bodyweight (BW) group. (b) High versus low PFV/total pancreas volume (TPV) group. (c) High versus low visceral fat volume (FV)/BW group. NS, not significant.

Table 3 | Factors associated with the high pancreatic fat group

Factors	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Visceral fat volume (cm^3)†	2.02 (1.55–2.63)	<0.0001	1.87 (1.34–2.71)	0.0004
Obesity (BMI ≥25.0 kg/m^2)	6.13 (2.93–13.34)	<0.0001	1.84 (0.68–4.95)	0.22
Male sex	1.91 (0.94–3.98)	0.08	0.74 (0.30–2.26)	0.81
Fatty liver‡	2.75 (1.26–6.27)	0.01	0.84 (0.30–2.35)	0.74
C-peptide-insulin resistance	3.54 (1.74–7.40)	<0.001	1.16 (0.45–3.00)	0.76
Increased triglycerides (≥150 mg/dL)	1.55 (0.71–3.47)	0.27	1.06 (0.39–2.85)	0.91
Decreased high-density lipoprotein-cholesterol (≤40 mg/dL)	1.41 (0.69–2.91)	0.34	0.70 (0.27–1.80)	0.46

BMI, body mass index; CI, confidence interval; OR, odds ratio. †OR is shown per 1,000-cm^3 increase. ‡We defined a presence of fatty liver using the computed tomography value of liver divided by spleen ≤1.0 according to evidence-based clinical practice guidelines for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, Japanese Society of Gastroenterology, 2014.

decreased insulin sensitivity, and (iii) a disease duration-dependent decrease in insulin secretion was more accelerated in type 2 diabetes patients with high PFV.

In the present study, PV and PFV, but not PPV, were significantly correlated with BW, a finding that was totally consistent with previous observations showing that pancreatic fat area evaluated by CT or MRI was positively associated with BW[1,27,28]. Furthermore, as visceral FV/BW was the strongest correlate of BW-adjusted PFV, the present study suggests that the SYNAPSE VINCENT image analysis system is a reliable tool for evaluating PFV in patients with type 2 diabetes, and that pancreatic fat is one of the representative visceral fats in humans.

In the present study, PFV/BW was positively and inversely associated with the CPR index and CPR-insulin resistance, respectively. This means that patients with high PFV might have hyperinsulinemia as a result of insulin resistance, as is the case for patients with central obesity. Here, we would like to propose a hypothesis that compensatory hypersecretion of insulin from β-cells in response to insulin resistance might be burned out with increased duration of diabetes. This is a possible reason why a disease duration-dependent decrease in the CPR index was more pronounced in the high PFV/BW patients compared with the low PFV/BW group patients.

Although there was a strong correlation between PFV and visceral FV, a duration-dependent decline in the CPR index was not observed in either the high or low visceral FV group patients. These results suggest that PFV might be a more sensitive marker than visceral FV that could predict the impaired secretion of insulin in type 2 diabetes patients with insulin

resistance. A previous report showing that pancreatic fat area evaluated by MRI was a stronger determinant of impaired insulin secretion than visceral fat in patients with impaired glucose tolerance could support our speculation[29]. Anyway, the present findings suggest that the reduction of PFV might be a novel therapeutic target for treatment of patients with type 2 diabetes.

There were several limitations to the present study. First, this was a retrospective cross-sectional study. Thus, longitudinal studies are required to clarify the clinical role of pancreatic fat accumulation in β-cell function. Second, Hounsfield units <0 in the pancreas were defined as pancreatic fat in this study. However, in another study, the CT value range of −190 to −30 Hounsfield units was used for assessment of pancreatic fat[30]. At present, it remains unclear which cut-off Hounsfield units are more sensitive for detecting the fat content in the pancreas by MDCT. However, the positive correlation between PFV and various metabolic parameters observed here might support the reliability of our detection and evaluation system for pancreatic fat. Third, as glycemic control of the patients in the present study was poor and their HbA1c values were 9.2%, and 71% of the patients received insulin, we cannot generalize the present findings to well-controlled diabetes patients of other ethnic backgrounds. In a subgroup with lower HbA1c (<8.0%) and oral therapy, there was no association between PFV/BW and C-peptide-based indices of insulin secretion, such as the homeostatic model assessment-2 β-cell function (HOMA2-%B)[31]. However, the number of participants in this group was small (n = 10), and had insufficient statistical power to detect the correlation of PFV/BW and HOMA2-%B. It would be interesting to examine the correlation of PFV/BW and HOMA2-%B in well-controlled type 2 diabetes patients. Fourth, in the present study, PFV means total fat volume in the entire pancreas. Unfortunately, we could not discriminate intralobular fat volume from interlobular fat volume by our imaging system.

In conclusion, the present study suggests that pancreatic fat accumulation might be attributable to longitudinal decline in β-cell function of type 2 diabetes patients with insulin resistance. Evaluation of PFV by MDCT might help identify diabetes patients who benefit most from improvement of central obesity. Further large-scale studies are warranted to clarify whether the reduction of PFV ameliorates the impairment of insulin secretion in patients with type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Multiple regression for the C-peptide immunoreactivity index.
Table S2 | Therapy for diabetes in the high pancreatic fat group.