


Pancreatic fat content assessed by ^1H magnetic resonance spectroscopy is correlated with insulin resistance, but not with insulin secretion, in Japanese individuals with normal glucose tolerance

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Keywords

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ABSTRACT

Aims/Introduction: Whereas some clinical studies have shown that excessive fat accumulation in the pancreas is associated with impairment of insulin secretion, others have not found such an association. ^1H magnetic resonance spectroscopy allows quantitative fat analysis in various tissues including the pancreas. The pathological relevance of pancreatic fat content (PFC) in Japanese individuals remains unclear, however.

Materials and Methods: We analyzed PFC in 30 Japanese individuals with normal glucose tolerance by ^1H magnetic resonance spectroscopy, and then investigated the relationships between PFC and indexes of insulin secretion and insulin sensitivity-resistance determined by an oral glucose tolerance test. We also measured hepatic fat content and intramyocellular lipid content by ^1H magnetic resonance spectroscopy, as well as visceral fat area and subcutaneous fat area by magnetic resonance imaging, and we examined the relationships between these fat content measures and oral glucose tolerance test-derived parameters.

Results: PFC was correlated with indexes of insulin sensitivity-resistance, but not with those of insulin secretion. Hepatic fat content and visceral fat area were correlated with similar sets of parameters as was PFC, whereas subcutaneous fat area was correlated with parameters of insulin secretion, and intramyocellular lipid content was not correlated with any of the measured parameters. The correlation between PFC and homeostasis model assessment of insulin resistance remained significant after adjustment for age, body mass index and sex. Among fat content measures, PFC was most highly correlated with hepatic fat content and visceral fat area.

Conclusions: PFC was correlated with indexes of insulin resistance, but not with those of insulin secretion in non-obese Japanese individuals with normal glucose tolerance.

INTRODUCTION

Obesity is the most common and important contributing factor to the development of insulin resistance and consequent pathological disorders including type 2 diabetes mellitus. Evidence

suggests that the exaggerated accumulation of fat in non-adipose insulin-sensitive tissues – that is, skeletal muscle and liver – is associated with insulin resistance^{1,2}, and that certain lipids impair the effects of insulin both in cells and in the living body³. Excess fat in these non-adipose tissues is thus thought to contribute to the pathogenesis of insulin resistance induced by obesity.

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The accumulation of fat also occurs in the pancreas^{4,5}. Evidence obtained from cell culture or animal studies suggests that excess fat inhibits insulin secretion or accelerates apoptosis in pancreatic β -cells^{6,7}, effects that also might be related to the pathogenesis of type 2 diabetes. Some clinical studies support the notion that pancreatic fat content (PFC) is negatively correlated with insulin secretion or β -cell function^{8–10}, whereas others have not detected such a correlation^{11–13}.

The impact of fat accumulation on the development of metabolic disorders is thought to differ among ethnicities¹⁴. Although the extent and prevalence of obesity are much lower in East Asian countries including Japan than in the USA and Europe¹⁵, the prevalence of obesity-related diseases, such as type 2 diabetes or non-alcoholic fatty liver disease, does not show such a difference^{16,17}. Given that relatively lower levels of fat accumulation likely elicit greater effects on the development of metabolic disorders in Japanese individuals, the definition of obesity in Japan (a body mass index [BMI] of $>25 \text{ kg/m}^2$)¹⁸ differs from that in the USA and European countries (BMI of $>30 \text{ kg/m}^2$)^{19,20}. However, information regarding the pathological relevance of PFC in Japanese people is limited. Pancreatic fat as assessed by computed tomography (CT) was shown to be correlated with impaired insulin secretion²¹ or to be independent of the incidence of type 2 diabetes mellitus²² in Japanese people.

PFC can be evaluated by several non-invasive techniques including CT, ultrasonography, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS)^{4,5}. PFC assessed by ¹H-MRS has been shown to be highly concordant with that determined by biochemical analysis of tissue homogenates²³. In addition, given that similar patterns of fat accumulation have been observed in the exocrine and endocrine pancreas of obese animals²⁴, PFC analysis by ¹H-MRS is thought to provide a good quantitative surrogate of fat accumulation in pancreatic islets^{4,5}. PFC has not previously been evaluated by ¹H-MRS in the Japanese population, however.

To provide further insight into the physiological relevance of excess fat in the pancreas, we have now measured PFC with the use of ¹H-MRS in Japanese individuals, and then examined the relationships between PFC and parameters of insulin secretion or insulin sensitivity-resistance determined by an oral glucose tolerance test (OGTT). To avoid secondary effects of treatment or hyperglycemia, we recruited volunteers with normal glucose tolerance (NGT) as study participants. We also measured fat accumulation in the liver and skeletal muscle, as well as the areas of subcutaneous and visceral fat tissues with ¹H-MRS or MRI, respectively. We found that PFC was correlated with parameters of insulin sensitivity-resistance, but not with those of insulin secretion, as well as with hepatic and visceral fat accumulation in Japanese individuals with NGT.

METHODS

Study participants

The study was approved by the ethics committee of Kobe University Graduate School of Medicine, conforms to the

provisions of the Declaration of Helsinki (as revised in 2013) and is registered in the University Hospital Medical Information Network (UMIN000003753). A total of 43 volunteers who had not been diagnosed with diabetes mellitus and whose first-degree relatives had no history of this disease were recruited at the Division of Diabetes and Endocrinology of Kobe University Hospital from January 2011 to August 2013. All these individuals provided written informed consent to participate in the study. They underwent a 75-g OGTT and comprehensive fat content analysis with the use of consecutive ¹H-MRS and MRI within a period of 2 weeks. Of the 43 individuals, 13 were found to manifest either impaired glucose tolerance (plasma glucose level at 120 min after initiation of the OGTT of $\geq 140 \text{ mg/dL}$ and $< 200 \text{ mg/dL}$) or impaired fasting glycemia (fasting plasma glucose level of $\geq 110 \text{ mg/dL}$ and $< 126 \text{ mg/dL}$). We therefore included the 30 individuals with NGT (fasting plasma glucose of 110 mg/dL and plasma glucose level at 120 min after initiation of the OGTT of $< 140 \text{ mg/dL}$) as study participants for further analysis.

OGTT-based clinical parameters

A standard 75-g OGTT was carried out in the morning after the participants had fasted overnight. Blood samples were collected before, and at 30, 60, 90, and 120 min after ingestion of glucose for the measurement of plasma glucose and serum insulin concentrations. For the assessment of insulin secretion, we calculated the insulinogenic index, homeostasis model assessment of β -cell function (HOMA- β), the area under the curve for serum insulin concentration ($\text{AUC}_{\text{ins}120}$) and the ratio of the area under the curve for serum insulin concentration to that for plasma glucose concentration ($\text{AUC}_{\text{ins}/\text{glu}120}$). The insulinogenic index was calculated as the change in serum insulin concentration divided by that in plasma glucose concentration from 0 to 30 min during the OGTT. For the assessment of insulin sensitivity-resistance, we calculated the composite index²⁵ and homeostasis model assessment of insulin resistance (HOMA-IR). An OGTT-based analog of the disposition index (DI), which we termed the oral DI, was calculated as the product of the composite index and $\text{AUC}_{\text{ins}/\text{glu}120}$, as described previously²⁶.

Comprehensive fat content analysis by ¹H-MRS and MRI

For fat content analysis, magnetic resonance scanning was carried out in the afternoon with participants in the non-fasted state and with the use of a 3.0-T whole-body system (Achieva 3.0T Quasar Dual; Philips Electronics, Amsterdam, the Netherlands). Participants were in the supine position with the body-array coil positioned at the upper abdominal region. Single-voxel spectra were acquired with the point-resolved spectroscopy sequence. Intracellular lipid content in skeletal muscle (intramyocellular lipid [IMCL]) and hepatic fat content (HFC) were determined by ¹H-MRS, and the areas of visceral fat tissue (VF) and subcutaneous fat tissue (SCF) were determined by MRI, as described previously^{27,28}. PFC was measured

within a volume of $15 \times 15 \times 15 \text{ mm}^3$ located in the head of the pancreas, avoiding visceral fat and vessels, with the use of ^1H -MRS. The measurement was carried out while the participant had stopped breathing. With this system, simulated lipid and water spectra are detected at 1.4 and 4.8 ppm, respectively (Figure 1). PFC was calculated as the ratio of the area under the lipid peak to the sum of the areas under the lipid peak and the water peak (internal standard), as previously described²⁹, with the use of Scion image analysis software (Scion Corporation, <http://www.scioncorp.com>). PFC measurement was carried out twice in 20 participants, with the coefficient of variation between the two repeated measurements being 7.4%.

Statistical analysis

Data are presented as mean \pm standard deviation. The relationships between PFC and other clinical parameters were assessed by univariate correlation and multivariate linear regression analysis with the use of SPSS version 11.0 for Windows software (SPSS, Chicago, IL, USA). We coded the sex variable as men = 0 and women = 1. A *P*-value of <0.05 was considered statistically significant.

RESULTS

The study participants included 16 men and 14 women with an age and BMI of 30.8 ± 6.5 years and $20.5 \pm 2.0 \text{ kg/m}^2$, respectively (Table 1). The results of comprehensive fat content analysis are shown in Table 2, and the relationships between PFC, HFC, IMCL, VF or SCF and clinical or OGTT-derived parameters are shown in Table 3. PFC was correlated with age, BMI, sex, fasting serum insulin level and serum triglyceride concentration. It was also correlated with indexes of insulin sensitivity-resistance including HOMA-IR and the composite index, but not with those of insulin secretion including HOMA- β , the insulinogenic index and $\text{AUC}_{\text{ins}/\text{glu}120}$. In addition, PFC was correlated with oral DI, an index of insulin

Table 1 | Demographics, serum lipid concentrations and oral glucose tolerance test-based parameters for the study participants

Age (years)	30.8 ± 6.5
BMI (kg/m^2)	20.5 ± 2.0
Sex (men/women)	16/14
FPG (mg/dL)	86.5 ± 6.8
F-IRI ($\mu\text{U/mL}$)	6.5 ± 2.3
Serum TG (mg/dL)	59.8 ± 21.2
Serum FFAs (mEq/L)	0.51 ± 0.25
HOMA-IR	1.40 ± 0.58
HOMA- β	104.5 ± 52.2
Insulinogenic index	1.20 ± 1.08
Composite index	6.99 ± 2.60
$\text{AUC}_{\text{ins}120}$ (min mg/dL)	4882 ± 1935
$\text{AUC}_{\text{ins}/\text{glu}120}$	0.34 ± 0.13
Oral DI	2.15 ± 0.52

Data are mean \pm standard deviation. $\text{AUC}_{\text{glu}120}$, area under the glucose concentration curve; $\text{AUC}_{\text{ins}120}$, area under the insulin concentration curve; BMI, body mass index; DI, disposition index; FFAs, free fatty acids; F-IRI, fasting serum insulin concentration; FPG, fasting plasma glucose concentration; HOMA- β , homeostasis model assessment of β -cell function; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride.

secretion adjusted for insulin sensitivity. HFC and VF were correlated with similar sets of parameters, as was PFC, with HFC showing significant correlations with age, BMI, sex, HOMA-IR, the composite index and oral DI, and VF with age, BMI, sex, fasting serum insulin level, serum triglyceride level, HOMA-IR and the composite index. IMCL was not correlated with any of the measured parameters, whereas it was previously shown to be correlated with insulin resistance²⁷. SCF was correlated with BMI, $\text{AUC}_{\text{ins}120}$ and $\text{AUC}_{\text{ins}/\text{glu}120}$.

Given that several measures of fat content including PFC, HFC, and VF were correlated with age, BMI and sex, we next

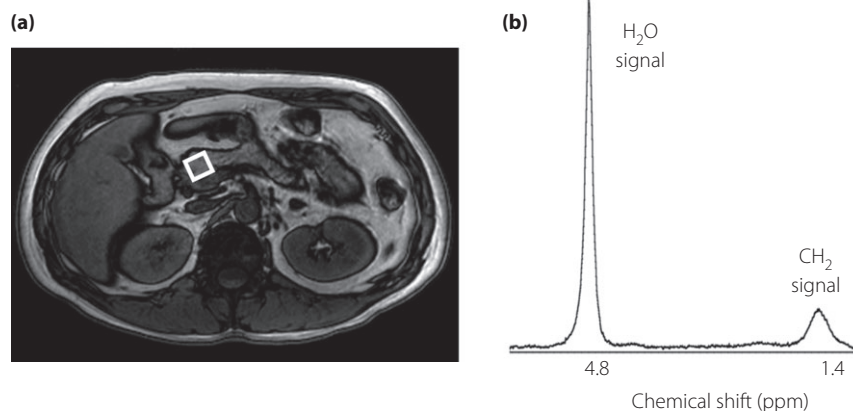


Figure 1 | ^1H magnetic resonance spectroscopy for analysis of pancreatic fat content. (a) Representative magnetic resonance imaging of the pancreas. The square indicates the measured area at the head of the pancreas. (b) Representative ^1H magnetic resonance spectroscopy for analysis of pancreatic fat content. The peak of the CH_2 signal is considered as the lipid peak.

Table 2 | Parameters of comprehensive fat content analysis for the study participants

PFC (%)	6.36 ± 3.49
HFC (%)	4.68 ± 3.48
VF (cm ²)	47.6 ± 24.3
SCF (cm ²)	112.5 ± 44.9
IMCL (AU/Cr)	9.18 ± 4.39

Data are mean ± standard deviation. AU/Cr, arbitrary unit per creatinine; HFC, hepatic fat content; IMCL, intramyocellular lipid content; PFC, pancreatic fat content; SCF, subcutaneous fat area; VF, visceral fat area.

analyzed the relationships between fat content measures and indexes of insulin secretion and sensitivity-resistance after adjustment for age, BMI, and sex (Table 4). After this

adjustment, PFC was correlated with only HOMA-IR, VF was correlated with HOMA-β and HOMA-IR, and SCF was correlated with AUC_{ins120} and AUC_{ins/glu120}, whereas HFC and IMCL did not show any significant correlations.

We finally analyzed the relationships between PFC and other fat content measures and BMI. PFC was significantly correlated with all these parameters with the exception of IMCL (Figure 2). The strongest correlation was observed with HFC, and the second strongest with VF.

DISCUSSION

As far as we are aware, the present study is the first to evaluate PFC by ¹H-MRS in Japanese individuals. We found that PFC was correlated with indexes of insulin sensitivity-resistance

Table 3 | Relationships between tissue fat content and clinical or oral glucose tolerance test-based parameters

	PFC		HFC		IMCL		VF		SCF	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	0.590	0.001	0.399	0.029	0.014	0.941	0.613	<0.001	0.030	0.873
BMI	0.501	0.005	0.527	0.003	0.191	0.311	0.606	<0.001	0.549	0.002
Sex	-0.392	0.032	-0.579	0.001	0.026	0.892	-0.484	0.007	0.037	0.846
FPG	0.489	0.006	0.466	0.009	-0.036	0.850	0.298	0.110	-0.017	0.929
F-IRI	0.520	0.003	0.361	0.050	0.050	0.792	0.481	0.007	0.223	0.237
Serum TG	0.439	0.015	0.345	0.062	-0.066	0.730	0.523	0.003	0.204	0.279
Serum FFAs	-0.036	0.849	-0.076	0.690	0.153	0.419	-0.085	0.654	-0.106	0.578
HOMA-β	0.074	0.696	0.076	0.690	0.073	0.700	0.231	0.220	0.167	0.378
Insulinogenic index	0.145	0.446	-0.123	0.517	-0.192	0.308	0.037	0.845	0.068	0.721
AUC _{ins120}	0.332	0.073	0.342	0.064	0.033	0.862	0.337	0.068	0.396	0.030
AUC _{ins/glu120}	0.203	0.282	0.173	0.360	0.036	0.850	0.200	0.290	0.397	0.030
HOMA-IR	0.619	<0.001	0.483	0.007	0.034	0.858	0.558	0.001	0.282	0.131
Composite index	-0.433	0.017	-0.416	0.022	-0.059	0.755	-0.388	0.034	-0.197	0.296
Oral DI	-0.403	0.027	-0.435	0.016	0.018	0.925	-0.347	0.060	0.184	0.330

AUC_{glu120}, area under the glucose concentration curve; AUC_{ins120}, area under the insulin concentration curve; BMI, body mass index; DI, disposition index; FFAs, free fatty acids; F-IRI, fasting serum insulin concentration; FPG, fasting plasma glucose concentration; HFC, hepatic fat content; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IMCL, intramyocellular lipid content; PFC, pancreatic fat content; SCF, subcutaneous fat area; TG, triglyceride; VF, visceral fat area.

Table 4 | Relationships between tissue fat content and indexes of insulin secretion or insulin sensitivity-resistance after adjustment for age, body mass index and sex

	PFC		HFC		IMCL		VF		SCF	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
HOMA-β	0.151	0.453	0.097	0.630	0.079	0.696	0.406	0.036	0.226	0.258
Insulinogenic index	0.219	0.273	-0.123	0.542	-0.157	0.435	0.104	0.607	0.259	0.193
AUC _{ins120}	0.276	0.164	0.189	0.346	0.027	0.893	0.260	0.190	0.506	0.007
AUC _{ins/glu120}	0.241	0.227	0.096	0.635	0.040	0.843	0.231	0.246	0.532	0.004
HOMA-IR	0.498	0.008	0.294	0.137	0.014	0.946	0.394	0.042	0.313	0.111
Composite index	-0.337	0.086	-0.218	0.275	-0.057	0.776	-0.232	0.244	-0.230	0.248
Oral DI	-0.177	0.378	-0.253	0.203	0.032	0.874	-0.050	0.804	0.318	0.106

AUC_{glu120}, area under the glucose concentration curve; AUC_{ins120}, area under the insulin concentration curve; DI, disposition index; HFC, hepatic fat content; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IMCL, intramyocellular lipid content; PFC, pancreatic fat content; SCF, subcutaneous fat area; VF, visceral fat area.

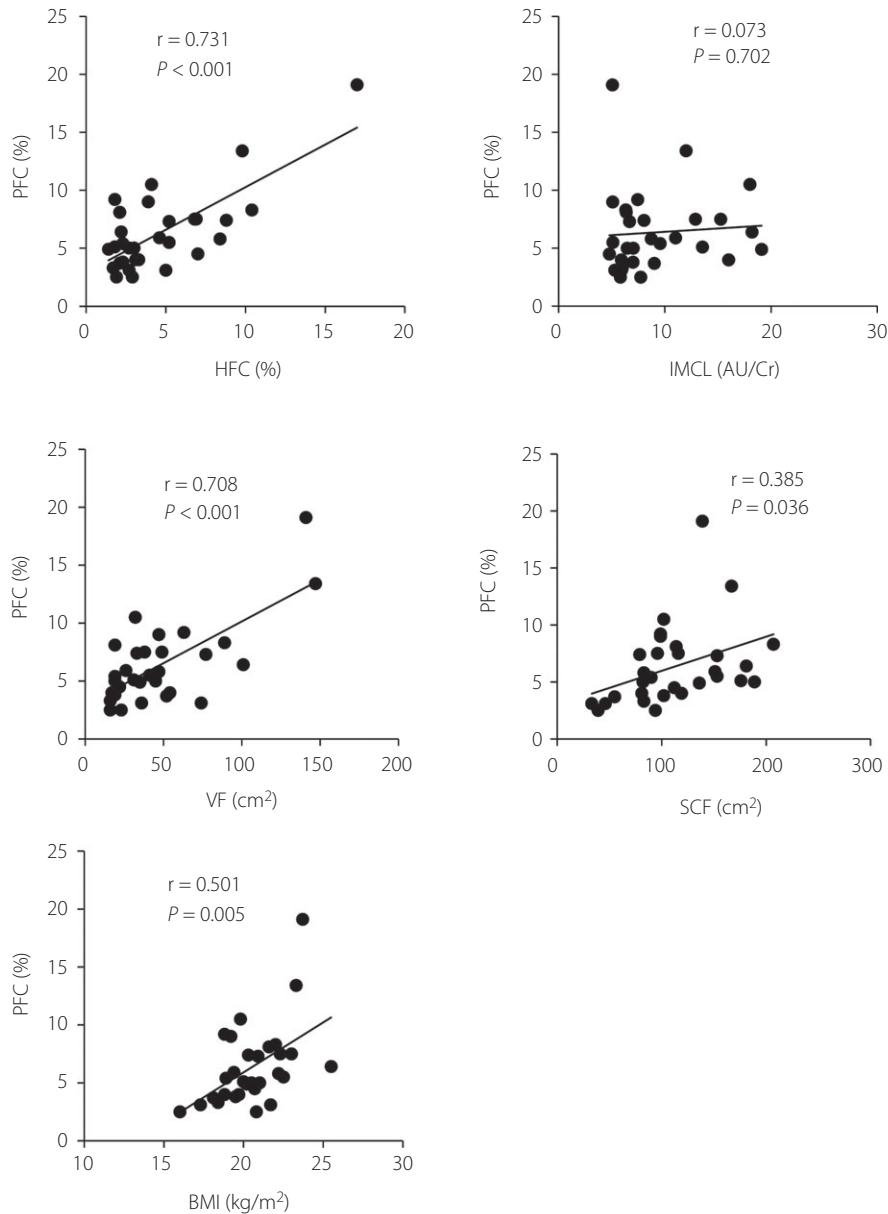


Figure 2 | Relationships between pancreatic fat content (PFC) and other parameters of fat analysis and body mass index (BMI) for the study participants. AU/Cr, arbitrary unit per creatinine; HFC, hepatic fat content; IMCL, intramyocellular lipid; SCF, subcutaneous fat tissue.

(HOMA-IR and the composite index), but not with those of insulin secretion (HOMA- β , the insulinogenic index or $AUC_{ins/glu120}$). A correlation between PFC and insulin sensitivity-resistance was previously described for overweight or obese non-Asian adults and children^{30,31}. We have now shown that this relationship is conserved in Japanese individuals with normal body mass (BMI of 20.5 ± 2.0 kg/m²). The correlation of PFC with HOMA-IR remained significant after adjustment for age, BMI and sex, showing that the relationship between PFC and insulin resistance is independent of these factors.

A previous study has shown that HFC and were correlated with indexes of insulin sensitivity-resistance²¹. In the present

study, although HF was correlated with both HOMA-IR and the composite index, these correlations did not remain significant after the adjustment of age, BMI and sex, suggesting that HF is heavily influenced by these parameters. IMCL of the current study participants was relatively low and distributed in a narrow range, which might explain the reason why the correlation of IMCL with insulin sensitivity-resistance was not observed.

Previous studies have yielded discrepant results regarding the relationship between PFC and the capacity for insulin secretion⁸⁻¹³. Although the reason for this discordance is unclear, one study found that PFC was correlated with parameters of

insulin secretion in Caucasians, but not in Hispanics, with NGT¹⁰. Furthermore, another study showed that the reduction in PFC after bariatric surgery was correlated with the improvement in insulin secretion in individuals with diabetes, but not in those with NGT³². It is thus possible that the influence of pancreatic fat on insulin secretion is dependent on various factors including ethnicity and the level of glucose tolerance. A previous study has shown that insulin secretory response of East Asians is lower than those of Caucasians or Africans³³. Such physiological characteristics of East Asian ethnicity might have influenced the results of the present study. CT values of the pancreas were shown to be correlated with the insulinogenic index in Japanese individuals undergoing a health checkup, including individuals with NGT, impaired glucose tolerance or diabetes mellitus²¹. The relationship between ¹H-MRS-based PFC and the capacity for insulin secretion thus warrants investigation in individuals other than those with NGT.

We found that PFC was highly correlated with HFC and VF. Similar observations were described for individuals with several pathological conditions, including non-alcoholic fatty liver disease and pediatric obesity^{29–31}. While VF is widely accepted as a contributing factor to insulin resistance^{34,35}, whether HFC is a cause or result of insulin resistance remains unclear^{36,37}. Although the nature of the causal relationship between PFC and insulin resistance is currently unknown, it is possible that PFC is a result of insulin resistance. The exaggerated accumulation of VF is associated with chronic inflammation in this tissue and with the alterations in the secretion of adipokines, as well as in the metabolism of fatty acids, which in turn contribute to the development of insulin resistance³⁷. It is thus possible that one of these factors is also related to the accumulation of fat in the pancreas. Given that fat accumulates only in parenchymal cells in the liver, HFC is upregulated by an increase in the influx or synthesis of fatty acids in, or by a decrease in the secretion of lipoproteins from, hepatocytes³⁸. Fat accumulation in the pancreas, in contrast, reflects the infiltration of adipocytes in interstitial tissue, replacement of parenchymal cells with fat and the accumulation of fat in parenchymal cells⁴. It remains to be elucidated why the accumulation of fat in these different tissues through apparently different mechanisms occurs concomitantly. Whatever the mechanism, PFC might serve as a clinical marker of insulin resistance as HFC does.

In conclusion, we have shown that insulin resistance, but not insulin secretion, is correlated with PFC in a manner independent of age, sex and BMI in Japanese individuals with NGT. Given that the BMI of the study participants was low and distributed within a narrow range, it is unclear whether the current findings are broadly applicable to the general Japanese population. Further studies of individuals with different backgrounds, such as those with different body compositions or different levels of glucose tolerance, are warranted to shed light on the physiological relevance of PFC.

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DISCLOSURE

The authors declare no conflict of interest.

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