Insulin secretion and computed tomography values of the pancreas in the early stage of the development of diabetes

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ABSTRACT

Aims/Introduction: The computed tomography (CT) value of the pancreas was examined across the range of glucose tolerance, and the relationships between pancreatic CT values and factors responsible for glucose intolerance were analyzed.

Materials and Methods: A total of 167 health-check examinees were classified into normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus (DM) according to 75 g oral glucose tolerance test (OGTT). Pancreatic and hepatic CT values were estimated at decreasing stages of glucose tolerance. The association of CT values of the pancreas and the indices of glucose tolerance were analyzed.

Results: Insulinogenic index (II) was decreased from NGT through IGT to DM. Mean pancreatic CT value was decreased significantly from NGT through IGT to DM. Mean area under the curves of glucose (AUC-G) was significantly associated with II and insulin sensitivity index (ISI) composite in univariate analysis. In multiple regression analysis, II was most strongly inversely correlated with mean AUC-G, suggesting that II is the strongest determinant of glucose tolerance in Japanese. In addition, II was significantly associated with mean pancreatic CT value in univariate analysis. In multiple regression analysis, mean pancreatic CT value was strongly correlated with II.

Conclusions: Pancreatic CT values were significantly decreased from NGT through IGT to DM. II was the strongest determinant of glucose tolerance, and was significantly influenced by pancreatic CT values. Thus, pancreatic fat deposition might impair insulin secretion in the early stage of development of type 2 diabetes, before overt deterioration of glucose tolerance.

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KEY WORDS: Computed tomography, Insulin secretion, Pancreas

INTRODUCTION

The development of type 2 diabetes is characterized by impaired insulin secretion and/or action that interferes with plasma glucose homeostasis[1,2], but the mechanism is not fully clarified. In a histopathological autopsy study, diabetic patients showed more frequent and severe intralobular and interacinar fibrosis, fat deposition, and atrophy of the parenchyma than control subjects[3]. Fat deposition in the pancreas is one of the most frequent histological changes in aging and overweight. Schmitz-Moormann *et al.*[4] found that the adipose tissue and total weight of the pancreas was positively correlated with age and bodyweight in 50 autoptic pancreases. In diabetic patients, studies of abdominal ultrasonography reported increased pancreatic echogenicity induced by pancreatic fat deposition[5]. In rodent models of obesity and diabetes, pancreatic steatosis was found to result in hyperglycemia with failure of β-cell function[6,7]. A human study suggested that pancreatic lipid content, as measured by proton-magnetic resonance spectroscopy (^{1}H-MRS), might contribute to reduced β-cell function[8]. We show here that pancreatic steatosis might also play a role in the pathogenesis of type 2 diabetes as a result of β-cell dysfunction.

Computed tomography (CT) is widely used for imaging of abdominal organs. Diagnostic criteria of hepatic steatosis assessed by attenuation of liver CT value has been well documented. However, there are few studies that compare pancreatic CT values at the different stages of glucose tolerance in relation to the factors responsible for glucose tolerance, insulin secretory capacity and insulin sensitivity.

In the present study, we examined the CT values of pancreas across the range of glucose tolerance, and analyzed the relationship of CT values of the pancreas with insulin secretory capacity and insulin sensitivity.

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MATERIALS AND METHODS

A total of 167 Japanese participants aged 36–87 years were recruited to undergo 75 g oral glucose tolerance test (OGTT) because of having a positive urine glucose test, >5.6% glycated hemoglobin (HbA_{1c}) level, >100 mg/dL fasting plasma glucose (FPG) level or a family history of diabetes at initial examination for a medical check-up at Takasago Municipal Hospital. The HbA_{1c} value was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the formula HbA_{1c} = HbA_{1c} (Japan Diabetes Society; JDS) +0.4%, considering the relational expression of HbA_{1c} (JDS) measured by the previous Japanese standard substance and measurement methods, and HbA_{1c} (NGSP)[9]. Standard OGTT was administered according to the National Diabetes Data Group recommendations, which require the subjects to fast overnight for 10–16 h. Fasting, 0.5, 1, 1.5 and 2 h blood samples for determination of plasma glucose and serum insulin levels after oral administration of 75 g OGTT were obtained. For international comparisons, World Health Organization criteria (1998) were used to evaluate the results of OGTT. Subjects in the three categories of glucose tolerance, normal glucose tolerance (NGT; n = 53: FPG level <110 mg/dL and 2 h-PG level <140 mg/dL), impaired glucose tolerance (IGT; n = 52: FPG level <126 mg/dL and 140 mg/dL ≤ 2h-PG level < 200 mg/dL) and diabetes mellitus (DM; n = 62: FPG level ≥126 mg/dL and/or 2h-PG level ≥200 mg/dL) were enrolled in the study. Subjects who had significant pancreatic disease, hepatic or renal dysfunction, endocrine or malignant disease, a history of heavy exercise, or a history of gastrectomy were excluded.

Estimation of Insulin Secretion and Insulin Sensitivity

Early-phase insulin secretion was evaluated by insulinogenic index (II) and insulin sensitivity index (ISI) composite was used to evaluate systemic insulin sensitivity during OGTT. The disposition index was expressed as the multiplex of the indices of insulin secretion and insulin sensitivity. The calculations were as follows:

$$\mathrm{II} = 0.5\,\mathrm{h\ immunoreactive\ insulin\ (IRI)} - \mathrm{fasting\ IRI\ (FI)}/0.5\,\mathrm{h\ PG} - \mathrm{FPG}$$

$$\mathrm{ISI\ composite} = 10000/(\mathrm{FPG} \times \mathrm{FI} \times \mathrm{mean\ OGTT\ glucose\ concentration} \times \mathrm{mean\ OGTT\ insulin\ concentration})^{0.5}$$

$$\mathrm{Disposition\ index\ (DI)} = \mathrm{II} \times \mathrm{ISI\ composite}.$$

Pancreas and Liver CT Values

CT images were acquired with standard clinical abdominal CT protocol utilizing a multi-slice CT scanner (LightSpeed Pro16; GE Healthcare UK Ltd, Little Chalfont, England). Pancreatic CT attenuations were determined by calculating the mean Hounsfield unit of two regions in the pancreas (one in the pancreas head, and the other in the pancreas body and tail); hepatic CT attenuations were determined similarly on the basis of the mean Hounsfield unit of two regions (one in the right lobe and one in the left lobe of the liver).

Statistical Analysis

Data are presented as mean values ± SE. Statistical analyses were carried out using SPSS (Statistical Package for Social Science) II for Windows, version 11.01 J. Differences between groups were calculated by Student's t-test for unpaired comparisons. The association of mean pancreas CT value and each measure of the variables was assessed by univariate and multiple regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the clinical and metabolic characteristics of 167 Japanese subjects classified with NGT, IGT and DM according to the results of OGTT. There were no significant differences in respect to age and body mass index (BMI). In respect to free fatty acid (FFA), that in DM was significantly higher than that in NGT. There were no significant differences in history of alcohol intake, blood pressure, hepatobiliary enzyme and cholinesterase (ChE) among the three subgroups. FPG and the mean area under the curves of glucose (AUC-G) were significantly increased from NGT through IGT to DM.

Insulin sensitivity was evaluated by ISI composite; insulin secretory capacity was evaluated by II. ISI composite was

Table 1 | Clinical characteristics of normal glucose tolerance, impaired glucose tolerance and diabetes mellitus

	NGT	IGT	DM
n	53	52	62
Male/female	29/24	28/24	39/23
Age (years)	61.2 ± 1.4	64.8 ± 1.4	64.6 ± 1.1
BMI (kg/m^2)	24.4 ± 0.5	24.5 ± 0.5	24.8 ± 0.4
Abdominal circumference (cm)	86.8 ± 1.4	87.3 ± 1.3	88.2 ± 1.2
TG (mg/dL)	124.8 ± 10.7	123.3 ± 9.1	131.4 ± 6.0
LDL (mg/dL)	132.3 ± 3.7	127.1 ± 3.8	129.1 ± 4.4
HDL (mg/dL)	67.5 ± 2.7	68.1 ± 2.5	64.9 ± 2.3
FFA (mg/dL)	387.4 ± 28.0	451.3 ± 26.6	491.6 ± 32.7*
Fasting PG (mg/dL)	101.1 ± 0.8	107.8 ± 1.4**	128.3 ± 2.8$^{\#\#**}$
mean AUC-G (mg/dL)	135.7 ± 2.5	169.4 ± 3.7**	225.1 ± 5.7$^{\#\#**}$
Fasting IRI (ull/mL)	7.0 ± 0.6	6.7 ± 0.8	8.1 ± 0.6
MeanAUC-I (uU/mL)	54.9 ± 5.3	46.5 ± 4.5	53.6 ± 4.8
HbA_{1C} (%)	5.75 ± 0.05	5.94 ± 0.04**	6.58 ± 0.10$^{\#\#**}$
ISI composite	5.85 ± 0.41	5.64 ± 0.38	4.36 ± 0.41$^{\#*}$
insulinogenic index	1.18 ± 0.20	0.71 ± 0.21	0.39 ± 0.05**
disposition index	5.87 ± 0.99	3.37 ± 0.91	1.38 ± 0.22$^{\#**}$

HDL, high-density lipoprotein cholesterol; IRI, immunoreactive insulin; LDL, low-density lipoprotein cholesterol; TG, triglyceride.
Data are means ± standard error.
$^{*}P < 0.05$ vs normal glucose tolerance (NGT), $^{**}P < 0.01$ vs NGT, $^{\#}P < 0.05$ vs impaired glucose tolerance (IGT), $^{\#\#}P < 0.01$ vs IGT.

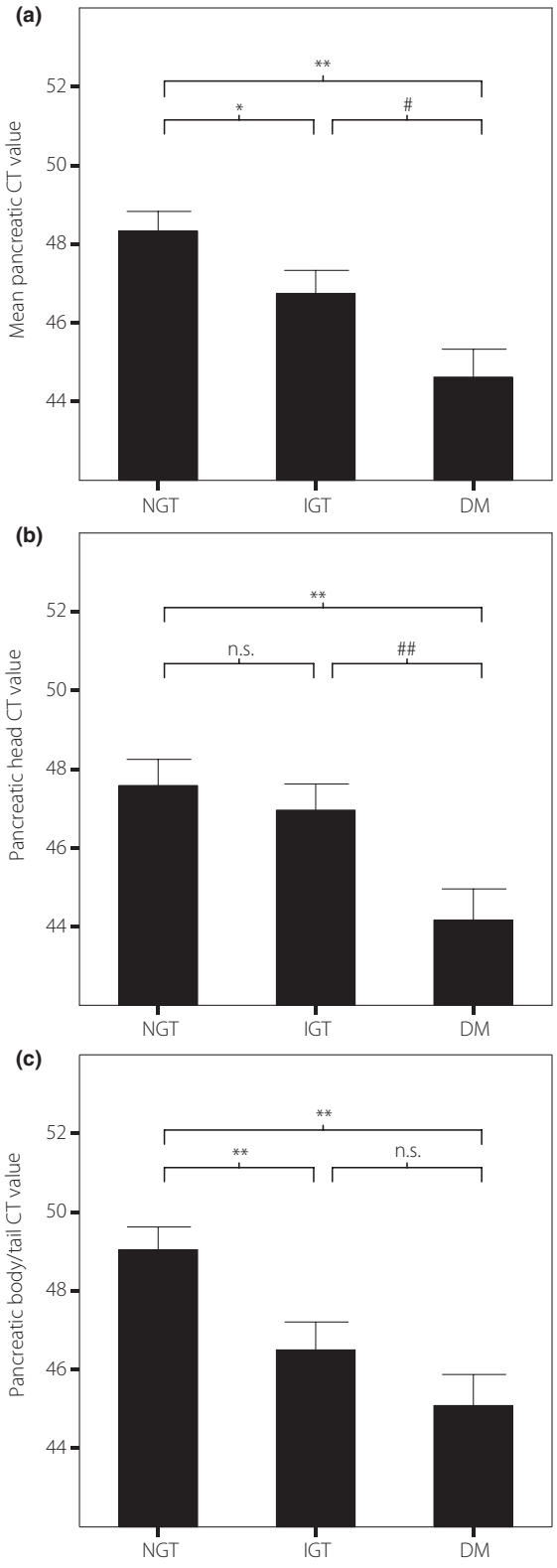

Figure 1 | Pancreatic head, body/tail and mean computed tomography (CT) values of normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus (DM) are shown (*$P < 0.05$ vs NGT, **$P < 0.01$ vs NGT, $^{\#}P < 0.05$ vs IGT, $^{\#\#}P < 0.01$ vs IGT). Pancreatic head and body/tail CT value are decreased from NGT through IGT to DM. In addition, mean pancreatic CT value is decreased significantly from NGT through IGT to DM (DM vs NGT $P < 0.01$, DM vs IGT $P < 0.05$, IGT vs NGT $P < 0.05$).

decreased gradually from NGT through IGT to DM, and showed a significant difference between NGT and DM ($P < 0.05$), and between IGT and DM ($P < 0.05$). II also was decreased from NGT through IGT to DM, and there were significant differences between NGT and DM ($P < 0.01$).

Figure 1 shows CT values of the liver and pancreas of the three subgroups. Mean pancreatic CT value was decreased significantly from NGT through IGT to DM (DM vs NGT $P < 0.01$, DM vs IGT $P < 0.05$, IGT vs NGT $P < 0.05$; Figure 1a). Pancreatic head CT value was decreased from NGT through IGT to DM, and diabetic patients had significantly lower values compared with those with NGT ($P < 0.01$) and IGT ($P < 0.01$) subjects (Figure 1b). Pancreatic body/tail CT value was decreased from NGT through IGT to DM (DM vs NGT $P < 0.01$, DM vs IGT $P = 0.189$, IGT vs NGT $P < 0.01$; Figure 1c).

The correlation of II to measures of variables in univariate and multiple regression analysis are listed in Table 2. II was significantly associated with mean pancreatic CT value, triglyceride (TG), high-density lipoprotein (HDL) cholesterol, abdominal circumference and BMI in univariate analysis. The relationship between mean pancreatic CT values and II are shown in Figure 2a. In multiple regression analysis, II was significantly associated with abdominal circumference and mean pancreatic CT value.

The correlation between mean AUC-G representing glucose tolerance and each measure of the factors was investigated (Table 3). Mean AUC-G had a significant association with II, ISI composite and FFA. In multiple regression analysis, II and ISI composite showed significant correlation with mean AUC-G. ISI composite representing insulin sensitivity was significantly inversely correlated with mean AUC-G, but II was most strongly inversely correlated with AUC-G (Figure 2b,c).

Table 2 | Correlation of insulinogenic index to measures of variables

	r	*P*	β
Age	−0.02	0.799	–
Sex	−0.073	0.345	–
BMI	0.248	0.001	–
Abdominal circumference (cm)	0.263	0.001	0.287
TG (mg/dL)	0.241	0.002	–
LDL (mg/dL)	0.032	0.678	–
HDL (mg/dL)	−0.197	0.011	–
FFA (mg/dL)	−0.129	0.158	–
Mean pancreatic CT value	0.247	0.001	0.272

FFA, free fatty acid; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride.

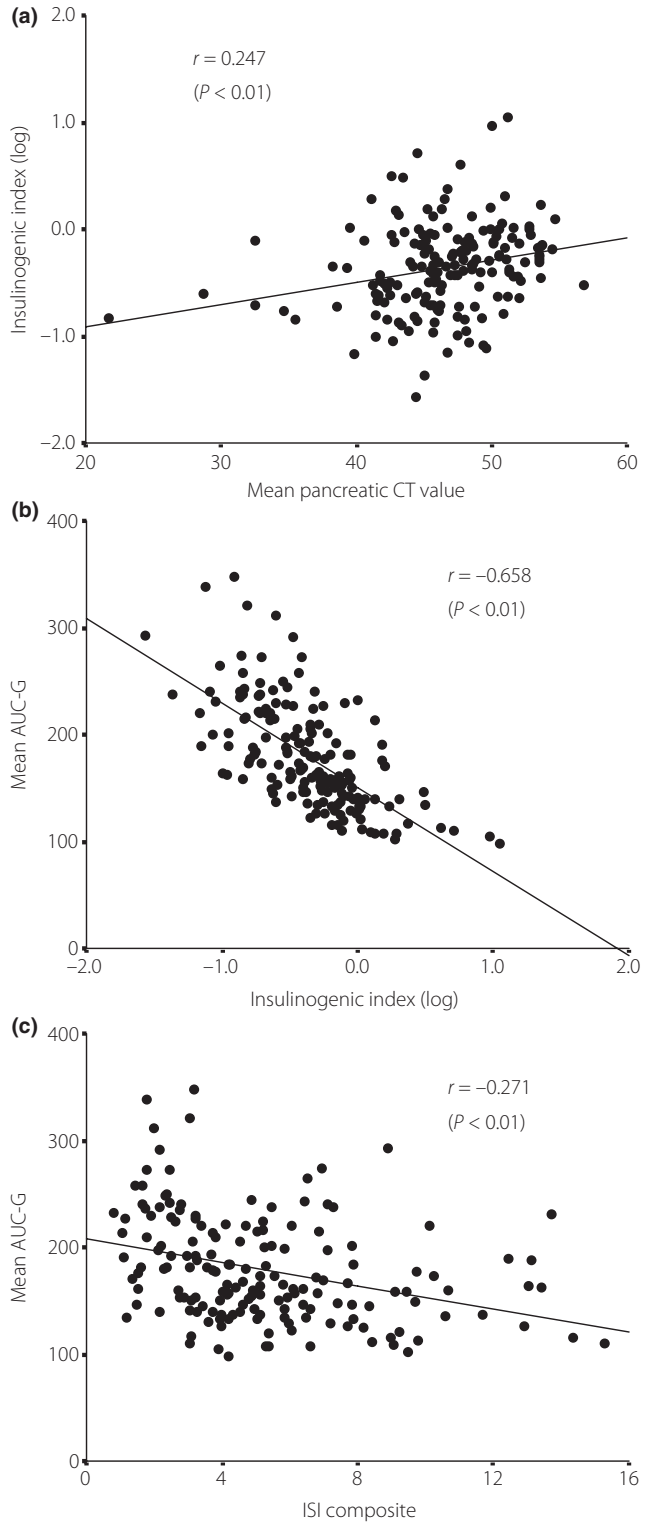

Figure 2 | (a) Mean pancreatic computed tomography (CT) values were significantly positively correlated with insulinogenic index (II) in multiple regression analysis ($r = 0.247$, $P < 0.01$). (b) Insulinogenic index and (c) ISI composite were significantly inversely correlated with area under the curves of glucose (AUC-G); however, II most strongly inversely correlated with AUC-G.

Table 3 | Correlation of mean area under the curves of glucose to measures of variables

	r	*P*	β
Age	0.007	0.931	–
Sex	0.134	0.085	–
BMI	0.063	0.421	–
Abdominal circumference (cm)	0.051	0.509	–
TG (mg/dL)	0.055	0.480	–
LDL (mg/dL)	0.01	0.902	–
HDL (mg/dL)	−0.046	0.555	–
FFA (mg/dL)	0.263	0.003	–
insulinogenic index (log)	−0.658	<0.001	−0.788
ISI composite	−0.271	<0.001	−0.387

BMI, body mass index; FFA, free fatty acid; HDL, high-density lipoprotein cholesterol; ISI, insulin sensitivity index; LDL, low-density lipoprotein cholesterol; TG, triglyceride.

DISCUSSION

In the present study, we found that pancreatic CT values are significantly decreased from NGT through IGT to DM in the early stage of the development of diabetes. Pancreatic CT values also had a significant correlation with II, which was the strongest determinant of glucose tolerance and was significantly influenced by pancreatic CT values. Thus, pancreatic fat deposition might impair insulin secretion early in the development of glucose intolerance.

Ectopic fat accumulation in skeletal muscle, liver and heart is associated with dysfunction of these organs[10,11]. However, it is not yet known whether fat accumulation in the pancreas causes β-cell dysfunction. Saisho *et al.*[12] found that pancreatic fat content increased with aging and obesity (mean age was approximately 65 years and mean BMI was 27.5 kg/m^2), but was not further increased in type 2 diabetes. In the present study, BMI resulted in having no significant correlation with mean pancreatic CT value in univariate analysis (mean pancreatic CT value vs BMI; $r = -0.104$, $P = 0.183$). This might be a result of the different profile of the subjects examined between the studies. The mean BMI of our subjects was 24–25 kg/m^2, which is the common feature of Japanese diabetic patients who do not show morbid obesity. It is comparable with the mean BMI of the representative epidemiological studies in Japanese being approximately 24 kg/m^2. In addition, aging did not have a significant correlation with mean pancreatic CT value in the present study (mean pancreatic CT value vs age; $r = -0.096$, $P = 0.215$). The reason might be because the main subjects in the present study were 40–75 years-of-age, which is the common feature of exhibiting type 2 diabetes in Japanese; in contrast, the age groups of their study[12] were widely distributed from birth to 100 years-of-age. It is still possible pancreatic fat deposition by aging results in the decrease of insulin secretion and glucose intolerance.

In the present study, we examined health-check examinees who had not been diagnosed with overt diabetes or received

any medication in relation to glucose intolerance. Thus, pancreatic steatosis might begin with a decline of insulin secretion from the very early stage of glucose intolerance. Tushuizen *et al.*[8] reported that in overt type 2 diabetic patients (BMI of approximately 30 kg/m^2) treated with diet and medication, pancreatic fat content measured by ^{1}H-MRS was higher than in non-diabetic control subjects matched by age and BMI, and pancreatic fat content was significantly associated insulin secretory capacity in non-diabetic subjects. Using ^{1}H-MRS, Heni *et al.*[13] reported a negative association between pancreatic fat content and insulin secretion in subjects with impaired glucose regulation. These reports using ^{1}H-MRS agree with our data in the present study on pancreatic steatosis using pancreatic CT value.

The mechanism by which pancreatic steatosis might affect insulin secretion early in the disease is not clear at present. In non-obese children with a heterozygous carboxyl-ester lipase mutation that causes diabetes, pancreatic fat content measured by ultrasound and ^{1}H-MRS is increased, and the first-phase insulin response to intravenous glucose is significantly decreased[14]. A rodent study reported that lipid deposition in pancreatic islet cells as a result of a high-fat/high-glucose diet can damage pancreatic β-cells and elevate plasma glucose levels[15]. Abnormal fat deposition of the pancreas has many harmful effects, including oxidative stress, inflammation and apoptosis of the islets[16].

As islet volume comprises just ∼2% of total pancreas mass, the CT attenuations of the pancreas induced by increased adipose mass are related to signals from outside the β-cell. However, it is difficult to discern where fatty infiltration occurs within the pancreas using ^{1}H-MRS, CT or any other of the *in vivo* examinations. According to some studies of pathological observations in the human pancreas[17,18], fat deposition appears mainly in interlobular septa rather than within cells. As the β-cell was suggested to be differentiated from the area near the pancreatic duct, it is possible that β-cell replication is decreased by the fatty infiltration that causes the decline in insulin secretion. Fatty replacement of the pancreas seems to occur primarily in the head of the pancreas where acinar tissue is most abundant, and it is reported that pancreatic islets are relatively more abundant in the caudal part than the head[19,20]. In the present study, we observed attenuations of CT values in the pancreatic head, body/tail and their mean from NGT through IGT to DM. However, the CT values in the pancreatic caudal part, where islets are more abundant, did not show a stronger decline than that in pancreatic head. Further studies using different populations and methods are required to clarify more precisely how regional fat distribution within the pancreas contributes to impaired insulin secretion. Previous studies have shown that liver steatosis can be evaluated by attenuation of liver CT value, and that fatty liver is associated with uptake of glucose in liver in type 2 diabetes[21,22]. In the present study, mean hepatic CT value decreased gradually from NGT through IGT to DM, and showed a significant difference between NGT and DM ($P < 0.05$). In addition, mean hepatic CT value was significantly associated with ISI composite ($r = 0.233$) in univariate analysis without a significant correlation with II ($r = -0.137$; data not shown). These results support evidence that liver CT attenuation has a closer relationship with insulin resistance than with insulin secretory capacity.

Several studies have found that insulin secretory capacity is lower in Japanese than in other populations[23,24]. We found that decreased insulin secretory capacity contributes more strongly to reduced glucose tolerance than insulin resistance in Japanese using minimal model analysis and OGTT[25]. Indeed, in the present study in Japanese, glucose tolerance assessed by AUC-G was shown to be most strongly correlated with II.

We described significant pancreatic CT attenuations from NGT through IGT to DM in the very early stage of the development of diabetes. Additionally, there was a significant positive correlation between II and pancreatic CT values. Because II is the strongest determinant of glucose tolerance in the Japanese population, we propose that pancreatic fat infiltration early in the course of the development of type 2 diabetes might contribute to impaired insulin secretion that results in deterioration of glucose tolerance.

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