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Longitudinal changes in pancreatic volume and pancreatic fat with weight gain in Japanese without diabetes: An analysis using health check-up data

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ABSTRACT

Aims/introduction: There have been few reports about the longitudinal changes in pancreas volume (PV) or pancreatic steatosis (PS) in response to obesity. In this longitudinal analysis using health check-up data, we explored changes in PV, PS and glucose metabolic indices that occurred after weight gain in Japanese without diabetes.

Materials/methods: Clinical data on 37 Japanese subjects with a $\geq$1 kg/m^2 increase in body mass index between two health check-ups and without diabetes were collected. PV, pancreas attenuation (PA) and splenic attenuation (SA) were evaluated using computed tomography (CT) images. The pancreas area was outlined by hand in multiple images with slice thickness of 2 mm, and the PV was computed by summing these areas. PS was defined as the difference between SA and PA (SA-PA). Medical records were collected, including findings on immunoreactive insulin (IRI), homeostasis model assessment of insulin resistance (HOMA-R) and beta cell function (HOMA-β). Paired *t*-test and Spearman's correlation coefficient were used in the analyses.

Results: The median follow-up period was 21.1 months and the mean BMI was increased from 25.5 $\pm$ 3.3 kg/m^2 to 27.0 $\pm$ 3.3 kg/m^2. PV (53.5 $\pm$ 15.9 cm^3 vs. 56.2 $\pm$ 16.4 cm^3) and SA-PA (8.7 $\pm$ 9.1 HU vs. 13.6 $\pm$ 10.9 HU) increased significantly after weight gain (both, $P < 0.001$). There were significant increases of IRI and HOMA-R with the weight gain (both, $P < 0.05$), whereas HOMA-β exhibited only a nonsignificant trend of increase (55.4% (41.5-65.5) vs. 56.8% (46.2-83.7), $P = 0.07$).

Conclusions: Both PV and PS were increased longitudinally with weight gain in Japanese without diabetes.

1. Introduction

Obesity is a major risk factor for type 2 diabetes (T2DM), and pancreatic fat content increases proportionally with obesity [1]. In an analysis of computed tomographic (CT) images, both parenchymal pancreas mass and pancreatic fat were reported to increase in subjects with obesity [2]. The CT-evaluated pancreas volume (PV) in Japanese has been positively correlated with body mass index (BMI) [3]. Moreover, lower pancreas volume and high pancreas fat have been reported to be associated with the incidence of T2DM [4,5]. On the other hand, there have been few longitudinal studies evaluating the relation between pancreatic volume or pancreatic fat and obesity. An annual health check-up system has been established in Japan, and there are abdominal images evaluated by using CT in addition to the medical data such as blood and urine examinations in our hospital. Therefore, the aim of this study was to explore the longitudinal changes in pancreatic volume, pancreatic fat and glucose metabolic indices (including beta cell function) that accompany weight gain in Japanese without diabetes.

2. Materials and methods

This retrospective study was approved by the Keio University Institutional Review Board for Clinical Research (IRB No. 20210014) as exempt from the requirement to obtain informed consent and conformed with Japanese ethical guidelines for clinical studies and the provisions of the Declaration of Helsinki.

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2.1. Study design

This study was a single-institution in the Center for Preventive Medicine of Keio University, retrospective, data-collection and analysis study. Of the 4369 participants who underwent health check-ups between April 2014 and March 2015, we collected the data on 287 subjects who met the following criteria: age of 20–80 years; health check-up between April 2015 to March 2017; increase in body mass index (BMI) of at least 1 kg/m^2; no diagnosis of diabetes mellitus (DM) (fasting plasma glucose (FPG) < 126 mg/dL, HbA1c <6.5% and not taking a drug for DM). After excluding subjects without a CT scan, those without CT images of sufficient quality to assess the pancreas volume, and those using steroids, the remaining 37 subjects were enrolled in this analysis.

2.2. Collection of medical data

Data of the following measures were collected from medical records of the health check-ups at baseline and after weight gain: age, sex, height, weight, BMI, FPG, fasting serum immunoreactive insulin (IRI), HbA1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), pancreatic amylase (P-AMY), creatinine (Cre), estimated glomerular filtration rate (eGFR), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Past medical history, family history and medication history were collected from self-administered questionnaires. A family history of DM in the second degree was defined as having a family history of DM. Homeostasis model assessment of insulin resistance (HOMA-R) was calculated as FPG (mg/dl) × IRI (μU/ml)/405. Beta cell function (HOMA-β) was calculated as IRI (μU/ml) × 360/[FPG (mg/dl) - 63]. The changes(Δ) in each parameter were calculated by subtracting the baseline value from the value after weight gain.

2.3. Image analysis

The waistline and visceral fat area (VFA) were measured at health check-ups of the Center for Preventive Medicine of Keio University using a CT scan (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). All images were transferred to a standard, commercially available workstation and analyzed using the Advantage Workstation Server 3.2 (GE Healthcare, Milwaukee, WI). The pancreas area was outlined by hand in multiple CT images with a slice thickness of 2 mm, and the PV was computed by summing these areas (cm^2) [3]. To evaluate pancreatic and liver steatosis (PS and LS) [6–8], pancreatic, splenic and liver attenuation (PA, SA and LA) were measured. Regions of interest (ROIs) with areas of 50 mm^2 were pointed in the head, body and tail of the pancreas and the upper and lower slices of the spleen, respectively. Three ROIs with areas of 200 mm^2 were pointed in three randomly selected slices of the liver. Mean attenuation of ROIs in each organ was calculated as PA, SA and LA, respectively. PS and LS were defined as the difference of SA and PA or LA (SA-PA and SA-LA) in this study, and high values of SA-PA or SA-LA were considered to indicate an increase in PS or LS. PS determined using a similar method with CT images has been reported to be correlated with the fat content evaluated by histological analysis [9].

2.4. Statistical analysis

All statistical analyses were performed using SPSS Statistics version 27 (IBM, Armonk, NY). A paired *t*-test was used to analyze changes in parameters between before and after weight gain. Spearman's correlation coefficient was used to assess associations between two variables. Data are shown as the means and standard deviations. P-values <0.05 were considered significant. Since the IRI, HOMA-R, HOMA-β and triglyceride values were not normally distributed, log-transformed values were used to analyze their changes, which were presented as the median (interquartile range).

3. Results

3.1. Participant characteristics

The characteristics of the 37 subjects are presented in Table 1. The mean age of participants in the baseline check-ups was 59.8 ± 10.8 years old. Among the 37 participants, 30 were male and 8 had a family history of DM. Mean weight and BMI in the baseline check-ups were 71.0 ± 10.9 kg and 25.5 ± 3.3 kg/m^2 and the mean follow-up period was 21.1 ± 5.4 months.

3.2. Changes in PV and CT attenuations

After weight gain, mean BMI was increased from 25.5 ± 3.3 kg/m^2 (71.0 ± 10.9 kg) to 27.0 ± 3.3 kg/m^2 (75.2 ± 11.2 kg). The waistline, VFA, HbA1c, AST and ALT values were increased, while HDL-C was decreased with the weight gain (all $P < 0.05$) (Table 1). The mean values of PV (53.5 ± 15.9 cm^3 vs. 56.2 ± 16.4 cm^3), SA-PA (8.7 ± 9.1 HU vs. 13.6 ± 10.9 HU), and SA-LA (−5.4 ± 8.9 HU vs. −0.7 ± 11.3 HU) increased after weight gain (all $P < 0.01$) (Fig. 1). There were significant increases of IRI and HOMA-R with the weight gain (both $P < 0.05$), whereas HOMA-β tended to increase with no significant difference ($P = 0.07$) (Table 1).

Next, we analyzed the correlation of the changes in each parameter (Table 2). There was no correlation between ΔBMI and the change of other parameters, including ΔPV. ΔVFA was positively correlated with ΔSA-LA ($R = 0.33$). In addition, ΔVFA and ΔSA-PA were negatively correlated with ΔIRI ($R = -0.48$ and $R = -0.34$, respectively) (Fig. 2). ΔBMI, ΔPV and ΔSA-LA were not significantly correlated with ΔIRI (Fig. 2).

3.3. Subgroup analysis

The subjects were divided according to BMI at baseline (<25, ≥25 kg/m^2) (Table 3), family history of DM in the second degree (absence or

Table 1
Subject characteristics at baseline and after weight gain.

	Baseline	After weight gain	*p* value
Age (years)	59.8 ± 10.8	–	–
Sex, Male (%)	81	–	–
Family history of DM (%)	21.6	–	–
Height (cm)	166.8 ± 8.3	166.7 ± 8.5	0.30
Weight (kg)	71.0 ± 10.9	75.2 ± 11.2	<0.001
BMI (kg/m^2)	25.5 ± 3.3	27.0 ± 3.3	<0.001
Waistline (cm)	87.3 ± 8.5	92.3 ± 7.5	<0.001
VFA (cm^2)	108.8 ± 37.9	136.6 ± 40.9	<0.001
FPG (mg/dL)	103 ± 7	104 ± 7	0.38
HbA1c (%)	5.6 ± 0.3	5.7 ± 0.3	<0.001
IRI (μU/mL)	6.0 (5.0-7.0)	7.0 (5.0-9.0)	0.03
HOMA-R (no unit)	1.6 (1.2-1.9)	1.8 (1.3-2.3)	0.03
HOMA-β (%)	55.4 (41.5-65.5)	56.8 (46.2-83.7)	0.07
AST (U/L)	24 ± 8	28 ± 18	0.04
ALT (U/L)	24 ± 14	33 ± 32	0.02
ALP (U/L)	216 ± 69	222 ± 88	0.40
γ-GTP (U/L)	49 ± 42	63 ± 73	0.06
P-AMY (U/L)	31 ± 9	32 ± 9	0.24
Cre (mg/dL)	0.89 ± 0.22	0.89 ± 0.22	0.51
eGFR (ml/min/1.73m^2)	68.0 ± 15.1	68.1 ± 14.0	0.87
TC (mg/dL)	211 ± 33	208 ± 28	0.61
TG (mg/dL)	102 (68-134)	109 (86-150)	0.08
LDL-C (mg/dL)	122 ± 29	123 ± 24	0.94
HDL-C (mg/dL)	57 ± 16	54 ± 12	0.04

DM, diabetes mellitus; BMI, body mass index; VFA, visceral fat area; FPG, fasting plasma glucose; IRI, immunoreactive insulin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; P-AMY, pancreatic amylase; Cre, creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

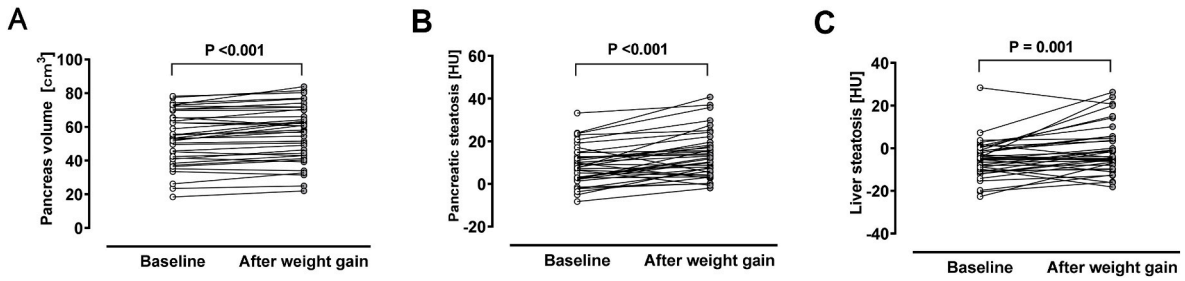

Fig. 1. Changes of pancreas volume (A), pancreatic steatosis (SA-PA) (B) and liver steatosis (SA-LA) (C) at health check-ups at baseline and after weight gain. PA, pancreatic attenuation; SA, splenic attenuation; LA, liver attenuation.

Table 2
Correlation among changes in each parameter.

Correlation coefficient (R)						
	ΔBMI	ΔPV	ΔSA-PA	ΔSA-LA	ΔVFA	ΔIRI
ΔBMI	–	0.182	−0.233	−0.128	0.229	−0.031
ΔPV	0.182	–	−0.200	−0.105	0.080	0.155
ΔSA-PA	−0.233	−0.200	–	0.094	0.033	−0.338*
ΔSA-LA	−0.128	−0.105	0.094	–	0.330*	−0.275
ΔVFA	0.229	0.080	0.033	0.330*	–	−0.483**
ΔIRI	−0.031	0.155	−0.338*	−0.275	−0.483**	–

*p < 0.05, **p < 0.01.
BMI, body mass index; PV, pancreas volume; PA, pancreatic attenuation; SA, splenic attenuation; LA, liver attenuation; VFA, visceral fat area; IRI, immunoreactive insulin.

presence) (Supplementary Table 1), ΔPV (<0, ≥0 cm^3) (Table 4) and ΔPS (ΔSA-PA <0, ≥ 0HU) (Table 5) in subgroup analysis. The baselines of weight, waistline, VFA, IRI, HOMA-R and HOMA-β in the group of subjects with BMI≥25 kg/m^2 (mean BMI 28.1 ± 2.2 kg/m^2, N = 19) were higher than those in subjects with BMI<25 kg/m^2 (mean BMI 22.7 ± 1.4 kg/m^2, N = 18) (Table 3). While, the baseline of HDL-C was lower than that in subjects with BMI<25 kg/m^2. There was no significant difference in PV at baseline between the two BMI groups (<25, ≥25 kg/m^2), but there was a significant correlation between BMI and PV at baseline (R = 0.34, P = 0.04). PV and SA-PA increased significantly after weight gain in both BMI groups (<25 and ≥ 25 kg/m^2). IRI, HOMA-R, HOMA-β, ALT and HDL-C changed only in the group of subjects with BMI <25 kg/m^2.

PV tended to increase (P = 0.07) after weight gain in the group with family history of DM (N = 8), and PV increased significantly in the group without family history of DM (N = 29) (Supplementary Table 1). SA-PA increased significantly after weight gain regardless of the family history.

There was no significant difference in the baseline parameters between the groups subdivided by ΔPV (<0, ≥0 cm^3) (Table 4) and ΔPS (ΔSA-PA<0, ≥0HU) (Table 5). In the group without an increase of PV (ΔPV<0 cm^3, N = 8), PV decreased, while SA-PA increased significantly after weight gain (Table 4 and Supplementary Fig. 1). In addition, IRI, HOMA-R and HOMA-β were unchanged in this group (all P > 0.9). On the other hand, PV, SA-PA, IRI, HOMA-R and HOMA-β increased significantly after weight gain in the group with the increase of PV (ΔPV ≥0 cm^3, N = 29).

In the group without an increase of PS (ΔSA-PA<0HU, N = 6), PV tended to increase (P = 0.07) (Table 5 and Supplementary Fig. 2). Moreover, IRI and HOMA-β increased significantly in this group. In the group with an increase of PS (ΔSA-PA≥0HU, N = 31), both PV and SA-PA increased significantly after weight gain. No significant differences in IRI, HOMA-R or HOMA-β were observed after weight gain in this group.

4. Discussion

Our present analysis of health check-up data showed that the changes in PV and PS after weight gain were significant irrespective of

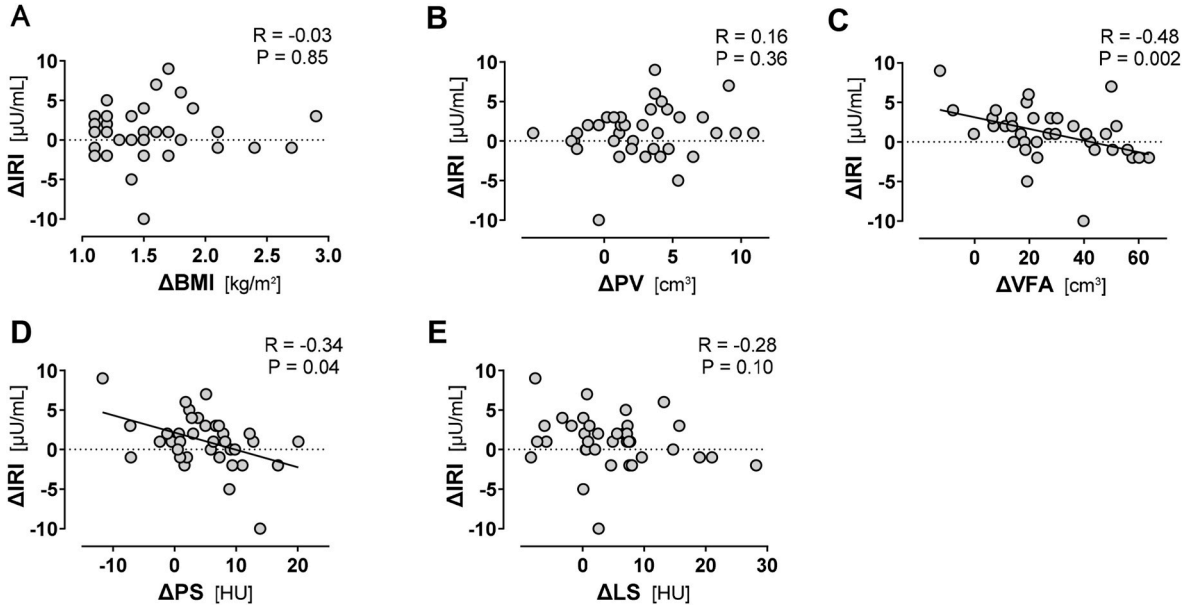

Fig. 2. Correlations of the change (Δ) in body mass index (BMI) (A), pancreas volume (PV) (B), visceral fat area (VFA) (C), pancreatic steatosis (PS, SA-PA) (D) and liver steatosis (LS, SA-LA) (E) with the change in immunoreactive insulin (IRI). PA, pancreatic attenuation; SA, splenic attenuation; LA, liver attenuation.

Table 3
Changes of the parameters in groups with BMI<25 kg/m^2 and BMI≥25 kg/m^2.

	BMI <25 kg/m^2 (n = 18)			BMI ≥25 kg/m^2 (n = 19)		
	Baseline	After weight gain	*p* value	Baseline	After weight gain	*p* value
Age (years)	60.9 ± 11.5	–	–	58.8 ± 10.3	–	–
Sex, male (%)	89	–	–	74	–	–
Family history of DM (%)	17	–	–	26	–	–
Height (cm)	167.9 ± 7.9	167.9 ± 7.9	0.70	165.7 ± 8.7	165.5 ± 9.0	0.35
Weight (kg)	64.4 ± 8.5	69.0 ± 8.7	<0.001	77.2 ± 9.3**	81.1 ± 10.0	<0.001
BMI (kg/m^2)	22.7 ± 1.4	24.4 ± 1.4	<0.001	28.1 ± 2.2**	29.6 ± 2.5	<0.001
Waistline (cm)	80.3 ± 4.6	86.6 ± 4.3	<0.001	94.0 ± 5.3**	97.8 ± 5.4	<0.001
VFA (cm^2)	93.3 ± 30.9	123.2 ± 41.0	<0.001	123.5 ± 38.7*	149.2 ± 37.7	<0.001
FPG (mg/dL)	102 ± 8	101 ± 7	0.79	104 ± 7	107 ± 7	0.24
HbA1c (%)	5.5 ± 0.3	5.7 ± 0.3	<0.001	5.6 ± 0.3	5.8 ± 0.3	<0.01
IRI (μU/mL)	5.5 (3.0-7.0)	6.0 (4.0-9.0)	<0.01	6.0 (6.0-8.0)*	8.0 (6.0-8.5)	0.49
HOMA-R (no unit)	1.4 (0.8-1.8)	1.4 (1.1-2.2)	0.01	1.7 (1.5-2.1)*	2.1 (1.6-2.3)	0.40
HOMA-β (%)	51.9 (30.9-58.1)	57.5 (34.0-85.3)	<0.01	62.1 (48.5-73.4)*	56.0 (47.9-77.9)	0.92
PV (cm^3)	49.0 ± 12.9	51.9 ± 14.0	<0.01	57.7 ± 17.7	60.2 ± 17.8	<0.01
SA-PA (HU)	7.0 ± 7.7	10.8 ± 10.1	0.01	10.4 ± 10.2	16.2 ± 11.2	<0.01
SA-LA (HU)	−8.1 ± 7.0	−4.1 ± 11.0	0.052	−2.8 ± 9.9	2.5 ± 10.9	0.01
AST (U/L)	24 ± 10	31 ± 25	0.08	25 ± 7	27 ± 8	0.24
ALT (U/L)	21 ± 15	37 ± 44	0.04	26 ± 13	29 ± 14	0.24
ALP (U/L)	214 ± 60	235 ± 100	0.13	218 ± 79	210 ± 76	0.34
γ-GTP (U/L)	48 ± 54	68 ± 101	0.16	49 ± 27	57 ± 32	0.12
P-AMY (U/L)	33 ± 9	34 ± 11	0.38	30 ± 8	30 ± 7	0.25
Cre (mg/dL)	0.93 ± 0.22	0.94 ± 0.23	0.63	0.86 ± 0.21	0.83 ± 0.21	0.22
eGFR (ml/min/1.73m^2)	65.4 ± 12.6	64.6 ± 12.1	0.52	70.3 ± 17.1	71.5 ± 15.1	0.53
TC (mg/dL)	219 ± 38	211 ± 27	0.29	203 ± 27	206 ± 30	0.59
TG (mg/dL)	83 (62-117)	96 (67-141)	0.15	109 (83-149)	109 (97-161)	0.31
LDL-C (mg/dL)	122 ± 31	121 ± 21	0.78	122 ± 27	124 ± 27	0.70
HDL-C (mg/dL)	65 ± 18	57 ± 14	0.01	50 ± 10**	51 ± 10	0.31

DM, diabetes mellitus; BMI, body mass index; VFA, visceral fat area; FPG, fasting plasma glucose; IRI, immunoreactive insulin; PV, pancreas volume; PA, pancreatic attenuation; SA, splenic attenuation; LA, liver attenuation. Significant differences in the patient background at baseline between groups are expressed as follows: *p < 0.05, **p < 0.01.

Table 4
Changes of the parameters in groups with or without an increase of pancreas volume.

	ΔPV <0 cm^3 (n = 8)			ΔPV ≥0 cm^3 (n = 29)		
	Baseline	After weight gain	*p* value	Baseline	After weight gain	*p* value
Age (years)	62.8 ± 5.0	–	–	59.0 ± 11.8	–	–
Sex, male (%)	75	–	–	83	–	–
Family history of DM (%)	13	–	–	24	–	–
Height (cm)	164.0 ± 6.3	163.7 ± 6.6	0.26	167.5 ± 8.7	167.5 ± 8.9	0.54
Weight (kg)	67.2 ± 12.5	70.8 ± 12.8	<0.001	72.0 ± 10.5	76.4 ± 10.6	<0.001
BMI (kg/m^2)	24.9 ± 3.7	26.3 ± 3.7	<0.001	25.7 ± 3.2	27.2 ± 3.2	<0.001
Waistline (cm)	86.0 ± 9.1	90.1 ± 8.7	<0.01	87.7 ± 8.5	93.0 ± 7.1	<0.001
VFA (cm^2)	105.8 ± 34.8	131.8 ± 38.1	<0.01	109.6 ± 39.2	137.9 ± 42.2	<0.001
FPG (mg/dL)	102 ± 7	102 ± 6	0.79	103 ± 8	105 ± 8	0.34
HbA1c (%)	5.6 ± 0.3	5.8 ± 0.4	0.04	5.6 ± 0.3	5.7 ± 0.3	<0.001
IRI (μU/mL)	6.0 (3.5-9.0)	8.0 (3.5-8.5)	0.96	6.0 (5.0-7.0)	6.0 (5.0-9.0)	0.02
HOMA-R (no unit)	1.7 (0.8-2.3)	2.1 (0.8-2.2)	0.98	1.6 (1.2-1.8)	1.7 (1.3-2.3)	0.02
HOMA-β (%)	53.6 (32.0-81.0)	65.1 (38.2-77.0)	0.94	55.4 (42.9-63.5)	56.0 (46.2-87.6)	0.046
PV (cm^3)	52.3 ± 15.1	50.3 ± 15.2	<0.01	53.8 ± 16.4	57.8 ± 16.6	<0.001
SA-PA (HU)	3.8 ± 6.4	10.5 ± 6.5	0.01	10.1 ± 9.4	14.5 ± 11.7	<0.01
SA-LA (HU)	−5.9 ± 5.7	−1.8 ± 9.9	0.12	−5.2 ± 9.6	−0.39 ± 11.8	<0.01
AST (U/L)	23 ± 4	25 ± 9	0.52	24 ± 9	29 ± 20	0.046
ALT (U/L)	26 ± 11	31 ± 17	0.42	23 ± 15	34 ± 35	0.03
ALP (U/L)	224 ± 61	214 ± 51	0.58	213 ± 72	224 ± 97	0.22
γ-GTP (U/L)	34 ± 18	42 ± 16	0.32	53 ± 45	68 ± 81	0.09
P-AMY (U/L)	32 ± 6	31 ± 8	0.73	31 ± 9	32 ± 10	0.14
Cre (mg/dL)	0.85 ± 0.15	0.84 ± 0.15	0.55	0.90 ± 0.23	090 ± 0.24	0.66
eGFR (ml/min/1.73m^2)	66.9 ± 10.0	67.6 ± 8.9	0.72	68.2 ± 16.3	68.3 ± 15.2	0.98
TC (mg/dL)	210 ± 23	202 ± 33	0.59	211 ± 36	210 ± 27	0.87
TG (mg/dL)	87 (71-140)	95 (74-113)	0.93	103 (68-134)	118 (90-155)	0.04
LDL-C (mg/dL)	126 ± 25	118 ± 19	0.56	121 ± 30	124 ± 26	0.43
HDL-C (mg/dL)	55 ± 11	53 ± 12	0.27	58 ± 18	54 ± 13	0.08

DM, diabetes mellitus; BMI, body mass index; VFA, visceral fat area; FPG, fasting plasma glucose; IRI, immunoreactive insulin; PV, pancreas volume; PA, pancreatic attenuation; SA, splenic attenuation; LA, liver attenuation.

the presence or absence of obesity, indicating that the pancreas volume and fat increased longitudinally along with weight gain in Japanese participants without diabetes. To our knowledge, this is the first study to clarify the longitudinal changes in PV, PS and glucose metabolic indices with weight gain in Japanese without diabetes. A previous study showed longitudinal decreases of PV and PS with weight loss in severely obese Japanese patients (N = 27, initial BMI 43.4 ± 5.5 kg/m^2 and 14 patients with type 2 diabetes) following laparoscopic sleeve gastrectomy [6], which was consistent with our present results.

In this study, there were no relations that PV or PS increased as more

Table 5
Changes of the parameters in groups with or without an increase of pancreatic steatosis.

	ΔSA-PA <0HU (n = 6)			ΔSA-PA ≥0HU (n = 31)		
	Baseline	After weight gain	*p* value	Baseline	After weight gain	*p* value
Age (years)	58.3 ± 12.6	–	-	60.1 ± 10.6	–	-
Sex, male (%)	83	–	-	81	–	-
Family history of DM (%)	0	–	-	26	–	-
Height (cm)	169.5 ± 7.8	169.4 ± 8.1	0.57	166.2 ± 8.4	166.1 ± 8.6	0.37
Weight (kg)	72.5 ± 12.8	76.9 ± 13.6	<0.001	70.7 ± 10.7	74.9 ± 10.9	<0.001
BMI (kg/m^2)	25.2 ± 3.9	26.8 ± 4.0	<0.001	25.6 ± 3.2	27.1 ± 3.2	<0.001
Waistline (cm)	87.5 ± 8.6	92.3 ± 6.1	0.03	87.3 ± 8.6	92.4 ± 7.8	<0.001
VFA (cm^2)	132.7 ± 43.0	156.1 ± 27.4	0.04	104.2 ± 35.7	132.8 ± 42.4	<0.001
FPG (mg/dL)	102 ± 9	102 ± 8	0.88	103 ± 7	104 ± 7	0.38
HbA1c (%)	5.6 ± 0.4	5.8 ± 0.4	0.09	5.6 ± 0.3	5.7 ± 0.3	<0.001
IRI (μU/mL)	6.0 (5.0-7.0)	7.0 (6.0-9.0)	0.04	6.0 (5.0-7.0)	7.0 (5.0-9.0)	0.11
HOMA-R (no unit)	1.6 (1.2-1.9)	1.9 (1.3-2.2)	0.07	1.6 (1.1-1.8)	1.8 (1.2-2.3)	0.11
HOMA-β (%)	55.5 (40.8-67.5)	71.5 (54.0-90.0)	0.02	55.4 (42.2-64.5)	56.0 (43.6-81.0)	0.22
PV (cm^3)	52.5 ± 13.0	56.2 ± 15.7	0.07	53.7 ± 16.6	56.2 ± 16.8	<0.001
SA-PA (HU)	9.0 ± 4.3	4.0 ± 3.1	0.04	8.7 ± 9.8	15.5 ± 10.9	<0.001
SA-LA (HU)	0.30 ± 14.0	−1.5 ± 13.7	0.56	−6.5 ± 7.4	−0.55 ± 11.1	<0.001
AST (U/L)	33 ± 16	42 ± 42	0.45	22 ± 5	26 ± 7	<0.01
ALT (U/L)	36 ± 26	57 ± 71	0.36	22 ± 9	28 ± 14	<0.001
ALP (U/L)	236 ± 87	272 ± 163	0.36	212 ± 66	213 ± 66	0.88
γ-GTP (U/L)	76 ± 76	118 ± 168	0.34	44 ± 31	51 ± 31	0.03
P-AMY (U/L)	31 ± 8	38 ± 10	0.08	31 ± 9	31 ± 9	0.74
Cre (mg/dL)	0.91 ± 0.11	0.92 ± 0.14	0.85	0.89 ± 0.23	0.88 ± 0.23	0.42
eGFR (ml/min/1.73m^2)	64.8 ± 11.1	64.0 ± 10.3	0.73	68.6 ± 15.8	68.9 ± 14.6	0.76
TC (mg/dL)	214 ± 26	204 ± 24	0.51	210 ± 34	209 ± 30	0.85
TG (mg/dL)	90 (76-126)	112 (92-138)	0.65	103 (66-137)	109 (81-164)	0.09
LDL-C (mg/dL)	118 ± 37	117 ± 34	0.97	123 ± 28	124 ± 22	0.90
HDL-C (mg/dL)	64 ± 23	56 ± 9	0.30	56 ± 15	54 ± 13	0.09

DM, diabetes mellitus; BMI, body mass index; VFA, visceral fat area; FPG, fasting plasma glucose; IRI, immunoreactive insulin; PV, pancreas volume; PA, pancreatic attenuation; SA, splenic attenuation; LA, liver attenuation.

weight gained. Furthermore, some subjects maintained no increase of PV or PS, while they gained body weight of BMI≥1 kg/m^2. These results suggest that there are individual differences in the longitudinal increase in PV or PS with weight gain. Since PS increased and PV decreased in subjects (N = 8) without an increase of PV, pancreatic parenchyma was suggested to be reduced in this group. Several histological studies in Caucasian populations have reported increases of beta cell mass in obese individuals without diabetes [10–12], while in our previous studies we observed that there was no increase in beta cell mass between lean and obese Japanese without diabetes in autopsy and surgical samples [13,14]. These reports suggest that ethnic differences exist in the change of beta cell mass in response to obesity, and Japanese have less beta cell capacity compared with Caucasians. Although we were unable to evaluate the volume of beta cell mass in this study, previous report has observed a correlation between beta-cell function and beta-cell mass [15]. In the group without the increase of PV, beta cell function did not increase with weight gain in consistent with the change of PV or pancreatic parenchyma. Although this group was not large, it might reflect characteristics of beta cell mass in response to obesity in Japanese. In contrast, the increase in beta cell function was observed in the group without an increase of PS after weight gain. This might suggest that there were some subjects with an increase of beta cell mass in response to obesity among Japanese without diabetes. In genome-wide association studies, many susceptibility loci associated with T2DM and beta cells have been discovered [16,17]. In the present study, we did not observe an effect of family history of DM as reported on the self-administered questionnaires, but genetic factors might be involved in an ethnic or individual difference in the change of beta cell mass or function. Since it is unclear whether the longitudinal change of PV or PS with weight gain is associated with the development of T2DM, further investigations with larger participants and longer follow-up are required.

An increase in IRI after weight gain was observed in this study. On the other hand, we also observed that IRI decreased with increasing PS or VFA. Moreover, IRI increased after weight gain in subjects without an increase of PS, while IRI was unchanged in subjects with an increase of PS. These results suggest that pancreatic fat depresses the increase of insulin secretion with the weight gain. The tissue dysfunction caused by increased ectopic fat in organs is known as lipotoxicity [18]. However, it is still unclear whether increased pancreatic fat causes decreased beta cell mass and function. In a histological study, no association was found between intrapancreatic fat area and beta cell mass [19]. Another study reported that pancreas fat evaluated by proton magnetic resonance spectroscopy correlated negatively with beta cell function [20]. Furthermore, pancreatic fat determined by using CT in patients with T2DM was reported to be associated with a longitudinal decrease in endogenous insulin-secreting capacity [21]. The present results do not definitively establish that there is an association between the pancreas fat and beta cell function, and further studies including a better method for evaluating the pancreatic fat are needed.

There were several limitations of this study. Fat infiltration of the pancreas is reported the heterogeneity by region [22]. We evaluated three ROIs for the CT attenuation measurements in the head, body and tail of the pancreas, but the evaluation of PS using CT images might not be perfectly representative of the fat of the entire pancreas. Second, the statistical power in each subgroup was limited by the small number of subjects. Third, the “weight gain” in this study was defined as an increase in BMI of at least 1 kg/m^2 from baseline check-ups, but the effect of weight gain might have been limited in subjects with obesity.

In conclusion, we found that both the volume and fat of the pancreas increased longitudinally with weight gain in a cohort of Japanese without diabetes. In addition, the present findings suggest that individual differences in the longitudinal change of pancreatic volume and fat with weight gain are associated with changes in beta cell function.

Credit Author Statement

Maria Sunouchi: wrote the manuscript, Formal analysis. Jun Inaishi: Writing – original draft, Formal analysis, guarantor of this work and, as such, had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data. Ryoko Shimizu-

Hirota: contributed to the discussion and reviewed and edited the manuscript. Yoshifumi Saisho: contributed to the discussion and reviewed and edited the manuscript. Kaori Hayashi: contributed to the discussion and reviewed and edited the manuscript. Hiromasa Takaishi: contributed to the discussion and reviewed and edited the manuscript. Hiroshi Itoh: contributed to the discussion and reviewed and edited the manuscript.

Declaration of competing interest

The authors declare that they have no conflicts of interest in relation to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2023.100250.

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