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Hyperplasia of Fat-Containing Cells With Mature Adipocyte Marker Is Associated With Pancreatic Fat Enlargement

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Objectives: To elucidate the specific characteristics of fat-containing cells in the pancreas and the mechanism of intrapancreatic fat deposition in humans.

Materials and Methods: Fifteen Japanese patients who had undergone pancreatic resection were enrolled, and the normal region from each samples was examined. Immunostaining for adiponectin and perilipin 1 was performed, and the relationships between the pancreatic fat-cell area or clinical parameters and the density or the diameter of the fat cells were analyzed.

Results: The expression of adiponectin in the cytoplasm and perilipin 1 along the plasma membrane was observed in fat-containing cells in the pancreas. The fat-containing cell area had a significant positive correlation with cell density. In addition, fat-containing cell density was significantly positively correlated with homeostasis model assessment insulin resistance. The diameter of fat-containing cells had significant positive correlations with BMI, fasting immunoreactive insulin, and homeostasis model assessment insulin resistance. Of all fat-containing cells, 10.4% were intralobular cells, and the diameter of intralobular cells showed a tendency for positive correlation with age.

Conclusions: The characteristics of fat-containing cells in the pancreas indicate that some of them may be mature adipocytes, and fat volume may be increased by hyperplasia of fat-containing cells associated with insulin resistance.

Key Words: pancreatic fat, adipocytes markers, hyperplasia of fat-containing cells, insulin resistance

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Human and animal rights: All procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institution and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Informed consent: Informed consent was obtained from all subjects who participated in the study.

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Abbreviations: F-IRI - fasting immunoreactive insulin; , FPG - fasting plasma glucose; , HOMA-IR - homeostasis model assessment insulin resistance; , NGT - normal glucose tolerance; , T2DM - type 2 diabetes mellitus

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Ectopic fat deposits have been attracting attention in recent years. Ectopic fat is the deposition of fat in and around organs that normally contain only small amounts of fat, and deposition of ectopic fat in the liver, heart, skeletal muscle, kidneys, and even the pancreas has been reported.[1] Ectopic fat causes damage to the organ in which it accumulates, and examples include nonalcoholic fatty liver disease,[2] cardiac dysfunction,[3] and chronic kidney disease.[4] The deposition of ectopic fat in the liver and the muscle is associated with insulin resistance and the development of type 2 diabetes mellitus (T2DM).[5]

Pancreatic fat is also considered to be a risk factor for diabetes.[6–8] We have previously shown that using specimens obtained from human pancreatic surgery that increased pancreatic fat, known as intrapancreatic fat deposition (IPFD),[9] was associated with a deterioration of glucose tolerance after pancreatic surgery in nondiabetic patients[10] and accompanied macrophage infiltration in the peri-islet area.[11] Furthermore, we have shown that IPFD is involved in the reduction of endogenous insulin secretory capacity in patients with T2DM in a study using computed tomography.[12] Considering these reports, an increase of IPFD may contribute to a deterioration in insulin secretion through inflammation of the pancreatic islets, thereby worsening glucose tolerance.

IPFD is morphologically characterized by the presence of the following components: (1) interlobular fat-containing cells; (2) intralobular fat, such as lipid droplets in acinar cells and islets of Langerhans, acinar-to-adipocyte transdifferentiation, and fatty replacement of apoptotic acinar cells; or (3) a combination of both.[9,13] The purpose of this study was to elucidate the specific characteristics of fat-containing cells in pancreas, which are assumed to be mature adipocytes, and the mechanism by which the volume of pancreatic fat increases in humans.

MATERIALS AND METHODS

Patients

Fifteen Japanese patients who had undergone pancreatic resection between 2008 and 2013 at the Department of Gastroenterological Surgery, Osaka University Hospital, were enrolled in this study and agreed to participate in this study. The study protocol was approved by the Ethics Committee of Osaka University (approval number: 13279-4). Patients with renal failure (estimated glomerular filtration rate of <30 mL/min/1.73 m^2) were excluded from this study. Nine patients were diagnosed as normal glucose tolerance (NGT) by a 75-g oral glucose tolerance test at

1–60 days before pancreatic resection. Six patients had been diagnosed with T2DM and had been undergoing treatment for more than 1 year at the time of enrolment.

Laboratory Tests

HbA1c (%), fasting plasma glucose (FPG) (mg/dL), fasting immunoreactive insulin (F-IRI) (μU/mL), and the homeostasis model assessment insulin resistance (HOMA-IR) were evaluated by blood tests at 1–60 days before pancreatic resection as well as the 75-g oral glucose tolerance test. HOMA-IR, an indicator of insulin resistance, was calculated by FPG (mg/dL) × F-IRI (μU/mL)/405.[14]

Pancreatic Tissue Processing

Normal regions of pancreas tissue samples from patients who had undergone pancreatic resection were obtained and analyzed. The tissue samples were isolated from around the resected margins after intraoperative consultation, fixed immediately in formaldehyde, and embedded in paraffin for subsequent analysis. Paraffin-embedded tissue was cut into 5-μm-thick sections, stained with hematoxylin and eosin, and we visually inspected the samples under an optical microscope and confirmed that they did not contain any cancerous elements.

Immunohistochemistry

Primary and secondary antibodies as well as chromogenic substrates are listed in the Supplemental Table 1, http://links.lww.com/MPA/B257. To characterize fat-containing cells in pancreatic parenchyma, we performed immunostaining for adiponectin and perilipin 1. First, the sections were incubated with rabbit anti-adiponectin or rabbit anti-perilipin 1 immunoglobulins as primary antibody, and next, goat anti-rabbit peroxidase-labeled polymer-conjugated immunoglobulin as secondary antibodies. The reactions were developed with a 3,3-diaminobenzidine tetrahydrochloride substrate. To evaluate the size and density of fat-containing cells, fluorescent immunostaining for perilipin 1 was performed. Pancreatic sections were incubated with rabbit anti-perilipin 1 immunoglobulin as the primary antibody and goat anti-rabbit biotinylated immunoglobulin as the secondary antibody, followed by Alexa Fluor 488–conjugated streptavidin. We examined under a fluorescence microscope (BX53; Olympus, Tokyo, Japan). In addition, cells stained with perilipin 1 were visually classified into intralobular and interlobular fat-containing cells (Supplemental Fig. 1, http://links.lww.com/MPA/B258).

Morphometric Analysis

The density and the diameter of fat-containing cells in the pancreas were analyzed by immunostaining for perilipin 1. Immunohistochemical analyses were performed on 1 section per patient. We analyzed a median of 2.33 cm^2 of pancreatic section per patient to evaluate the size and the density of fat-containing cells. The density was calculated as the number of cells per square centimeter. The fat-containing cell area (%) was evaluated as the ratio of the sum of the interlobular and intralobular fat-containing cell area to the entire pancreatic section, and that was defined as "fat-cell area (%)."[9] The diameter of fat-containing cells, the area of pancreatic sections, and fat-cell area were quantified digitally with the WinROOF software program (Mitani Corporation, Fukui, Japan). The cell diameter was measured as the maximum diameter (μm).

Statistical Analysis

Normally distributed data are presented as mean ± SD and compared by Student *t* test. *P* values less than 0.05 denoted a statistically significant difference. All statistical analyses were performed with JMP Pro 16 software (Statistical Analysis System Inc, Cary, NC).

RESULTS

Clinical Characteristics and Laboratory Data

Table 1 lists the clinical characteristics of the patients. There were 9 NGT patients and 6 T2DM patients. Clinical diagnosis of primary diseases included cystic lesions of the pancreas (including

TABLE 1. Clinical Characteristics of Patients and Laboratory Data

	NGT	T2DM	Total
N (male/female)	9 (3/6)	6 (4/2)	15 (7/8)
Clinical diagnosis			
Cystic lesions of the pancreas	5	3	8
Pancreatic cancer	3	2	5
Tumor of the ampulla of Vater	1	0	1
Pancreatic metastasis of renal cell carcinoma	0	1	1
Operative procedure (PD/DP)	7/2	5/1	12/3
Preoperative anticancer agents (yes/no)	2/7	0/6	2/13
Age (years)	57 ± 17	70 ± 3	62 ± 15
BMI (kg/m^2)	20.1 ± 0.9	19.2 ± 1.1	19.7 ± 2.6
HbA1c (%)	5.4 ± 0.4	7.7 ± 1.2 *	6.3 ± 1.4
FPG (mg/dL)	92 ± 5	137 ± 8 (n = 4) *	105 ± 26
F-IRI (μU/mL)	7.1 ± 1.0	5.0 (n = 2)	6.7 ± 3.1
HOMA-IR	1.61 ± 0.74	1.93 (n = 2)	1.67 ± 0.87
Fat cell area (%)	1.33 ± 1.68	2.00 ± 2.84	1.59 ± 2.15
Antidiabetic agents		Diet: 1, SU: 3, SU+αGI: 1, insulin: 1	

Data are mean ± SD. Statistical analyses were performed by Student *t* test.

*$P < 0.01$.

PD, pancreaticoduodenectomy; DP, distal pancreatectomy; SU, sulfonylurea; αGI, alfa glucosidase inhibitor.

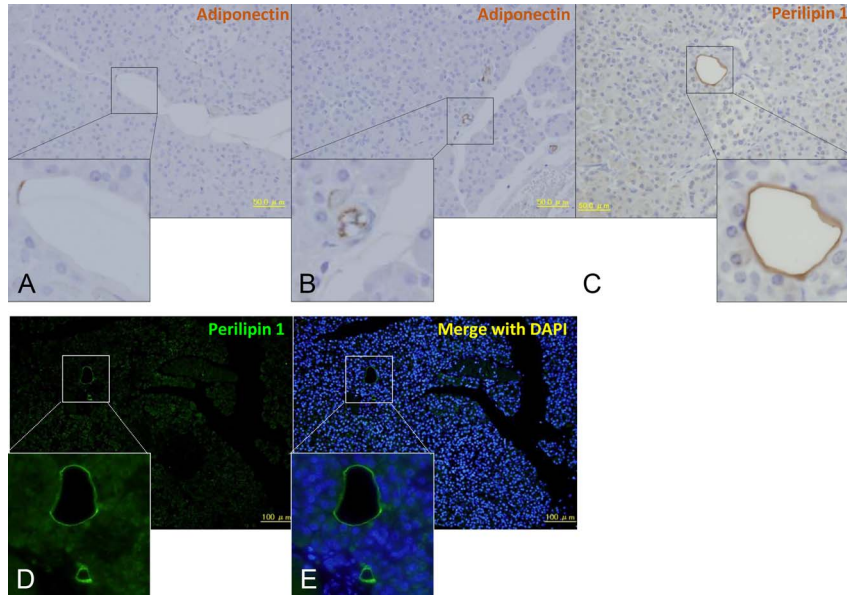

FIGURE 1. Immunostaining of pancreatic tissue samples for adiponectin and perilipin 1. A and B, Images display a representative image of immunostaining for adiponectin in an NGT patient. C–E, Images display representative images of immunostaining for perilipin 1 in a different NGT patient. Immunostaining for perilipin 1 by 3,3-diaminobenzidine (C) and by immunofluorescence (D and E) in another NGT subject. Bars are 50 μm in A and B, 100 μm in C–E.

intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, and nonneoplastic cyst) (n = 8) and pancreatic cancer (n = 5). The operative procedures were pancreatoduodenectomy (n = 12) and distal pancreatectomy (n = 3). Two patients were treated with anticancer agents before surgery. The averages for the following parameters are as follows: age (62 ± 15 years), BMI (19.7 ± 2.6 kg/m^2), HbA1c (6.3% ± 1.4%), FPG (105 ± 26 mg/dL), F-IRI (6.7 ± 3.1 μU/mL), HOMA-IR (1.67 ± 0.87), and fat-cell area (1.59% ± 2.15%). There were no significant differences in age and BMI between NGT and T2DM patients. HbA1c and FPG were significantly higher in the T2DM group than that in the NGT group ($P < 0.01$). Treatment for T2DM consisted of dietary control in 1 patient, sulfonylureas alone in 3 patients, a combination of sulfonylureas and α-glucosidase inhibitor in 1 patient, and insulin in 1 patient.

Adipocyte Markers

Figure 1 shows representative image of pancreatic tissue from an NGT patient stained with antibodies for adiponectin and perilipin 1. Figures 1A and B show immunostaining for adiponectin, not only hypertrophied cells (Fig. 1A) but also small cells containing only a small amount of (Fig. 1B) expressed adiponectin in the cytoplasm. Figures 1C–E show representative images for pancreatic tissue stained with antibodies for perilipin 1 in a different NGT patient. Immunostaining for perilipin 1 by 3,3-diaminobenzidine (Fig. 1C) showed that perilipin 1 was expressed along the plasma membrane of the fat-containing cells. In the fluorescent immunostaining images (Figs. 1D and E), perilipin 1 expression was similar to adiponectin expression, and it was found in small cells as well as in hypertrophied cells. On the other hand, expression of perilipin 1 was not observed in islet and acinar cells.

Association Between Fat-Cell Area and Total Fat-Containing Cell Density

We investigated the relationships between density or diameter of total fat-containing cells (including both of intralobular and interlobular fat-containing cells) and fat-cell area as well as the clinical indicators, because we consider the density and the size of fat-containing cells to be factors that define fat-cell area. Figures 2A–I show the relationships between the density of total fat-containing cells and fat-cell area or clinical parameters. Fat-cell area had a significant positive correlation with the total density of fat-containing cells ($r = 0.58$, $P = 0.023$) (Fig. 2A). There was no significant difference in the density of total fat-containing cells between NGT and T2DM patients ($P = 0.928$) (Fig. 2B), and between male and female (Fig. 2C). The density of total fat-containing cells had a significant positive correlation only with HOMA-IR ($r = 0.61$, $P = 0.045$) (Fig. 2I), whereas it did not correlate with patient age ($r = 0.22$, $P = 0.423$) (Fig. 2D), BMI ($r = 0.27$, $P = 0.317$) (Fig. 2E), HbA1c ($r = 0.11$, $P = 0.678$) (Fig. 2F), FPG ($r = 0.51$, $P = 0.070$) (Fig. 2G), or F-IRI ($r = 0.30$, $P = 0.363$) (Fig. 2H).

To evaluate the association between the density of total fat-containing cells and fat-cell area based on the cell size, fat-containing cell sizes were divided into 2 groups: less than 60 μm in diameter and larger than 60 μm in diameter, as the median of fat-containing cell diameter was 59.8 μm. In cells with a diameter of less than 60 μm, there was no association between fat-containing cell density and fat-cell area ($r = 0.30$, $P = 0.283$); however, in cells with a diameter larger than 60 μm, there was a significant positive correlation area and density ($r = 0.69$, $P = 0.004$) (Supplemental Fig. 2, http://links.lww.com/MPA/B259).

Association Between Fat-Cell Area and Fat-Containing Cell Size

Figures 2J–R show the relationships between the diameter of total fat-containing cells and fat-cell area or clinical parameters. The fat-cell area had no significant correlation with the diameter of total fat-containing cells ($r = 0.45$, $P = 0.095$) (Fig. 2J). There was no significant difference in the diameter of total fat-containing cells between NGT and T2DM patients ($P = 0.905$) (Fig. 2K) and between male and female (Fig. 2L). However, the diameter of total fat-containing cells was significantly positively

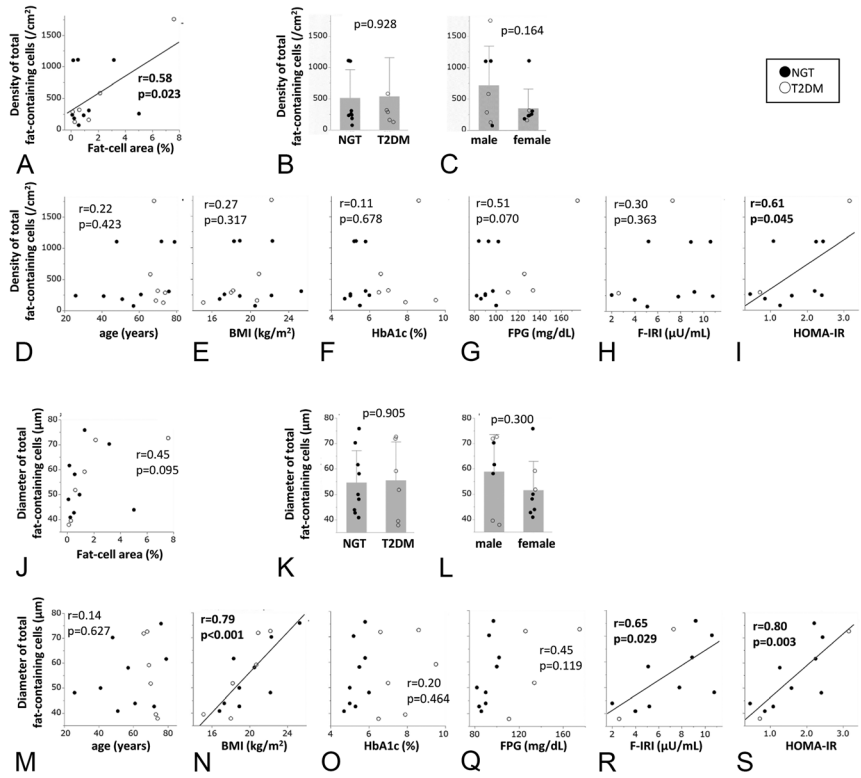

FIGURE 2. Relevance between the density of fat-containing cells and various clinical parameters in normal glucose tolerance and type 2 diabetes mellitus patients. Single regression analysis of density of fat-containing cells and fat-cell area (A). The average density of fat-containing cells was compared between NGT and T2DM by *t* test (B). Single regression analysis of fat-containing cell density with age (C), BMI (D), HbA1c (E), FPG (F), F-IRI (G), and HOMA-IR (H). Closed circles (●), NGT; open circles (○), T2DM.

correlated with BMI (r = 0.79, P < 0.001) (Fig. 3N), F-IRI (r = 0.65, P = 0.029) (Fig. 3Q), and HOMA-IR (r = 0.80, P = 0.003) (Fig. 3R). The diameter of fat-containing cells did not correlate with age (r = 0.14, P = 0.627) (Fig. 3M), HbA1c (r = 0.20, P = 0.464) (Fig. 3O), or FPG (r = 0.45, P = 0.119) (Fig. 3Q).

Difference Between Intralobular and Interlobular Fat-Containing Cells

Next, we show each data of intralobular and interlobular fat-containing cells. The mean diameter of intralobular fat-containing cells was 65.1 ± 17.0 μm, and the mean diameter of interlobular fat-containing cells was 54.0 ± 13.2 μm, The diameter of intralobular fat-containing cells was significantly larger (P = 0.045). For all fat-containing cells, 10.4% ± 11.6% were intralobular cells.

Figures 3A–I show the relationships between the diameter of intralobular fat-containing cells and parameters, and Figures 3J–R show the relationships between the diameter of interlobular fat-containing cells and parameters. The diameter of intralobular fat-containing cells was not related to fat-cell area (r = 0.20, P = 0.485) (Fig. 3A), glucose tolerance group (P = 0.464) (Fig. 3B), gender (P = 0.175) (Fig. 3C), BMI (r = 0.19, P = 0.504) (Fig. 3E), HbA1c (r = 0.09, P = 0.757) (Fig. 3F), FPG (r = 0.17, P = 0.586) (Fig. 3G), F-IRI (r = −0.38, P = 0.285) (Fig. 3H), and HOMA-IR (r = −0.18, P = 0.611) (Fig. 3I). However, in elderly subjects (over 60 years old) only, the diameter of intralobular fat-containing cells showed a significant positive correlation with BMI (r = 0.72, P = 0.043) (Supplemental Table 2A, http://links.lww.com/MPA/B260). On the other hand, that had tendency for a positive correlation with age (r = 0.52, P = 0.057) (Fig. 3D); moreover, the diameter of intralobular fat-containing cells had a significantly positive correlation with age in female only (r = 0.83, P = 0.010) (Supplemental Table 2B, http://links.lww.com/MPA/B260).

The diameter of interlobular fat-containing cells was not related to glucose tolerance group (P = 0.864) (Fig. 3K), gender (P = 0.267) (Fig. 3L), age (r = 0.14, P = 0.616) (Fig. 3M), HbA1c (r = 0.22, P = 0.427) (Fig. 3O), and FPG (r = 0.47, P = 0.108) (Fig. 3P); however, that had significant positive correlations with BMI (r = 0.81, P < 0.001) (Fig. 3N), F-IRI (r = 0.67, P = 0.025) (Fig. 3Q), and HOMA-IR (r = 0.82, P = 0.002) (Fig. 3R), and that had a tendency for a positive correlation with fat-cell area (r = 0.64, P = 0.097) (Fig. 3D).

DISCUSSION

The nature of fat-containing cells in the pancreas and whether they are mature adipocytes or other cells that look like adipocytes have not been reported. In the present study, we found that fat-containing cells in the pancreas expressed adiponectin and perilipin 1, which are markers for mature adipocytes.[15] Expression of perilipin 1 was not observed in islet cells, although many lipid droplets are deposited in those cells.[16] These results imply that some of IPFD may be composed of mature adipocytes.

In the present study, we also found that fat-cell area is increased by an increment in the density of the fat-containing cells, although the mechanism, specifically, regarding the hyperplasia (proliferation, differentiation, and neogenesis of adipocytes or preadipocytes) or hypertrophy of adipocytes, has not yet been

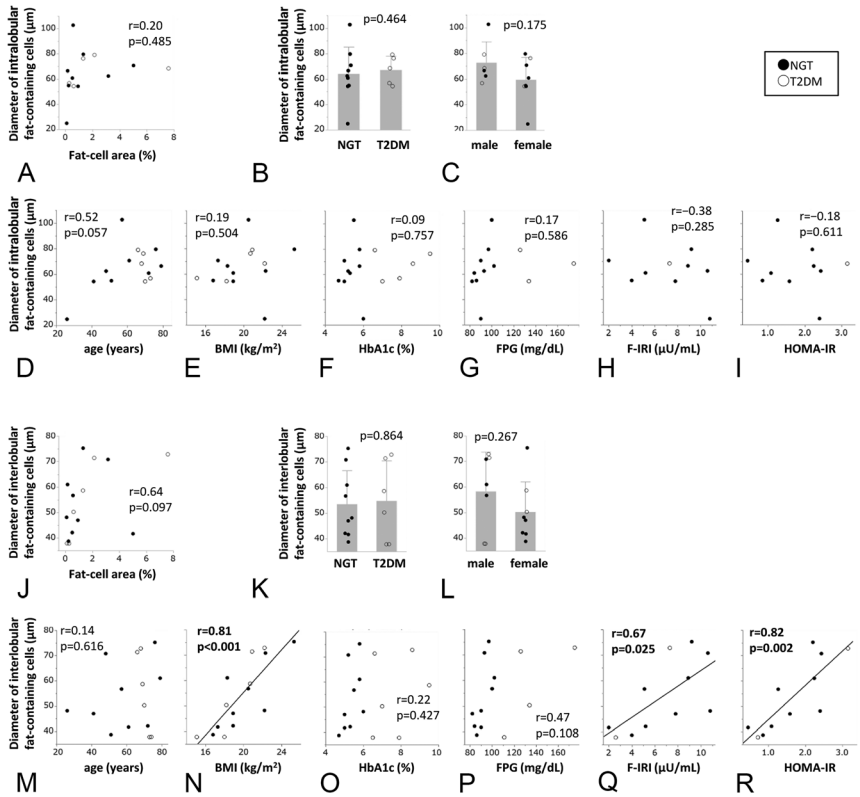

FIGURE 3. Relationship between the diameter of fat-containing cells and various clinical parameters in normal glucose tolerance and type 2 diabetes mellitus patients. A single regression analysis of the diameter the fat-containing cells and the fat-cell area (A). Comparison of the diameter of fat-containing cells between NGT and T2DM by *t* test (B). Single regression analysis of the diameter of fat-containing cells with age (C), BMI (D), HbA1c (E), FPG (F), F-IRI (G), and HOMA-IR (H). Closed circles (●), NGT; open circles (○), T2DM.

clarified. The increase of cell density implies that there is hyperplasia, and the increase of the cell diameter implies hypertrophy of the fat-containing cells. The increase of the number of fat-containing cells along with the increase of insulin resistance (HOMA-IR) in this study may suggest that insulin promotes the differentiation of adipocytes, especially interlobular fat-containing cells,[17] resulting in hyperplasia. On the other hand, it is reported that insulin resistance in new-onset prediabetes/diabetes after acute pancreatitis appears to be predominantly driven by increased IPFD,[18] and therefore, it is assumed that the enlarged adipose tissue caused by the increased insulin resistance may further aggravate insulin resistance.

To evaluate fat-containing cells proliferation as a potential mechanism for the increase in pancreatic adipocytes, we tried to observe Ki67 expression in adiponectin-positive cells, but we could not identify adipocytes expressing Ki67 (data not shown). Therefore, the proliferation of the fat-containing cells themselves is not likely to be occurring at a fast rate. It has been suggested that subcutaneous fat is more hyperplastic than visceral fat because of the abundance of progenitor cells with high potential for proliferation and differentiation.[19,20] Conversely, visceral adipocytes are thought to have higher capacity to take up fatty acids than subcutaneous adipocytes.[21] Based on these ideas, visceral fat is considered to have low differentiation potential, and rather, the cells increase in volume by absorbing fatty acids and enlarging cell size. Abdominal obesity is thought to be caused by hypertrophy of adipocytes in response to excess energy intake without increasing the number of adipocytes. This is described as unhealthy expansion because it causes systemic inflammation and increases insulin resistance.[22] As the increase of pancreatic fat is associated with insulin resistance and infiltration of macrophages into islets,[10] physiological properties of pancreatic fat may be similar to those of visceral fat. However, fat-containing cells in the pancreas seem to have the capacity to increase cell number, which suggests that fat-containing cells in the pancreas may not have the exact same properties as visceral adipocytes.

The fat-containing cell diameter was significantly associated with BMI and insulin resistance, but not statistically significant with fat-cell area, although a trend toward a positive correlation was observed. Fatty acids stored in adipocytes can also be synthesized from glucose taken up via the insulin-sensitive glucose transporter GLUT4 in addition to lipid sources.[23] Thus, hyperinsulinemia may be involved in hypertrophy as well as hyperplasia of adipocytes. There was a significant positive correlation between density and fat-cell area only in larger adipocytes, suggesting that an increase in the number of hypertrophied adipocytes is a factor that may define pancreatic fat volume.

The perilipin 1 positive fat-containing cells included in IPFD are thought to be identified as interlobular fat-containing cells, acinar-to-adipocyte-transdifferentiated cells, or cells that might replace apoptotic acinar cells. It has been reported that IPFD is increased with age and in males compared with females, but the gender difference disappears in the elderly.[9] In the present study, the same trend was observed only in intralobular fat-containing cells and not in interlobular cells. The diameter of interlobular fat-containing cells was associated with BMI and insulin resistance, whereas the size of intralobular fat-containing cells was related to age, suggesting that interlobular and intralobular fat-containing cells have different origins. There are several limitations that should be considered when interpreting the results of

this study. First, this study included few obese patients. The association between pancreatic fat and diabetes is more pronounced in nonobese patients, and there are some articles finding no association with diabetes in obese patients.[6] These results may be limited to only nonobese subjects. Second, this study had a small number of cases. One reason for this is that only large specimens were used in this study so that there was a sufficient number of cells in each specimen to be evaluated. The possibility of selection bias cannot be ruled out. Unfortunately, the scope of this study did not allow for the elucidation of more specific characteristics of fat-containing cells in the pancreas and the mechanism by which the volume of pancreatic fat increases in humans.

In conclusion, some of the pancreatic fat is likely composed of fat-containing cells with markers of mature adipocytes, and IPFD may be due to hyperplasia of those fat-containing cells associated with insulin resistance.

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