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Quantitative CT assessment of pancreatic fat in type 2 diabetes mellitus

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Objective: To characterize the pancreatic fat deposition (PFD) in patients with type 2 diabetes mellitus (T2DM) by quantitative computed tomography (QCT) and investigate the relationship between PFD and clinical metabolic parameters and islet function.
Materials and Methods: A total of 150 patients with T2DM and 93 age-matched healthy subjects underwent QCT to quantify PFD were included. PFD and various biochemical parameters were correlated by statistical methods and multiple stepwise linear regression modeling.
Results: PFD measured by QCT in the T2DM group was statistically higher than that in the healthy control group, and the pancreatic CT value was statistically lower than that in the control group. The QCT measured PFD was negatively correlated with the pancreatic CT values ($P < 0.001$), and positively correlated with triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), visceral fat area (VAT) and insulin resistance index (HOMA-IR) ($P < 0.05$) in the T2DM patients. Multiple stepwise linear regression analysis identified PFD as the dependent variable factor for T2DM.
Conclusion: This study suggests QCT as a reliable technique in measuring PFD in T2DM. High PFD is positively correlated with the degree of insulin resistance and may play an important role in islet cell dysfunction in T2DM.

Keyword: Pancreatic fat deposition, quantitative computed tomography, type 2 diabetes mellitus, insulin resistance

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, heterogeneous metabolic disorder caused by multiple factors and is a major global public health problem. By T2DM is expected to become the most common disease in the world in causing death [1-3]. Recent studies have shown that ectopic fat may accumulate in the pancreas when the storage capacity of adipose tissue is insufficient due to obesity, which is called ectopic pancreatic fat deposition (PFD) [1]. Excessive fat can be deposited near insulin-secreting β cells in the pancreas, which implies its association to both β cell function and insulin resistance in adults and youth with obesity [2]. As obesity is known to be the main risk factor for T2DM [3], quantification of PFD is of great significance for early detection, prevention and treatment of T2DM.

Various imaging methods are used to quantify PFD including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). Conventional ultrasound is simple and convenient, but can only provide semi- quantitative analysis, and the location of pancreas at the retroperitoneum behind the stomach or colon limits the accessibility, plus, the intestinal gas can easily interfere with the examination [4]. MRI is currently the most accurate way to quantify PFD [5, 6], but it is time-consuming and expensive compared to CT, thus not ideal for routine use. Conventional CT scan is a practical modality for quantifying PFD [7]. Quantitative CT (QCT), which is a medical technique that measures bone mineral density [8], has become an emerging screening tool to measure visceral fat [9, 10]. It is a combination of quantitative phantom and conventional CT. QCT has the advantage of intuitive and accurate fat measurement, and QCT scan protocols are usually low-dose which is typically less than a standard CT exam [11]. Yao *et al*. [12] reported a good correlation between the PFD measured by QCT and by MRI chemical-shift imaging, serving as a strong rational for us to adopt QCT to quantify PFD in patients with T2DM, which has not been investigated before. In this study, we characterized PFD in 150 T2DM patients in comparing to 93 age-matched healthy subjects, also explored the correlation between PFD with various clinical biochemical indicators of T2DM, and finally performed a multiple stepwise linear regression analysis to identify the role of PFD as a dependent variable factor for T2DM.

Materials and Methods

Study Population

The study was conducted according to the Declaration of Helsinki and subsequent revisions and was approved by the Ethics Committee of Dhanalaxmi Srinivasan Medical College and Hospital. Written informed consent was waived due to the study's retrospective design, all the patients' data was anonymized and maintained with confidentiality. A total of 150 patients with 1–20 years T2DM were retrospectively collected as the T2DM group (62 males and 88 females), 93 age- matched healthy subjects underwent routine physical examination during the same period were included as the healthy control group (48 males and 45 females). All subjects underwent QCT imaging for upper abdomen. Inclusion criteria: 1). According to the American Diabetes Association (ADA) criteria, a clear diagnosis of T2DM; 2). Complete medical history, physical examination, and laboratory tests; 3). Good quality of CT images; Exclusion criteria: 1). Patients with pancreatic diseases, such as inflammation, tumors and cysts, etc.; 2). Acute complications of diabetes, such as hypertonic coma, ketoacidosis, lactic acidosis, etc.; 3). Those who cannot undergo CT examination during lactation and preg- nancy; 4). Liver, kidney, and cardiac insufficiency; 5). CT images not suitable for delineation of the area of interest.

QCT Imaging Technique

Routine CT scans of the chest or upper abdomen were performed on all subjects using a Siemens Somatom Force dual- source CT scanner combined with a Mindways QCT sample solid phantom. All subjects were fasted and watered for 4–6 hours before the examination. During the examination, they were placed supine on the examination bed, and the scan was completed by holding their breath at one time. The scanning conditions were as follows: bed height 120 cm, pitch 0.985, tube voltage 120 kVp, automatic tube current, scanning layer spacing and interlayer thickness were both 0.5 mm, FOV: 50 cm × 50 cm, standard algorithm reconstructed layer thickness and layer spacing, both 1.25 mm.

Mindways 5-sample calibration phantom which contains different equivalent concentrations of K_2HPO_4 (mg/cm^3) was placed under the waist of the examinee (covering the entire abdomen), with no gap between the solid phantom and the lower back to be examined. If the examinee is skinny with less soft tissue in the lower back, a liquid equivalent material was placed between the two.

The QCT solid body template produced by Mindways was placed in the center of the examination table of the CT machine, and then the quality control (QA) was placed vertically on the body template. The head side directions of QA and body template were consistent. After scanning, images were sent to the workstation for calibration using the "QA Exam" function key, appropriate conditions were set to pass the QA, and the scanning conditions were kept unchanged until the next QA.

The 1.25mm slice thickness image after CT reconstruction was transferred to the QCT pro software workstation and the bone mineral density (BMD) value of the pancreas was measured by lumbar bone densitometry. Three regions of interest (ROI) were manually placed by each of the independent radiologist on the head, body, and tail of the pancreas, and the placement was avoided to the areas of peripancreatic fat, main pancreatic duct and surrounding great blood vessels. Each ROI was 100–140mm^2, three measurements of each ROI were taken. The field uniformity correction (FUC), corresponding calibrated slope (slope) and BMD values of the three measurements were exported in the QCT Pro software database. Fat percentage was measured using the method published by Cheng *et al*. [9] as the following equation:

% fat = ((HUlean-HUpancreas)/(HUlean-HUfat))*100%

The HUpancreas value represents the HU value of pancreatic sampling tissue, which is obtained by converting the BMD value measured by the Mindways software into the HU value through the calibration of QCT Pro scan software. HUfat and HUlean represent the HU value of 100% pure adipose tissue and fat-free pancreatic tissue, respectively. The two values are expressed by their equivalent densities. The scanning calibration data of the QCT Pro software was used to adjust the tube voltage and beam hardening variations, represented by water (H2O) and dipotassium hydrogen phosphate (K2HPO4).

"Tissue Composition" program in the QCT pro software workstation was selected to imaging cross-sectional level of L2/L3 intervertebral space, and then the "Auto Snake" option was chosen to automatically set the threshold after calibration, and automatically calculate the abdominal subcutaneous fat area (SAT) and Visceral fat area (VAT) (Figure 1).

Conventional CT Measurements

CT images of all subjects were reviewed and evaluated by two experienced radiologists independently. The pancreatic CT value was measured on the CT image workstation with 3 ROIs in consistent with those on the QCT images. An average of three measurements for each ROI was used as the pancreatic CT value. At the same time, 3 ROIs of spleen were measured to get an average spleen CT value, then difference between the pancreas and spleen CT values (P-S) and ratio of the pancreas versus spleen CT values (P/S) were calculated. P/S was used to determine PFD with the diagnostic criteria for fatty pancreas of P/S <0.7 [10].

Clinical Indicators

An experienced endocrinologist reviewed the patients' electronic medical records to evaluate T2DM-related indicators, including gender, age, body mass index (BMI), fasting blood glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbA1c), fasting C-peptide (FCP), insulin resistance index (HOMA-IR) and insulin secretion index (HOMA-β), calculated by the formulas of: HOMA-IR = FPG × FCP/22.5, and HOMA-β = 20 × FCP/(FDG −3.5), respectively [11].

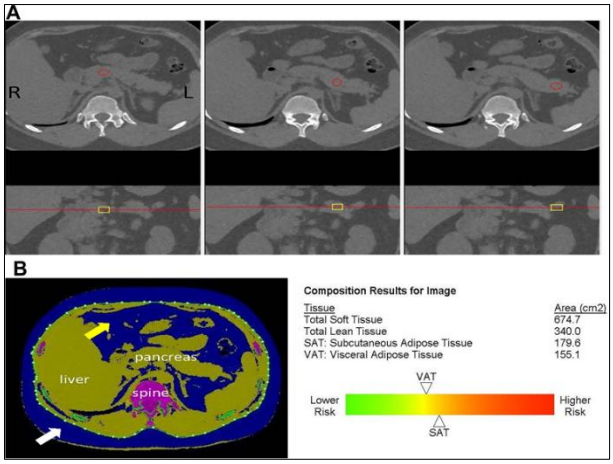

Fig 1: QCT measuring of the fat content at pancreatic head ((A)-left), body ((A)-middle) and tail ((A)-right), and at subcutaneous adipose tissue (SAT, indicated by the white arrow) and visceral adipose tissue (VAT, indicated by the yellow arrow) at the pancreas level (B).

Abbreviations: R, right; L, left

Statistical Analysis

SPSS26.0 statistical software was used for all statistical analysis. Quantitative data conforming to the normal distribu- tion was expressed as the mean ± standard deviation, and data conforming to the skewed distribution was expressed as the median (25th quantile value, 75th quantile value); *t*-test and Mann–Whitney *U*-test were used to compare the difference between T2DM and healthy control groups. Chi-square test was used to compare the gender differences between the two groups. Pearson and Spearman correlation analysis were used for correlation analysis. Multiple stepwise linear regression analysis (a combination of forward and backward selection) was performed with the full model of QCT measured pancreatic fat percentage and all other clinical parameters and at each step gradually eliminated variables from the regression model to find a reduced model that best explains the data. $p < 0.05$ was considered statistically significant.

Results

The age, BMI, FBG, TG, HbA1c, HDL-C, percentage of pancreatic fat, VAT, and SAT in the T2DM group were statistically higher than those in the control group, and the pancreatic CT value, P-S value, and P/S value were statistically lower than those in the control group ($p < 0.05$) (Table 1). There were no significant differences in gender, TC, and LDL-C between the two groups ($p > 0.05$).

In the T2DM group, the QCT measured pancreatic fat percentage was negatively correlated with the P-S ($r = -0.808$, $p < 0.001$) and P/S ($r = -0.798$, $p < 0.001$) values, and positively correlated with TG, HDL-C, and VAT ($p < 0.05$). There was no significant correlation with age, BMI, TC, FBG, HbA1c, LDL-C, and SAT ($p > 0.05$). The QCT measured pancreatic fat percentage was also positively correlated with the HOMA-IR ($p < 0.05$), but not with the HOMA-β ($p > 0.05$) (Table 2, Figure 2). Using the QCT measured pancreatic fat percentage as the dependent variable and all others as the independent variables, the backward multiple stepwise linear regression analysis identified that the effect of percentage of pancreatic fat on T2DM was statistically significant ($p < 0.05$) (Table 3).

Discussion

PFD in the pathogenesis of T2DM and its clinical relevance are being valued and becoming a research hotspot [13]. Our study provided evidence on QCT could serve as a reliable technique in quantifying PFD in patients with T2DM, and we found that high PFD positively correlated with the degree of insulin resistance and may play an important role in islet cell dysfunction in the late-stage T2DM [14-17].

It has been reported in the literature that long-term exposure to a high-fat diet leads to interlobular and intralobular fat accumulation, inflammatory cell infiltration, and pancreatic fibrosis in rat pancreas, thereby impairing normal pancreatic architecture, resulting in pancreatic fat fibrosis and impaired islet function. Due to the inability to distinguish the deposition of fat within acinar cells, β-cells, or pancreatic adipose tissue, various synonyms have been used for the

accumulation of pancreatic fat, including pancreatic hyperlipidemia, pancreatic steatosis, pancreatic fat replacement, and pancreatic fat infiltration, fatty pancreas and NAFPD (non-alcoholic fatty pancreas). Although more research has been done on pancreatic fat in recent years, our understanding of it is still in its infancy, and there is no consensus on the terms, definitions, normal thresholds, and diagnostic criteria for pancreatic fat deposition.

Table 1: General Characteristics of the Study Subjects

	n	Age	Sex (M/F)	HbA1c (%)	BMI (kg/m^2)	HDL-C (mmol/L)	LDL-C (mmol/L)	TC (mmol/L)
T2DM group	150	56.49±13.6	62/88	8.49±1.87	24.62±2.12	1.05 (0.91,1.20)	2.64 (2.13,3.31)	4.35 (3.84,4.78)
Control group	93	53.31±11.2	48/45	5.80±0.68	23.58±2.66	1.30 (1.30,1.88)	2.40 (2.10,2.95)	4.30 (3.95,4.50)
P value	-	0.049	0.132	0.000	0.002	0.000	0.165	0.308
	FBG (mmol/L)	TG (mmol/L)		VAT (cm^2)	SAT (cm^2)	P/S (HU)	P-S (HU)	Pancreatic fat percentage (%)
T2DM group	7.63 (7.00,9.00)	1.61 (1.09,2.25)		150.67±51.89	102.64±50.38	0.69±0.08	-16.0±4.26	5.47±3.83
Control group	5.25 (4.89,5.67)	1.14 (0.76,1.46)		136.32±55.38	88.13±52.28	0.91±0.07	-4.54±3.53	0.03±2.87
P value	0.000	0.000		0.042	0.032	0.000	0.000	0.000

Table 2: Correlation Analysis between Pancreatic Fat Percentage and Various Indexes in the T2DM Group

	Age	HbA1c (%)	BMI (kg/m^2)	HDL-C (mmol/L)	LDL-C (mmol/L)	TC (mmol/L)	FBG (mmol/L)
r	0.113	0.034	0.110	0.178	0.032	0.022	0.099
P	0.169	0.679	0.180	0.029	0.695	0.792	0.229
	TG (mmol/L)	VAT (cm^2)	SAT (cm^2)	P/S (HU)	P-S (HU)	HOMA-β	HOMA-IR
r	0.230	0.330	0.068	−0.808	−0.798	0.072	0.388
P	0.005	0.000	0.082	0.000	0.000	0.384	0.000

Table 3: Multivariate Stepwise Linear Regression Analysis of Influencing Factors of Pancreatic Fat Percentage in T2DM Group

Factor	Unstandardized Coefficients		Standardization Coefficient β	t	P
	B	Standard Error			
	−2.963	1.135		−2.354	0.020
HOMA-IR	8.281	1.686	0.349	4.913	0.000
VAT	0.022	0.005	0.296	4.186	0.000
TG	0.708	0.277	0.181	2.557	0.012

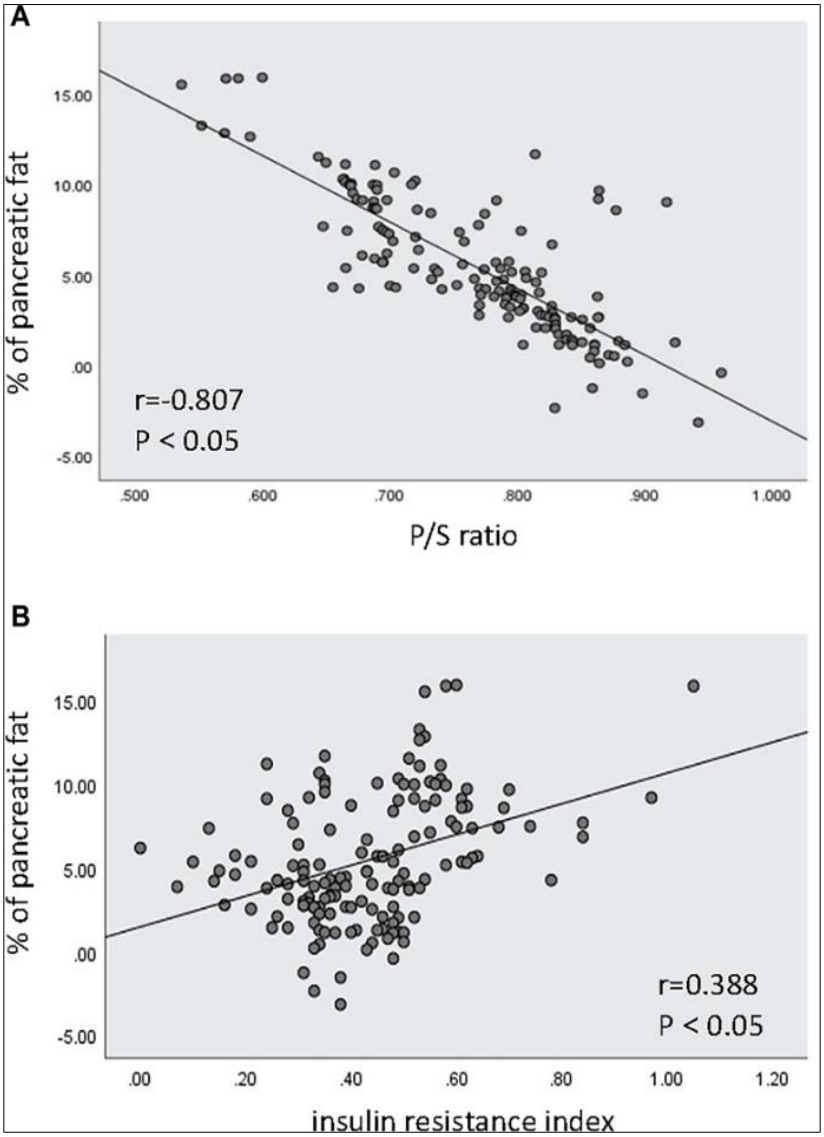

Fig 2: Relationship between QCT pancreatic fat percentage (The ordinate) with P/S ratio (the abscissa) (r=−0.807, $p < 0.05$) in (A), and with insulin resistance index (r=0.388 $p < 0.05$) in (B), in the T2D group

PFD refers to the deposition of circulating TG and free fatty acids in the pancreas in exceed of adipose tissue metabolism [12]. Epidemiological studies estimated the prevalence of nonalcoholic fatty pancreatic disease in Asian population to be 16–35% [19, 20]. While most of the PFD do not lead to specific clinical symptoms in the early stage, as disease progresses, pancreatic atrophy, degeneration, and pancreatic steatosis can lead to chronic pancreatitis and pancreatic fibrosis, resulting in decreased release of pancreatic enzymes, as referred of pancreatic endocrine and exocrine dysfunction [21, 22]. Chronic exposure to a high-fat diet has been reported to induce interlobular and intralobular fat accumulation, inflammatory cell infiltration, and pancreatic fibrosis, thereby impairing normal pancreatic architecture and islet function in rats [23, 24]. Similarly, pancreas of high-fat diet-fed C57BL/6 mice developed intracellular lipid vesicles in acinar cells, fatty infiltration, and ectopic deposition of interlobular fat, making mice insulin resistant and β-cell dysfunction [25]. These studies suggest that PFD may play a certain role

in the process of T2DM. However, recent studies showed a controversial result on fat deposited in the pancreas may help maintain insulin secretion and slow the onset of T2DM by promoting the capacity of glycerolipid/NEFA cycling thereby helping β cells to deal with glucotoxic conditions.13 These different findings may be attributed by the different exposure duration of the pancreas to excessive fat, and also indicate that PFD may play differential roles in early or late stage T2DM.

To quantify PFD in a practical and accurate way, we tested the QCT imaging in comparing to the conventional CT imaging. Our studies with 150 T2DM patients and 93 control subjects showed that the PFD quantified by QCT was highly consistent with that measured by conventional CT. While the conventional CT relies on calculated CT values of P-S and P/S to diagnose fatty pancreas, the QCT uses an intuitive percentage of fat to indicate the extent of PFD. Both of them are correlated with pancreatic histopathology [26, 27], but the QCT measured percentage of fat would potentially be used to indicate more detailed categories in relating to the disease stages or islet dysfunctions. The high correlation between the two methods, and high accuracy of QCT in quantifying PFD12 indicate that the QCT technique is feasible to serve as a screening tool for PFD.

We found the percentage of pancreatic fat in T2DM patients was significantly higher than that of healthy control subjects, similar as been reported by Lu *et al*. [28] The plasma TG and HDL-C of the T2DM patients were significantly elevated, may imply that the increased TG and HDL-C could also deposit into pancreatic cells. Importantly, the percentage of pancreatic fat in our T2DM patients was positively correlated with the insulin resistance index. However, we found an inconsistent report by Li *et al*., [29] in which newly diagnosed T2DM patients were evaluated. With a larger sample size and focused on hospitalized T2DM patients, our study indicated that the pancreatic fat accumulation likely contributes to the insulin resistance along the time as the course of T2DM progresses. Both the Li study and ours found no correlation between the fat content with the insulin secretion index, suggesting that the β cells dysfunction may be less affected by the fat accumulated in the pancreas at early and late stages of T2DM. It is noted that in order to exclude the interference of treatment, this study uses C-peptide instead of insulin to evaluate the function of islet β cells, a more accurate method. However, lipotoxicity has been postulated to harm β cells, 30 especially long-term lipotoxicity has been implicated with a profound inhibition of insulin release in rats [29]. Whether and how PDF would affect β cells function in T2DM patients remain to be further explored.

Our study also found that the VAT of T2DM patients was significantly higher than that of healthy controls. Furthermore, the higher of fat percentage the higher of VAT been examined in the T2DM cohort, but BMI and SAT had no significant correlation with the pancreatic fat content, indicated the role of increased VAT may contribute into increased pancreatic fat content in T2DM that is related to central obesity.31 Through the stepwise multiple regression modeling, HOMA-IR, VAT, and TG were risk factors for PFD in the T2DM patients. Therefore, reducing visceral fat, reducing TG levels and improving insulin resistance all contribute to reducing fatty pancreas in patients with T2DM. T2DM patients with visceral fat deposition are also a related factorial that significantly increases the risk for cardiovascular disease [32]. Studies have suggested that low calorie diets, exercise, and antidiabetics may reduce the deposition of epicardial and pericardial adipose tissue, improve the metabolic profile and lower the cardiovascular disease burden.

There are several limitations of our study: 1). Fat deposition in the pancreas is sometimes non-uniform, so the partial measurement of the pancreas may not be representative of the whole pancreas fat, and sampling error may exist. 2). The relationship between pancreatic fat content

and islet function in healthy people was not evaluated.

Abbreviations

PFD, pancreatic fat deposition; T2DM, type 2 diabetes mellitus; QCT, quantitative computed tomography; TG, trigly- ceride; HDL-C, high-density lipoprotein cholesterol; VAT, visceral fat area; HOMA-IR, insulin resistance index; CT, computed tomography; MRI, magnetic resonance imaging; BMD, bone mineral density; ROI, regions of interest; FUC, field uniformity correction; SAT, subcutaneous fat area; P-S, difference between the pancreas and spleen CT values; P/S, ratio of the pancreas versus spleen CT values; BMI, body mass index; FPG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; FCP, fasting C-peptide; HOMA-β, insulin secretion index.

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