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ORIGINAL RESEARCH

CT Quantitation and Prediction of the Risk of Type 2 Diabetes Mellitus in Non-Obese Patients with Pancreatic Fatty Infiltration

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Purpose: To examine the risk of type 2 diabetes mellitus in non-obese patients with pancreatic fatty infiltration through abdominal computed tomography (CT) quantitation.

Patients and Methods: We carried out a retrospective analysis of abdominal CT and inpatient medical records of 238 inpatients from July 2019 to April 2021. The patients were divided into a normal non-obese group (BMI < 25, n = 135) and diabetic non-obese group (BMI < 25, n = 103). Abdominal CT-related parameters included body width; mean CT values of the pancreas, liver, and spleen; difference between pancreas and spleen CT values (P−S); pancreas-to-spleen attenuation ratio (P/S); and liver-to-spleen attenuation ratio (L/S). Logistic regression was used to estimate the risk factors for comorbid diabetes in a non-obese population.

Results: The P-values of the pancreas CT value, P−S, P/S, body width, and L/S were all <0.05 and correlated to comorbid diabetes in non-obese patients. Worsening pancreatic fatty infiltration increased the risk of developing diabetes. Using a P/S of 1.0 as reference, every successive decrease in this ratio by 0.1 increases patient risk by 3.981, 4.452, 6.037, and 12.937 times.

Conclusion: The risk of developing type 2 diabetes mellitus in non-obese patients increases with the degree of pancreatic fatty infiltration as assessed by CT.

Keywords: computed tomography, non-obese patients, pancreatic fatty infiltration, type 2 diabetes mellitus

Introduction

Obesity is one of the risk factors for developing Type 2 diabetes mellitus,[1] but Type 2 diabetes mellitus is also common in non-obese people. According to an epidemiological study, over 60% of people with T2DM were not obese.[2] Another study reported that 68.2% of newly detected T2DM cases were non-obese T2DM.[3] Many T2DM patients do not present obesity, and the specific etiology of T2DM in these non-obese individuals is still unclear.[4] Some studies have reported that T2DM in non-obese individuals may be related to lifestyle, intestinal microbiota structure, as well as genetic and environmental factors.[4–6] Versus obese individuals, the key defect that leads to the development of hyperglycemia in T2DM in non-obese individuals is impaired pancreatic insulin secretion and decreased insulin resistance.[2,7] Visceral fat is mainly deposited in the liver, pancreas, and heart.[8–10] Prior work showed that visceral fat accumulation is one of the main causes of T2DM.[11] The pancreas usually contains low amounts of fat, and deposition of a large amount of fat in the pancreas is known as pancreatic fatty infiltration.[12,13] Excessive pancreatic fat accumulation is associated with pancreatic impairment and non-adipocyte apoptosis.[14,15] In several studies, we have shown the association of raised intrapancreatic

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fat with T2DM as well as lowered fat with remission.[16–18] Central obesity is an independent factor associated with fatty pancreas, but nearly half of the pancreatic fatty infiltration is seen in non-obese individuals.[19] Understanding that T2DM occurs in non-obese pancreas with high amounts of pancreatic fat is particularly important in predicting the risk of T2DM.

The objective of this study was to use Hounsfield units [HU] upon computed tomography (CT) as a quantitative parameter and to examine the relationship between pancreatic fatty infiltration and T2DM incidence in non-obese patients.

Materials and Methods

General Information

We recruited inpatients from the endocrinology department of Fushun Central Hospital from July 2019 to April 2021. This retrospective study has obtained approval from the ethics committees of Fushun Central Hospital (Number: zzyyll2023008), with the committees waiving the requirement for written informed consent from patients. All patients had complete clinical examination data and had a definitive diagnosis of T2DM based on the Standards of Medical Care in Diabetes published by American Diabetes Association (ADA) in 2019. The diagnostic cut point was ≥126 mg/dl (7.0 mmol/l) for FPG and 2-h PG value of ≥200 mg/dl (11.1 mmol/l). The body mass index (BMI) is a routine clinical index obtained by our hospital for health guidance of patients, and those with a body mass index (BMI) <25 kg /m^2 were included in the diabetic non-obese group. Patients that were not from the endocrinology department during the same period with admission examination and showed no elevation in diabetes-related markers (FPG, 2h-PG, and HbA1C) and with a BMI <25 kg/m^2 were selected. They were examined by abdominal CT to determine whether there were abdominal diseases; those without history and diseases related to the pancreas were enrolled. These patients were matched with diabetic group by age and gender and used as the normal non-obese group. All enrolled patients underwent abdominal CT scan without intravenous or oral contrast. We excluded patients with other types of diabetes, acute diabetic complications, spleen diseases, comorbid malignancies, kidney failure, systemic infection as well as those on glucocorticoids, who underwent malignancy surgery, with significant weight loss within a short period of time, poor CT images, blurred pancreatic margins, and pancreatic atrophy.

Equipment and Examination Method

A Siemens SOMATOM Perspective 64-slice or PHILIPS Brilliance 128-slice spiral CT was used. The parameters for abdominal non enhanced CT scan are as follows: detector combination 0.625 mm×64; 120kV tube voltage; A tube current of 300mAs; The spacing is 0.984. The scan area was from the apex of the diaphragm to the iliac ala. The reconstruction slice thickness was 1.0 mm, and the reconstruction interval was 1.0 mm.

Image CT Value Measurement Method

For body width measurements, the sum of the left-right diameter and anteroposterior diameter of the body at the right kidney hilum level in CT was measured in cm (Figure 1A).

Pancreas CT value measurements used two ROI regions drawn by senior radiologists using uniform criteria (area: 1.0–2.0 cm^2) at the head, body, and tail of the pancreas as well as the pancreatic parenchyma. These were included as much as possible while avoiding interference from the pancreatic parenchymal margin and blood vessels of adjacent organs. The mean CT value was calculated. At the same time, 2–3 ROI regions of the liver and spleen parenchyma were measured (area: 2.0 cm^2) and the mean CT value was calculated (Figure 1B–1D). The liver-to-spleen CT value ratio (L/S), difference between pancreatic and splenic attenuation (P−S), and pancreas-to-spleen attenuation ratio (P/S) were calculated. Lower P−S and P/S values implied more severe pancreatic fatty infiltration.

Statistical Methods

SPSS 23.0 statistical software was used for analysis. Quantitative data were expressed as $\bar{x} \pm s$, and independent sample *t*-test was used for inter-group comparison. Ranked data was expressed as frequency (percentage). Binary data was

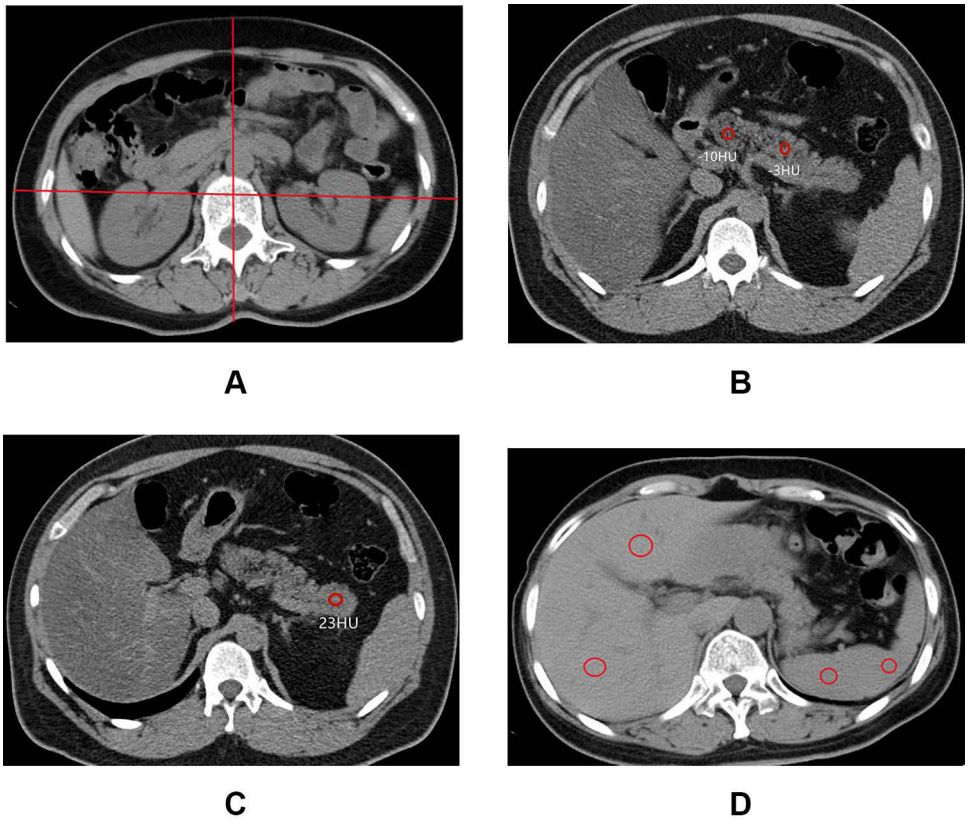

Figure 1 (**A**) Body width measurement; (**B** and **C**) are CT values of the pancreatic head, body, and tail to obtain the mean CT value of the pancreas; (**D**) is the measurement of CT values of the liver and spleen to obtain the mean CT value of the liver and spleen.

expressed as a percentage and the X^2 test was used for comparison. Univariate logistic regression analysis was carried out. The pancreatic CT value, P-S, and P/S were included in the model for statistical analysis and preliminary screening of statistically significant variables. Next, the P/S percentage was used for group and further logistic regression. Finally, the relationship between the degree of pancreatic fatty infiltration and risk of developing diabetes was analyzed. A difference of $P < 0.05$ was considered statistically significant.

Results

Comparison of General Information, Laboratory, and Abdominal CT Markers

There were 238 patients enrolled in this study: 135 were in the normal non-obese group (80 males and 55 females). The age range was 22–88 years, and mean age was 57.8 ± 14.2 years. There were 103 patients in the diabetic non-obese group (60 males and 43 females). The age range was 27–89 years, and the mean age was 58.8 ± 12.3 years. When both groups were compared, the body width, systolic blood pressure, and diastolic blood pressure of the normal non-obese group were significantly lower than the diabetic non-obese group; these differences were statistically significant. The L/S, pancreas CT value, P−S, and P/S of the normal non-obese group were significantly higher than the normal non-obese group ($P < 0.05$). The differences were statistically significant. The other differences were not statistically significant (Table 1).

Univariate Regression Analysis Results of Pancreatic Fatty Infiltration-Related Markers and T2DM

Pancreas CT value, P-S, and P/S were used as independent variables, and comorbid diabetes was used as a dependent variable during univariate logistic regression analysis. The Results showed that the pancreas CT value, P-S, and P/S are correlated with comorbid diabetes in non-obese patients ($P < 0.01$). The pancreas CT value (OR: 0.930, 95% CI: 0.891–0.970, $P < 0.001$),

Table 1 Comparison of General Information and Various Markers

Marker	Normal Non-Obese Group	Non-Obese Diabetic Group	P-value
Age (years)	57.81±14.17	58.83±12.28	0.537
Males (n)	80 (59.3%)	60 (60.2%)	0.884
Body fat	21.67±2.29	22.15±2.18	0.104
Body width	50.14±5.12	52.97±4.16	<0.001
Systolic blood pressure	130.01±20.74	142.82±21.45	<0.001
Diastolic blood pressure	80.04±13.89	87.11±13.54	<0.001
Liver-to-spleen ratio	1.11±0.17	1.03±0.23	0.003
Blood glucose		16.87±6.90	
Glycemic control achievement rate		10 (9.7%)	
Pancreas CT value (HU)	41.66±5.64	38.26±8.57	<0.001
P–S	−6.00±5.78	−9.83±9.05	<0.001
P/S	0.88±0.13	0.80±0.19	<0.001

Abbreviations: CT, computed tomography; HU, Hounsfield units.

P-S (OR: 0.926, 95% CI: 0.888–0.966, P < 0.001), and P/S (OR: 0.029, 95% CI: 0.004–0.208, P < 0.001) were all protective factors for developing diabetes in non-obese patients (Table 2).

Regression Analysis Results of Self-Defined P/S Group and T2DM Risk

Figure 2 shows the histogram of P/S distribution of the normal non-obese group and diabetic non-obese group. The P/S was used for grouping in a descending order. According to population concentration trends, every decrease in 0.1 was taken as a group. The final groups were a (P/S ≥ 1.0), b (0.90 ≤ P/S ≤ 0.99), c (0.80 ≤ P/S ≤ 0.89), d (0.70 ≤ P/S ≤ 0.79), and e (P/S < 0.7).

Groups a-e were used as independent variables and group a was used as the reference and the stepwise method was used. First, only group a was used as the independent variable in the model before another independent variable was added to see if the dependent variable variance (that can be explained by the entire model) is significantly increased. This process is repeated for several iterations until there is no independent variable that meets the criteria for model inclusion. Comorbid diabetes in non-obese patients was used as a dependent variable for logistic regression analysis. The results showed that groups b-e are correlated with comorbid diabetes in non-obese patients compared with group a (P < 0.05). Groups b, c, d, and e had an increased risk of developing diabetes by 3.981, 4.452, 6.037, and 12.937, respectively, versus group a. Therefore, a higher greater degree of pancreatic fatty infiltration implies a higher risk of developing diabetes in the non-obese population. This shows an increasing trend (Table 3).

Discussion

In this study, participant enrollment and grouping were based on the WHO classification criteria for BMI and T2DM, and all patients with BMI <25 kg/m^2 were enrolled. In consideration of statistical accuracy, the age distribution and gender ratio of the two groups were matched strictly, therefore there were no statistical differences in age and gender.

In 2008, the twin cycle hypothesis postulated that there are vicious cycles of fat accumulation in the liver and pancreas that lead to the development of T2DM over at least a decade. The increased exposure of β cells to fat metabolites was postulated to lead ultimately to β cell failure.[20] Studies have increasingly shown that pancreatic fatty infiltration is a cause of T2DM.[21,22] However, there is no unified and standard method in imaging studies for quantitative markers to analyze the correlation

Table 2 Univariate Logistic Regression Analysis for Non-Obese Diabetics

Variable	β-value	Wald value	OR value	95% CI	P-value	r value
Pancreas CT value	−0.073	11.338	0.930	0.891−0.970	<0.001	−0.233
P–S	−0.077	12.869	0.926	0.888−0.966	<0.001	−0.250
P/S	−3.543	12.419	0.029	0.004−0.208	<0.001	−0.245

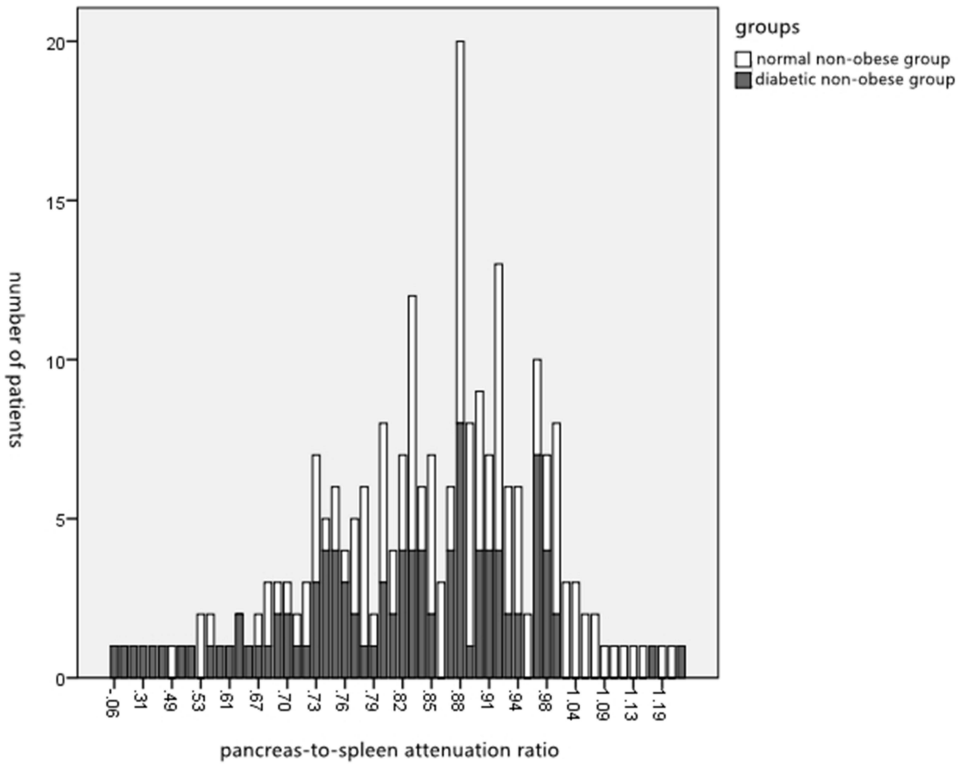

Figure 2 Histogram of pancreas-to-spleen attenuation ratio distribution in the normal non-obese group and the diabetic non-obese group.

between pancreatic fatty infiltration and T2DM. Wagner et al focused on the differences in correlation for pancreas head, body, and tail fatty infiltration.[13] Kim et al used pancreatic volume for analysis.[14] In this study, pancreas CT HU value, P−S, and P/S were used as reference values for pancreas, which is similar to the study methods of Kim[22] and Yamazaki.[12] Yamazaki applied the mean CT HU value of pancreas from all patients as a grouping marker, and used that value to distinguish the pancreatic fat infiltration group from the control group. A mean CT HU value greater than this was considered to be non-fatty infiltration while a mean CT HU value lower than this was considered to be fatty infiltration. This value was biased among different subgroups of non-obese individuals. Our study considered that the concept of pancreatic fatty infiltration is very close to that of nonalcoholic fatty liver disease, and the measurement method of fatty liver disease has been widely used and recognized. The definition was based on liver and spleen CT HU value ratio <1.[23] Based on this criteria, P/S was used as a grouping marker. The degree of pancreatic fatty infiltration assessed was hence more objective and accurate. A lower P/S value implies more severe pancreatic fat infiltration.

In this study, the pancreas CT value, P−S, and P/S were used for univariate logistic regression analysis. These three markers were found to be protective factors for T2DM in a non-obese population. This means that a greater marker implies a lower degree of pancreatic fatty infiltration and a lower risk of T2DM. Conversely, a higher degree of pancreatic fatty infiltration implies a greater risk of T2DM. Upon comparing the statistical values of the three

Table 3 Regression Analysis of the Pancreas-to-Spleen Attenuation Ratio in the Normal Group and the Diabetes Group

Variable	β-value	Wald value	OR value	95% CI	P-value
a (reference)		15.074			0.005
b	1.381	5.605	3.981	1.268–12.493	0.018
c	1.493	6.069	4.452	1.357–14.604	0.014
d	1.798	8.266	6.037	1.772–20.567	0.004
e	2.560	13.827	12.937	3.356–49.877	<0.001

markers (pancreas CT value OR: 0.930, P−S OR: 0.926, P/S OR:0.029), we found that P/S was a more effective risk marker for the non-obese population. This suggests that it is practical to use P/S as a grouping marker in a non-obese population.

We excluded all possible confounding factors and performed grouping via P/S with P/S of >1 as the reference. This ensures that the number of people in each group is relatively uniform because every decrease in 10% was set as a group. The population with a ratio < 70% pancreatic fatty infiltration was the most severe group, and there were five groups in total. Statistical analysis suggests that the risk of developing diabetes increases as the degree of pancreatic fatty infiltration increases: The risk of developing the diabetes was increased by 3.981, 4.452, 6.037, and 12.937 in groups b ($0.90 \leq P/S \leq 0.99$), c ($0.80 \leq P/S \leq 0.89$), d ($0.70 \leq P/S \leq 0.79$), and e ($P/S < 0.7$), respectively, versus group a ($P/S \geq 1.0$).

CT was used to collect two indexes for quantitation. They could detect the presence/absence of fatty liver disease and measure body width. Both indexes were statistically significant. Fatty liver disease often occurs in the obese population, but the high ratio of fatty liver disease in the non-obese population should not be overlooked. In this study, the L/S of diabetic non-obese patients was significantly lower than the normal non-obese group, which indicated that fatty liver disease may predict T2DM. In addition, abdominal CT body width measurement is more intuitive than conventional abdominal circumference measurement and has more accurate data. Even if BMI does not meet the criteria for obesity, abdominal CT body width of diabetic non-obese patients is significantly higher than the normal non-obese group. This suggests that body width is a risk factor for T2DM.

There are some limitations of this study: First, the retrospective nature of the study prevented us from doing any temporal comparison and also exposed to a risk of patient selection. Second, the sample size in this study is also low. Future studies will increase the sample size, adjust the male/female ratio, and increase laboratory test markers. Third, Narisada et al suggested that the association between fatty liver and T2DM in non-obese populations is different by sex: Fatty liver increases diabetes risk among male but not female non-obese populations.[24] Further studies should explore whether the risk of pancreatic fat infiltration for T2DM in non-obese populations is different between males and females. Fourth, the pancreas most often shows high heterogeneous morphology on CT. There is a chance of bias of selecting when manually selecting a couple ROIs across the pancreas. Upgrading the measurement tools should enable researchers to examine the entire volume of the pancreas.

In summary, we focused on the risk of T2DM in non-obese populations. We used CT to predict pancreatic fatty infiltration and the risk of T2DM. We found that body width, L/S, pancreas CT value, P−S, and P/S could be used as quantitation indexes to predict the risk of T2DM. Among them, the P/S ratio is more objective than the other markers. This suggests that more severe pancreatic fatty infiltration leads to a greater risk of developing diabetes. These indexes are correlated with the predicted risk of T2DM.

Abbreviations

ADA, American diabetes association; BMI, Body mass index; CT, Computed tomography; HU, Hounsfield units; L/S, liver-to-spleen attenuation ratio; P−S, pancreas and spleen CT values; P/S, pancreas-to-spleen attenuation ratio; T2DM, Type 2 diabetes mellitus; FPG, fasting plasma glucose; 2h-PG, 2-hour postprandial blood glucose; HbA1C, glycated hemoglobin.

Ethical Statement

This retrospective study has obtained approval from the ethics committees of Fushun Central Hospital (Number: zzyyll2023008). The Institutional Review Board approved the retrospective study and informed patient consent was waived. This study kept all the patients' data confidentiality and was compliance with the Declaration of Helsinki.

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Disclosure

Yi Tang and Zemin Wei are co-first authors for this study. Zhe Wu and Hao Sun are co-last authors for this study. All authors declare no conflicts of interest in this work.

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