

Computed Tomography-Estimated Pancreatic Steatosis is a Risk Factor for Carotid Plaque in Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study

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Abstract

Background Pancreatic steatosis correlates with the thickness of arterial intima. However, the correlation between pancreatic steatosis and carotid atherosclerosis plaque, which better predict the prognosis of cardiovascular disease, is unclear. We aimed to explore potential effects of pancreatic fat content measured by computer tomography (CT) on carotid plaque in patients with type 2 diabetes mellitus (T2DM).

Methods Patients with T2DM who underwent CT scan of the upper abdomen and ultrasound of the carotid artery were consecutively enrolled. Based on ultrasound results, the patients were divided into non-plaque group and plaque group, and the latter was categorized into hypoechoic plaque subgroup and non-hypoechoic plaque subgroup. The CT attenuation of pancreas and spleen were measured. Pancreas-to-spleen attenuation ratio (P/S) and difference between pancreatic and splenic attenuation (P-S) were calculated. The cut-off values of P/S and P-S were obtained using receiver operating characteristic (ROC) curves. Logistic regression models were used to evaluate association of P/S or P-S with carotid plaque or hypoechoic plaque.

Results A total of 337 patients with T2DM were enrolled, including 101 cases (30.0%) in the non-plaque group, 146 cases (43.3%) in the hypoechoic plaque subgroup, and 90 cases (26.7%) in the non-hypoechoic plaque subgroup. P/S and P-S in plaque group were lower than those in non-plaque group, with a cut-off value of P/S and P-S as 0.72 and -13.33, respectively. After adjusting for risk factors, P/S and P-S correlated with carotid plaque [for low P/S: OR (95% CI): 3.15 (1.47-6.73), $P=0.0031$; for low P-S: OR (95% CI): 2.84 (1.42-5.66), $P=0.0031$] as well as carotid hypoechoic plaque [for low P/S: OR (95% CI): 1.82 (1.07-3.08), $P=0.0259$; for low P-S: OR (95% CI): 1.82 (1.09-3.02), $P=0.021$].

Conclusions T2DM patients with carotid plaque have higher pancreatic fat content than those without. Pancreatic steatosis correlates with carotid plaque and hypoechoic plaque in T2DM patients.

Background

Carotid plaque is the main pathological feature of carotid atherosclerosis, which is closely related to the development of cerebral infarction [1]. Furthermore, hypoechoic carotid plaque associated with adverse cerebrovascular outcome independent of stenosis severity [2]. To evaluate risk factors of carotid plaque for cerebral infarction will facilitate its prevention and treatment. Ectopic fat deposition, characterized by accumulation of fat tissue in the liver, pancreas, and skeletal muscle [3], may release various bioactive factors to promote the development of cardiovascular diseases [4]. Ectopic fat deposition in the pancreas is defined as pancreatic steatosis [5]. Histology is the gold standard for diagnosis of pancreatic steatosis. However, it is an invasive examination, which limits its wide application. Computed tomography (CT) quantitative measurement of pancreatic fat content has high accuracy, proven to be a reliable non-invasive method [6]. In recent years, pancreatic steatosis was diagnosed by CT in burgeoning literatures [7, 8].

Although several reports indicated relationship between pancreatic steatosis measured by CT and atherosclerosis, most of them focused on arterial intima-media or intima thickness [9, 10]. However, carotid plaque may provide more direct evidence of subclinical atherosclerosis than intimal thickness. In addition, predictive value of carotid plaque for cardiovascular adverse events may be higher than carotid intima-media thickness [11]. Thus, demonstrating relationship between pancreatic steatosis and carotid plaque may be more useful to identify patients at high risk of ischemic stroke. Indeed, pancreatic steatosis was related to arterial calcified plaque in healthy people [12]. However, there are very few reports on the relationship between pancreatic steatosis and carotid plaque (especially hypoechoic plaque) in patients with type 2 diabetes mellitus (T2DM). Therefore, our study aims to investigate if pancreatic steatosis confers increased risk of carotid plaque in patients with T2DM.

Methods

This study retrospectively analyzed 337 patients with T2DM from January 2016 to January 2020. Inclusion criteria were as follows: (1) age \geq 20 years old; (2) diagnosis according to 2010 American Diabetes Association standards [13]; (3) with complete information on upper abdominal CT scan, carotid artery ultrasound and biochemical examination; and (4) all the above examinations were performed within 2 weeks. Exclusion criteria were as follows: (1) complicated pancreatic diseases (e.g., acute or chronic pancreatitis, pancreatic neoplasms); (2) liver and kidney failure; (3) systemic infectious diseases; (4) malignant tumors; (5) treatment with glucocorticoids. Basic information was recorded, including age, gender, blood pressure, height, weight, and smoking history, diabetes duration and biochemical examination.

Carotid Ultrasound Examination And Plaque Assessment

An ultrasonic detector (Philips iE33 or GE Logic E9) with a 10 MHz linear array probe was used to evaluate carotid artery. Patients were examined in supine position, and intima-media thickness (IMT) of bilateral carotid arteries (including common and internal carotid artery, as well as bifurcations) were measured. Carotid plaque was defined as $IMT \geq 1.5$ mm or local thickness exceeding 50% of the adjacent lumen [14]. Plaques were classified into hypoechoic plaque and non-hypoechoic (either mixed echoic or hyperechoic) plaque. According to the presence or absence of carotid plaque, patients were divided into non-plaque group and plaque group. The plaque group were classified into hypoechoic plaque subgroup and non-hypoechoic plaque subgroup according to the presence or absence of hypoechoic plaque.

Ct Scan And Pancreatic Fat Content Measurement

Upper abdominal CT scan was performed on a spiral CT scanner (Siemens Somatom Sensation 16 CT or Brilliance iCT, Philips Healthcare). Scan parameters were as follows: kVp, 100–120; mAs, 100–250; pitch 1; slice thickness and slice spacing, 2 mm. Attenuation within the head, body and tail, respectively, of the pancreas was measured on CT axial images, where the largest diameter of anatomical part was

observed. The ROI area was 1.0 cm². The main pancreatic duct, pancreatic edge and splenic vessels were carefully avoided during measurement. CT attenuation of 3 different parts of the spleen was measured. The average CT attenuation of the pancreas and spleen, respectively, was calculated. The difference between pancreatic and splenic attenuation (P-S), and pancreas-to-spleen attenuation ratio (P/S) were calculated.

Statistical analysis

Statistical analysis was performed using SAS version 9.1 (SAS, Cary, NC, USA). Basic clinical data and CT measurements were compared by using Kruskal-Wallis rank test or chi-square test. Cutoff values of P/S and P-S were obtained using receiver operating characteristic (ROC) curves. Low P/S or low P-S was defined as pancreatic steatosis. Carotid plaque or hypoechoic plaque was considered as dependent variable. Univariate logistic regression was created to analyze relationship of plaque with P/S or P-S. Statistically significant factors in univariate logistic regression as well as clinical factors, such as age, gender, obesity (body mass index ≥ 30 kg/m²), duration of diabetes, hypertension, smoking, total cholesterol, triglycerides and high-density lipoprotein, were selected for multivariate logistic regression. Statistical significance was defined at a $p < 0.05$ (2-sided).

Results

Patients characteristics

A total of 337 patients with T2DM were enrolled in this study, with an average age of 60.1 ± 11.7 years old. Among them, 201 cases (59.6%) were male with an average age of 57.4 ± 11.9 years old, while 136 cases (40.4%) were female with an average age of 64.2 ± 10.3 years old. There were 101 cases (30.0%) in non-plaque group, whereas 236 cases (70.0%) in plaque group; 146 cases in hypoechoic plaque subgroup (43.3%) and 90 cases (26.7%) in non-hypoechoic plaque subgroup. Basic information of study population is summarized in Table 1.

Table 1
Clinical and laboratory characteristics of study population

Index	Non-plaque	Plaque		P-value
		Hypoechoic	Non-hypoechoic	
Male, n (%)	58 (57.4)	92 (63.0)	51 (56.7)	0.54
Age (years)	52.8 ± 11.8	63.0 ± 10.8	63.7 ± 9.2	< .0001
Smoking, n (%)	34 (33.7)	48 (32.9)	25 (27.8)	0.63
Hypertension, n (%)	55 (54.4)	108 (73.9)	75 (83.3)	< .0001
SBP (mm Hg)	132.0 ± 17.0	134.8 ± 19.1	133.8 ± 13.9	0.45
DBP (mm Hg)	83.1 ± 11.9	81.2 ± 11.0	79.9 ± 9.1	0.38
MAP (mm Hg)	99.4 ± 12.6	99.0 ± 12.4	97.8 ± 9.2	0.98
BMI (kg/m ²)	26.1 ± 4.1	25.7 ± 3.1	26.0 ± 3.2	0.70
DD, IQR (years)	6 (1–10)	10 (5–16)	14 (6–20)	< .0001
FPG (mmol/L)	8.38 ± 2.90	8.67 ± 4.03	8.55 ± 3.67	0.92
HbA1c (%)	7.67 ± 1.36	8.05 ± 2.14	7.59 ± 1.53	0.80
TC (mmol/L)	4.70 ± 1.24	4.41 ± 1.13	4.16 ± 0.96	0.0074
TG, IQR (mmol/L)	1.81 (1.17–3.09)	1.63 (1.16–2.44)	1.65 (1.07–2.59)	0.50
HDL-C (mmol/L)	1.06 ± 0.29	0.99 ± 0.25	1.05 ± 0.26	0.09
LDL-C (mmol/L)	2.41 ± 0.83	2.43 ± 0.81	2.26 ± 0.80	0.21
<p><i>SBP</i> Systolic blood pressure, <i>DBP</i> Diastolic blood pressure, <i>Map</i> Mean arterial pressure, <i>BMI</i> Body mass index, <i>DD</i> Diabetes duration, <i>IQR</i> interquartile range, <i>FPG</i> Fasting plasma glucose, <i>TC</i> Total cholesterol, <i>TG</i> Triglycerides, <i>HDL-C</i> High density lipoprotein cholesterol, <i>LDL-C</i> Low density lipoprotein cholesterol</p>				
<p>Patients in plaque group were elder, with longer duration of T2DM. Hypertension was more common in plaque group. Total cholesterol level was higher in non-plaque group. Gender, smoking ratio, systolic blood pressure, diastolic blood pressure, mean arterial pressure, BMI, fasting blood glucose, HbA1c, triacylglycerol, high-density lipoprotein, and low-density lipoprotein were comparable between the two groups.</p>				

Ct Evaluation Of Pancreatic Steatosis

Compared with non-plaque group, CT attenuation of the pancreas, P/S and P-S were lower in plaque group. There was no difference in CT attenuation of the spleen between the two groups (Table 2).

Table 2
Comparison of pancreatic fat content

Index	Non-plaque	Plaque		P-value
		Hypoechoic	Non-hypoechoic	
Pancreas (HU)	39.84 ± 14.59	35.42 ± 13.35	35.91 ± 13.09	0.001
Spleen (HU)	51.57 ± 2.83	51.16 ± 3.15	50.80 ± 3.68	0.29
P/S	0.77 ± 0.27	0.69 ± 0.25	0.70 ± 0.25	0.0029
P-S	-11.72 ± 14.07	-15.74 ± 13.01	-14.89 ± 12.86	0.004
<i>P/S</i> Pancreas-to-spleen attenuation ratio				

P-S Difference between pancreatic and splenic attenuation

Based on ROC curves, the cutoff value of *P/S* was 0.72, and the area under the curve was 0.61. The sensitivity and specificity of *P/S* for predicting carotid plaque was 41.1% and 80.2%, respectively ($P = 0.0005$). The cutoff value of *P-S* was -13.33, and the area under the curve was 0.61. The sensitivity and specificity of *P-S* for predicting carotid plaque was 45.8% and 75.3%, respectively ($P = 0.0009$). Patients with low *P/S* (≤ 0.72) or low *P-S* (≤ -13.33) was defined as pancreatic steatosis. Patients with low *P/S* or low *P-S* accounted for 34.7% ($n = 117$) and 39.5% ($n = 133$), respectively.

Risk Factors For Carotid Plaque

As shown in Table 3, univariate logistic regression model identified low *P/S* (OR = 2.83, 95% CI = 1.62–4.91, $P = 0.0002$) and low *P-S* (OR = 2.57, 95% CI = 1.52–4.31, $P = 0.0004$) as risk factors of carotid plaque. Furthermore, low *P/S* (OR = 1.93, 95% CI = 1.22–3.03, $P = 0.0047$) and low *P-S* (OR = 1.97, 95% CI = 1.26–3.07, $P = 0.0028$) were risk factors of hypoechoic plaque.

Table 3
Univariate logistic regression models for carotid plaque and hypoechoic plaque

Factor	Plaque		Hypoechoic plaque	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Low P/S	2.83 (1.62–4.91)	0.0002	1.93 (1.22–3.03)	0.0047
Low P-S	2.57 (1.52–4.31)	0.0004	1.97 (1.26–3.07)	0.0028
Age (\geq 60 years)	4.78 (2.85–7.99)	< .0001	2.24 (1.43–3.47)	0.0004
Male	1.14 (0.71–1.82)	0.59	1.28 (0.82–1.99)	0.27
Smoking	0.88 (0.53–1.45)	0.62	1.10 (0.69–1.74)	0.70
Obesity	0.58 (0.27–1.18)	0.13	0.65 (0.31–1.35)	0.25
Hypertension	2.89 (1.75–4.74)	< .0001	1.33 (0.82–2.15)	0.24
SBP	1.01 (0.99–1.02)	0.25	1.01 (0.99–1.01)	0.31
DBP	0.98 (0.95–1.01)	0.06	0.99 (0.97–1.01)	0.72
MAP	0.99 (0.97–1.01)	0.54	1.00 (0.98–1.02)	0.78
DD	1.10 (1.05–1.13)	< .0001	1.01 (0.98–1.04)	0.34
FPG	1.02 (0.95–1.09)	0.57	1.02 (0.95–1.08)	0.59
HbA1c	1.07 (0.85–1.33)	0.55	1.14 (0.93–1.38)	0.20
TC	0.74 (0.60–0.92)	0.0069	0.97 (0.79–1.17)	0.74
TG	0.89 (0.81–0.98)	0.0207	0.97 (0.88–1.06)	0.52
HDL-C	0.51 (0.21–1.20)	0.13	0.40 (0.17–0.93)	0.0346
LDL-C	0.94 (0.69–1.25)	0.66	1.15 (0.87–1.50)	0.32
<i>P/S</i> Pancreas-to-spleen attenuation ratio, <i>P-S</i> Difference between pancreatic and splenic attenuation, <i>SBP</i> systolic blood pressure, <i>DBP</i> Diastolic blood pressure, <i>Map</i> Mean arterial pressure, <i>DD</i> Diabetes duration, <i>FPG</i> Fasting plasma glucose, <i>HbA1c</i> glycated hemoglobin, <i>TC</i> Total cholesterol, <i>TG</i> Triglycerides, <i>HDL-C</i> High density lipoprotein cholesterol, <i>LDL-C</i> Low density lipoprotein cholesterol				

After adjusting for conventional cardiovascular risk factors (including age, gender, smoking, duration of diabetes, hypertension, obesity, total cholesterol, triglycerides, high-density lipoprotein), multivariate logistic regression model identified low P/S (OR = 3.15, 95% CI = 1.47–6.73, P = 0.0031) and low P-S (OR = 2.84, 95% CI = 1.42–5.66, P = 0.0031) as independent risk factors of carotid plaque (Table 4).

Furthermore, low P/S (OR = 1.82, 95% CI = 1.07–3.08, P = 0.0259) and low P-S (OR = 1.82, 95% CI = 1.09–3.02, P = 0.021) were independent risk factors of hypoechoic plaque (Table 5).

Table 4
Multivariate logistic regression models for carotid plaque

Factor	Low P/S		Low P-S	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Low P/S	3.15 (1.47–6.73)	0.0031	-	-
Low P-S	-	-	2.84 (1.42–5.66)	0.0031
Age (\geq 60 years)	4.56 (2.20–9.44)	< .0001	4.68 (2.25–9.69)	< .0001
Male	2.34 (1.03–5.29)	0.041	2.39 (1.06–5.39)	0.0354
Smoking	0.98 (0.45–2.11)	0.97	1.02 (0.47–2.18)	0.97
Obesity	1.03 (0.41–2.55)	0.95	0.99 (0.40–2.45)	0.99
Hypertension	2.73 (1.42–5.20)	0.0024	2.96 (1.55–5.62)	0.001
DD	1.08 (1.02–1.13)	0.0021	1.08 (1.02–1.13)	0.0022
TC	1.07 (0.76–1.51)	0.68	1.04 (0.73–1.46)	0.84
TG	0.89 (0.74–1.05)	0.17	0.91 (0.76–1.07)	0.25
HDL-C	0.33 (0.07–1.34)	0.12	0.38 (0.09–1.53)	0.17

P/S Pancreas-to-spleen attenuation ratio, *P-S* Difference between pancreatic and splenic attenuation, *TC* Total cholesterol, *TG* Triglycerides, *HDL-C* High density lipoprotein cholesterol

Table 5
Multivariate logistic regression models for carotid hypoechoic plaque

Factor	Low P/S		Low P-S	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Low P/S	1.82 (1.07–3.08)	0.0259	-	-
Low P-S	-	-	1.82 (1.09–3.02)	0.021
Age (\geq 60 years)	2.05 (1.14–3.65)	0.0151	2.05 (1.15–3.66)	0.0148
Male	1.26 (0.68–2.32)	0.46	1.27 (0.68–2.33)	0.45
Smoking	1.24 (0.67–2.28)	0.48	1.27 (0.68–2.34)	0.44
Obesity	0.80 (0.35–1.80)	0.60	0.78 (0.34–1.76)	0.56
Hypertension	1.20 (0.69–2.07)	0.51	1.23 (0.71–2.12)	0.45
DD	1.00 (0.96–1.03)	0.97	1.00 (0.96–1.03)	0.96
TC	1.26 (0.94–1.67)	0.11	1.24 (0.93–1.64)	0.14
TG	0.92 (0.79–1.05)	0.23	0.93 (0.80–1.06)	0.28
HDL-C	0.27 (0.08–0.87)	0.0286	0.29 (0.08–0.93)	0.0377

P/S Pancreas-to-spleen attenuation ratio, *P-S* Difference between pancreatic and splenic attenuation, *TC* Total cholesterol, *TG* Triglycerides, *HDL-C* High density lipoprotein cholesterol

Discussion

Our study has demonstrated that *P/S* and *P-S* in T2DM patients with carotid plaque, especially with hypoechoic plaque, are lower than those without carotid plaque. After adjusting for covariates, multivariate logistic regression model identifies low *P/S* and low *P-S* as independent risk factors for carotid plaque, in particular carotid hypoechoic plaque.

Ct Quantitative Evaluation Of Pancreatic Steatosis

Pancreatic steatosis has been indicated in various diseases [5, 7, 8]. Therefore, a simple and accurate method for evaluating pancreatic fat content is of clinical significance. Ultrasound and magnetic resonance imaging (MRI) have been used to measure pancreatic fat content [15, 16]. However, ultrasound results may be affected by the operator's experience, while MRI is expensive and time-consuming, which limit their clinical application. Histologically, pancreatic CT density index (*P/S*, *P-S*) had a good correlation with pancreatic fat content [6]. Therefore, CT, which is widely used in clinical practice, is a

reliable tool to evaluate pancreatic fat content. Rather than CT attenuation, P/S and P-S were applied to quantify pancreatic fat content in many studies [17–19], which was also applied in this study.

At present, no uniform CT cutoff value has been applied for the diagnosis of pancreatic steatosis. In this study, cutoff values of P/S (0.72) and P-S (-13.33) were obtained from ROC curves, consistent with previous reports [5, 20]. In this study, there were 117 patients (34.7%) with low P/S and 133 patients (39.5%) with low PS. The incidence of pancreatic steatosis was higher than previously reported in healthy Chinese adults [21], indicating that diabetes patients are more likely to suffer from pancreatic steatosis [22].

Relationship Between Pancreatic Steatosis And Carotid Plaque

Ectopic fat deposition is closely related to atherosclerotic plaque and cardiovascular disease [23]. Pancreatic steatosis is manifestation of ectopic fat deposition, characterized by fat accumulation in the pancreas [5, 24]. Pancreatic steatosis was related to carotid-femoral pulse wave velocity, which might predict carotid atherosclerosis in patients with non-alcoholic fatty liver disease [9]. Pancreatic steatosis was in proportion to aortic intima thickness [25] and systemic arterial calcification [12]. Ectopic fat deposition in the pancreas increased risk for carotid atherosclerosis in non-obese T2DM patients, but not in obese patients [26]. In this study, after adjusting for obesity and other traditional risk factors, low P/S and low P-S remain correlated with carotid plaque. Thus, pancreatic steatosis is an independent risk factor for carotid atherosclerosis.

Hypoechoic plaque is characteristic manifestation of unstable plaque, which is highly enriched in lipids and more prone to cerebrovascular diseases [27]. Previous study reported that hypoechoic plaque was independently related to progression of atherosclerosis [28]. The size of juxtaluminal hypoechoic area in asymptomatic carotid plaque linearly correlated with the risk of stroke [29]. Additionally, carotid hypoechoic plaque predicted adverse cardiovascular events in asymptomatic carotid stenosis [30]. Furthermore, hypoechoic plaque indicated cognitive impairment among patients with acute ischemic stroke [31]. We propose that pancreatic steatosis confers increased risk of hypoechoic carotid plaque. Therefore, for patients with T2DM, pancreatic fat content on CT images can help identify those at high risk of stroke, and guide early clinical intervention to prevent cerebrovascular diseases.

Pathological mechanisms underlying how pancreatic steatosis increases susceptibility to carotid plaque remain unclear. Pancreatic steatosis impairs insulin secretion in patients with T2DM [32], resulting in decreased insulin secretion. Moreover, pancreatic steatosis may contribute to insulin resistance [33], leading to relatively insufficient insulin. Consequently, elevated blood glucose causes damage to blood vessel wall through a variety of molecular pathways [34], and ultimately promotes the formation of atherosclerosis plaque.

There are several limitations in the current study. Firstly, ultrasound, instead of MRI, is applied in this study. Although MRI is superior to ultrasound in evaluating plaque composition, it is not widely used in clinical practice, since most radiologists have insufficient experience in this field. By contrast, ultrasound is easy to operate and widely applied to evaluate carotid plaque. Although ultrasound is not accurate enough to distinguish stable or unstable plaque according to echo features, hypoechoic plaque remains a certain value in predicting cardiovascular events [29, 30]. Secondly, all subjects in this study are patients with T2DM and cannot represent the general population. Thirdly, as a cross-sectional study, cause and effect relationship between pancreatic steatosis and carotid plaque needs to be further explored in future prospective studies with larger sample sizes.

Conclusions

In conclusion, T2DM patients with carotid plaque, especially hypoechoic plaque, may have more pancreatic fat content. Pancreatic steatosis may confer an independent increased risk of carotid (hypoechoic) plaque in T2DM patients.

Abbreviations

BMI: body mass index; CT: computer tomography; DBP: diastolic blood pressure; DD: diabetes duration; IQR: interquartile range; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; IMT: intima-media thickness; LDL-C: low density lipoprotein cholesterol; Map: mean arterial pressure; MRI: magnetic resonance imaging; P/S: pancreas-to-spleen attenuation ratio; P-S: the difference between pancreatic and splenic attenuation; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; T2DM: type 2 diabetes mellitus.

Declarations

Ethics approval and consent to participate

This study has been approved by Ethics Committee of Institutional Review Board (IRB) at Beijing Shijitan Hospital (sjtkyll-ix-2020 (36)).

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

All the authors declare that they have no conflict of interest.

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Authors' contributions

All authors contributed to the content and critical review of the manuscript. All authors read and approved the final manuscript.

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